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2021 High School Research Conference Agenda

Date: June 12, 2021
Location: Online

12:00 pm Registration

12:15 pm Workshops

- GEO2R and String-db: Learn computational resources used in the research process
- Transition from high school to college
- Pseudo-code: For better coding practice and for first-time coders
- Healthy mind: Self-knowledge to maintain a positive mindset, even during the pandemic

1:00 pm Greetings from miRcore President | **Inhan Lee**, Ph.D.

1:05 pm Student Oral Presentations I

Session Chair: Kaitlyn Sadtler, Ph.D.
Earl Stadtman Investigator | Chief, Section for Immuno-Engineering, National Institute of Biomedical Imaging and Bioengineering (Forbes 30 Under 30 | TED Fellow)

1:50 pm Student Poster Session

2:50 pm Break

3:00 pm Keynote Address: *COVID-19, Health Disparities, and Precision Medicine*

Francis Collins, M.D., Ph.D.
Director, National Institutes of Health

4:00 pm Student Oral Presentations II

Session Chair: David Burke, Ph.D.
Professor of Human Genetics, University of Michigan

4:45 pm 2020-21 GIDAS Activity Reports and Conference Awards

5:10 pm Closing

Welcome to the 8th miRcore High School Research Conference!

We have all learned to adapt, understanding our own resilience. Still, everyone has scars from the pandemic, some large, some small. This conference shows that we keep moving forward.

Let us celebrate this collective effort of students, parents, teachers, mentors, and scientists (please see the full list at the end of these proceedings), including NIH Director Francis Collins.

Many helped one another in preparing for today. I am grateful to the University of Michigan GIDAS, whose trained members guided miRcore volunteers for their research each weekend. miRcore volunteers impressively led their school GIDAS in researching, publishing, and presenting. I am indebted to University of Michigan faculty members and National Human Genome Research Institute investigators who shared their insights on our volunteer students' research despite their busy family and work schedules. I am in awe of our parent research group, which met weekly and wrote their own research abstracts.

It is fair to say that through your efforts, this conference fulfills our values of science, compassion, and collaboration.

Thank you so much,

Inhan Lee, Ph.D.
President, miRcore

Keynote Speaker:
Francis S. Collins, MD, PhD
Director, National Institutes of Health

Photos and Biosketch Credit: National Institute of Health

Biographical Sketch of Francis S. Collins, M.D., Ph.D.

NIH Director Francis Collins was appointed the 16th Director of the National Institutes of Health (NIH) by President Barack Obama and confirmed by the Senate. He was sworn in on August 17, 2009. In 2017, President Donald Trump asked Dr. Collins to continue to serve as the NIH Director. President Joe Biden did the same in 2021. Dr. Collins is the only Presidentially appointed NIH Director to serve more than one administration. In this role, Dr. Collins oversees the work of the largest supporter of biomedical research in the world, spanning the spectrum from basic to clinical research.

Dr. Collins is a physician-geneticist noted for his landmark discoveries of disease genes and his leadership of the international Human Genome Project, which culminated in April 2003 with the completion of a finished sequence of the human DNA instruction book. He served as director of the National Human Genome Research Institute at NIH from 1993-2008.

Dr. Collins is an elected member of both the National Academy of Medicine and the National Academy of Sciences, was awarded the Presidential Medal of Freedom in November 2007, and received the National Medal of Science in 2009. In 2020, he was elected as a Foreign Member of the Royal Society (UK) and was also named the 50th winner of the Templeton Prize, which celebrates scientific and spiritual curiosity.

Francis S. Collins, MD, PhD
Director, National Institutes of Health

Keynote Address:

COVID-19, Health Disparities, and Precision Medicine

Twenty years ago, through a cooperative global effort, humanity finally had a working draft of its own genetic instruction book. There was broad recognition that knowledge of the human genome holds vast potential for transforming our health: as individuals, as societies, and even as global citizens. But harnessing that potential would require new tools, technologies, and programs – all of which would in turn generate vast amounts of new data. A close and thorough "reading" of that data could point the way toward precision medicine.

The recent COVID-19 pandemic has demonstrated how a data-driven, precision medicine approach would work. It helped identify the disease's etiological agent, develop diagnostics and treatments, and create vaccine candidates. It underscored the behaviors that allowed the virus to spread, the risk factors that increased individuals' susceptibility, and the clinical variability of its expression. It helped uncover evidence of the virus's long persistence in some patients, and the consequences for viral evolution. Moreover, it has cast a bright light on the health disparities inherent in our medical system.

In this talk, I will review the development of genomic knowledge and precision medicine, with special focus on relevance for the COVID pandemic. I will suggest ways a precision medicine approach could help us address lingering pandemic challenges. And I will argue for its transformative promise – for today, and for the future of medicine.

The Role of OAS1 in the Prognosis and Severity of COVID-19 Infection by Means of the Hepatitis C Receptor Pathway

Disha Iyengar[1], Ava Barbano[2], Amrita Kondur[3], Alycia Mann[4], Eric Li[5], Kayli Bannon[6]

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Introduction

The COVID-19 pandemic has proved an immense challenge. Despite the development of vaccines and new treatment plans, much is still unknown about the disease's lingering side effects. Patients with chronic liver disease have been found to experience more severe cases of COVID-19, and higher hospitalization rates than those without pre-existing liver disease. Increased rates of liver damage have also been found in COVID-19 patients with no history of liver disease. While the significance of this relationship is strong, the underlying mechanisms remain unclear. We focused on the similar mRNA expression levels in patients with Hepatitis C and MERS (Middle Eastern Respiratory Virus), specifically in respect to the OAS gene family, which is associated with liver fibrosis and high ALT/AST levels.

Methods

We focused our research on the National Center for Biotechnology Information (NCBI) dataset GSE81909. It consists of human epithelial cells samples infected with wild type MERS-CoV, corresponding control samples, and non-infected samples at 0, 12, 24, 36, and 48 hours post infection, collected in quintuplet, for a total of 50 data points. To narrow our focus, we compared the 0h and 48h MERs-CoV cells (5 samples per group) using GEO2R. The top 250 genes by p-value ($\leq 1.27 \times 10^{-8}$) were further analyzed using STRING-db. The KEGG pathway for Hepatitis C was enriched within this set (gene count 9 of 131, strength 0.81, false discovery rate 0.00055), with all genes involved in this signaling pathway upregulated within our top genes.

Results

The enzymatic commonality between some COVID-19 and Hepatitis C patients, in regards to elevated levels of ALT and AST (both indicators of liver damage), can be explained by analyzing the interplay between the defense and adverse responses of the immune system. Increasing the level of infection potentiates the immune response, and corresponding adverse effects. In a patient with Hepatitis C, the immune system mounts a defense response against the liver pathogen, as evidenced by elevated transaminases. If patients with Hep C contracted COVID-19, both the immune response and adverse effects would amplify. A diminished version of this immune response occurs in COVID-19 patients with no pre-existing liver damage.

Conclusion

Additional research could provide insight into whether or not the connection between COVID-19 severity and liver infection is causational, and would allow physicians to identify which patient cohorts are more likely to experience severe COVID-19 infection. More generally, research into the interconnectedness between body systems can help researchers discover links between COVID-19 and seemingly unrelated diseases. The current treatment for Hepatitis C, which mainly consists of direct acting antivirals, could be used as a blueprint for potential COVID-19 treatments, and a patient's specific upregulated genes could indicate possibilities for future targeted treatments.

NF-κB Enrichment Leads to Hyperinflammation in Patients with Severe Coronavirus Infections

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[3]12th, Glenbrook North HS, Northbrook, IL

Introduction

COVID-19 is caused by a coronavirus called SARS-CoV-2. There have been 32,722,464 total reported cases and 582,263 total reported deaths in the United States since January 21, 2020. Those with underlying medical conditions, such as diabetes or lung and heart problems, and older adults are at higher risk for developing serious long-term health issues from COVID-19. In particular, inflammation could lead to further health problems post-recovery. This study aims to identify genetic markers of the biological response to coronavirus infection, specifically the NF-κB pathway's role in lung inflammation after MERS-CoV infection.

Methods

We used the publicly available microarray dataset GSE81909 to compare gene expression between 5 mock and 5 wild type MERS-CoV (icMERS) infected primary human airway epithelial cell samples at 48 hours post-infection. Next, using GEO2R, we determined the top 250 differentially expressed genes with p-values at or below 5.02E-08. For genes with multiple probe IDs, we used the ID with the best (lowest) p-value. Then, in order to identify enriched cell functions, we ran these top 250 genes through String-db. We further explored the roles of the enriched pathways obtained from String-db using the public databases Gene Cards and KEGG.

Results

Ten of the 250 genes we examined in String-db were associated with the NF-κB signaling pathway (strength = 1.0, false discovery rate = 3.31E-06). These NF-κB-associated genes were significantly upregulated in the icMERS-infected sample group, yielding logFC values ranging from 1.15 to 3.89. A significant gene family we identified among these ten upregulated genes was the CXC chemokine family. Specifically, we found that CXCL8 (logFC = 2.60) and CXCL2 (logFC = 3.89) are both actively involved in the cellular inflammatory response to infection. Upregulation of these CXC genes suggests enrichment of the NF-κB pathway.

Conclusion

The NF-κB pathway regulates immune and inflammatory responses to infection. Enrichment of this pathway can lead to excess inflammation. Our results align with existing research suggesting that the upregulation of CXC genes in MERS-CoV patients results in NF-κB enrichment. Targeted treatments suppressing gene expression within the NF-κB pathway could reduce inflammation in patients infected with coronaviruses. Furthermore, because inflammation has been cited as a significant long-term concern for COVID-19 patients, most recently in the brain, we suggest further studies examining the expression of NF-κB-associated genes in brain tissue post-infection. Studies like these could determine if early pharmacological inhibition of NF-κB could prevent the development of neuroinflammatory diseases like Alzheimer's in patients with severe COVID-19.

References

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Impact of SARS Coronavirus on Innate Immune System Compared to Influenza A

Noah Black[1], Ashi Jain[2], Keerthana Danasekaran[3], Jasmine Wisniewski[4], Praveena Mohanraj[5]

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Introduction

As the coronavirus continues to rage around the world, understanding its functions is key to developing preventative measures and medication. In respiratory infections, type III interferons play a major role in the body's innate immune response by inhibiting viral replication. Many viruses suppress the production of interferons. In our study, we analyzed the effectiveness of a SARS Coronavirus strain - SARS Coronavirus Urbani - and compared it to an Influenza A strain - A/CA/04/2009 Influenza virus - in order to analyze their abilities to inhibit type III interferons. Our objective is to gauge immuno-circumvention measures in each virus.

Methods

We used GEO datasets GSE37571 and GSE37827 to analyze Influenza A and SARS Coronavirus, respectively. Viruses from both datasets infected Calu-3 lung cells. We extracted mRNA expression data for the cells at 7hr, 12hr, 24hr, 36hr, and 48hr, which were each compared to controlled expression data at 0hr. Using Python, we reduced each datasheet by deleting blank entries in the Gene.symbol column. We entered the top 250 genes (arranged by smallest p-value) for the SARS Urbani data (Gene.symbol values) into STRINGdb. In the 48hr graph, The GO process "Regulation of Type III interferon Production" contained 3 genes from our STRING graph: IFIH1, DDX58, and TLR3.

Results

We emphasized the IFIH1, DDX58, and TLR3 genes, since these genes are part of the "Regulation of Type III Interferon Production" GO Process. When isolating the emphasized genes, a pattern emerged; compared to SARS Urbani Coronaviruses, Influenza A exhibits a higher expression of the IFIH1, DDX85, and TLR3 genes until 36, 30, and 24 hours respectively. KEGG Pathways shows that these genes are involved in the JAK-STAT Signaling pathway, a pro-inflammatory pathway, for SARS Coronaviruses. In Influenza A, though, these 3 genes lead to the production of Interleukins, which simulate the host's immune response.

Conclusion

The decreased expression of the DDX58, IFIH1, and TLR3 genes, as well as their function in the JAK-STAT pathway, indicates that the SARS Urbani virus can more successfully evade the body's innate immune system within 24 hours from infection compared to Influenza A. This reduced expression also implies that the body may produce relatively fewer type III interferons in SARS Coronavirus infections, which would inhibit the immune system from inducing apoptosis in infected cells, leading to stronger viral presence and infection of SARS Coronaviruses than Influenza A. Parallels could be drawn between SARS Urbani and SARS-CoV-2 because SARS Coronaviruses are genetically similar. Furthermore, using DGIdb, we found that the drug Rintatolimod may be an effective treatment option for SARS Coronaviruses, since it activates increased expression of TLR3.

Connections Between the IL-17 Pathway and MERS Infection

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Introduction

There have been 2,519 cases of MERS-CoV worldwide and counting, with a death rate of 34%. SARS-CoV2, a virus also in the Coronavirus family, COVID-19, has infected 157,289,118 and killed 3,277,272 people worldwide. Similar to SARS-CoV2, MERS-CoV binds to the same ACE2 receptor and invokes similar symptoms (acute respiratory and inflammatory issues) largely targeting the same cells (epithelial lung cells). Given the recent success of mRNA vaccines for SARS-CoV2, it is important to develop a better understanding of the coronavirus family to develop effective treatments for already infected individuals. In our research, we analyzed the relationship between MERS-CoV infection and the upregulation of the IL-17a and IL-17f pathways (signalling molecules in the immune system) to gain a better understanding of how MERS impacts the body.

Methods

We used the GSE Dataset GSE56677 from NCBI which contained microarray expression profiling data from 33 samples of human airway epithelial cells. These samples were either mock-infected (controls) or infected with one of two different MERS-CoV strains in humans, MERS-CoV-EMC and MERS-CoV-London, and then analyzed at various time points post infection. We then used GEO2R to run a two-tailed t-test of our two comparison groups: LoCov at 12 hours post-infection (hpi) and mock at 12 hpi. We used STRING-db to conduct enrichment testing on the top 300 differentially expressed genes (p-value <0.001) to find enriched KEGG Pathways and biological processes. We analyzed the connections between the top differentially expressed genes and enriched KEGG Pathways like IL-17a and IL-17f using KEGG.

Results

We found the IL-17 pathway to be upregulated in the infected sample, with increased production of CXCL1 and CXCL2, along with MAPKs and FOS/AP-1 (all positive logFC and within our p-value cutoff). These are specifically related to epithelial cell responses to IL-17a and IL-17f, which causes cell production of cytokines, chemokines, tissue remodeling proteins, and antimicrobial compounds, which leads to autoimmune pathology, recruitment of neutrophils, and immunity to extracellular pathogens.

Conclusion

Since the IL-17a and f are upregulated in infected people, using IL-17 pathway components as biomarkers in diagnosing people with MERS or similar diseases is possible. Furthermore, IL-17a production is inversely related to age (increased production in children) and Science Translational Medicine Pierce et al. claimed in 2020 that when compared to other factors like T cell response and neutralizing antibody production, increased IL-17a in children gave them an advantage over adults in overcoming COVID-19 even if they had other concomitant immune system issues. Being able to separate the autoinflammatory functions of IL-17a and IL-17f from those of neutrophil recruitment and antibacterial functions would be an advancement in combating the inflammatory side effect of COVID-19 and MERS that causes severe cases. So far, there are only drugs that decrease IL-17A function by preventing its binding to the receptor, but a potential way to increase IL-17A in patients sans drugs is IL-17A harvested from bacteria with engineered plasmids-- and the downstream effects causing inflammation could be inhibited with drugs targeting specific proteins later in inflammatory pathways.

Potential Effect of Adhatoda Vasica on Chemokine Signaling and Applications Towards COVID-19

Emily Kang[1], Niharica Suri Kannan[2], Annabel Yang[3], Jeremy Nelson[4], Zaina Al Habash[5]

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Introduction
This study explores the potential application of Adhatoda Vasica (AV) aqueous extract towards SARS-CoV-2 infection. AV is an ayurvedic, plant-based drug with anti-hypoxic and anti-inflammatory properties. COVID-19 is a highly virulent and contagious disease that has claimed over 3 million lives. The frequent mutations and various strains of COVID, along with lack of knowledge and education about the virus, made treatment inefficient, and so far, there is no definitive cure. This study explores AV in relation to a cluster of co-expressed genes, all connected to chemokine signaling, to evaluate its effectiveness as a treatment for SARS-CoV-2.

Methods
We researched the GEO dataset GSE156759, which treated mice using Adhatoda Vasica in 4 groups; a control group with no treatment, a group of 4 with low dose (0.130mg/kg), a group of 5 with medium dose (130 mg/kg), and a group of 4 with high dose (260 mg/kg). Gene expression profiles were taken from lung tissue total RNA. We statistically analyzed the expression differences between the high dosage and the control mice using GEO2R, retrieving the top 250 genes with the lowest p-values. We inputted these genes into String-DB to observe the pathways and interactions, and further evaluated the data with additional resources.

Results
The following gene cluster was selected from the String-DB map: Ccl3 (P-value = 2.40E-0), Ccr1 (P-value = 5.98E-04), Ccr2 (P-value = 1.37E-04), and Ccl9 (P-value = 1.78E-04), which were all downregulated. According to protein-protein interaction predictions, the genes are associated but likely not co-expressed. All four genes are involved in the chemokine signaling and cytokine-cytokine receptor interaction KEGG pathways, with false discovery rates of 3.21e-08 and 6.21e-08, respectively.

Conclusion
Severe COVID-19 is often complicated by the onset of cytokine storm, a condition in which the immune system overproduces cytokines, which target the body and damage tissue and organs instead of targeting the virus. The downregulation of the listed genes, being associated with cytokine pathways, suggest that treatment using AV on healthy mice could be associated with lower activity of these pathways. If this mechanism holds true in the event of SARS-CoV-2 infection, AV could potentially aid with the hyperactive immune response and help COVID-19 prognoses. However, despite these findings, the conditions of these experiments make this study unable to reach a robust conclusion due the fact that healthy mice were treated instead of sick mice. Further experiments that test the effects of AV treatment on transgenic, SARS-CoV-2 infected mice are needed in order to further support the aforementioned connections and confirm whether AV treatment changes the outcome of SARS-CoV-2 infection; such studies would also provide valuable evidence to further explore the hypotheses of this study.

Keywords: adhatoda vasica, cytokine, chemokine, SARS-CoV-2, COVID-19

Direct RNA Hybridization Probes for Rapid Identification of SARS-CoV-2 Variants of Concern

Diya Ramesh

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Introduction

During the course of the COVID-19 pandemic, numerous mutations in the genetic sequence resulted in several variants of the SARS-CoV-2 virus. With serious consequences such as increased infectivity, a simple method to quickly identify variants is crucial. This study proposes an alternative method to the standard genetic sequencing (costly, slow and cumbersome) by utilizing RNA probes for direct in-situ hybridization in biologic specimens or RT-PCR product to conveniently and rapidly identify known SARS-CoV-2 variants of concern in infected individuals.

Methods

Three variants of concern B.1.1.7, B.1.351, and P.1 (UK, South Africa, and Brazil variants, respectively) were chosen for this study. The spike protein mutations of N501Y (present in all 3 variants), S982A (specific to B.1.1.7), and D138Y (specific to P.1) were targets. The position and nucleotide changes for each spike protein mutation was derived using the UCSC Genome Browser. Variant sequences submitted to NCBI were used to retrieve segments 21 nucleotides long inclusive of the mutation. Using the Reverse Complement Tool from Bioinformatics.org, the probe sequences for all three retrieved sequences were created. As part of a molecular beacon, 6 nucleotides (3 for the N501Y probe) were then added to the 5' end of the probe sequence with the complementary 6 nucleotides on the 3' end. Using the RNAhybrid tool in Linux, each probe was tested against the targets and the probes themselves to find the minimum free energy (MFE) of the hybridization. Finally, using the NCBI BLAST tool, the probe sequences were aligned against human RNA sequences from the NCBI RefSeq RNA Database to rule out false positives.

Results

The MFE value for the target specific probe hybridization was more negative than the other probes indicating stronger hybridization and target specificity. Additionally, the MFE values for probe-probe hybridizations were less negative than those for probe-target hybridizations indicating that the probes will likely not dimerize. Lastly, the NCBI BLAST run for the probes did not identify any complementary human RNA sequences proving that the probes are viral target-specific. The probe targeting N501Y can be used as a screening tool for presence of variants of concern and the other probes used subsequently will be target specific to identify particular variants B.1.1.7, and P.1 with no further hybridization indicating the presence of B.1.351 variant.

Conclusion

This study proves that direct RNA hybridization probes can be used to identify known SARS-CoV-2 variants of concern. Clinical testing should be done in biologic specimens of SARS-CoV-2 infected individuals to verify the in-silico results. Applications of the probe include use for direct in-situ hybridization in the biologic specimens such as nasopharyngeal samples and also after RT-PCR from a standard COVID-19 test using the same sample type. Denaturing of RNA/DNA needs to occur in both potential test applications, as viral RNA forms secondary structures, and RT-PCR product is double-stranded DNA. This same methodology can be easily adopted to develop probes for future SARS-CoV-2 variants.

Pathology from Envelope Proteins to Heat Shock Response and Cytokine Storms in SARS-CoV-1 and 2

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Introduction

Taking over 3 million lives, the novel coronavirus (SARS-CoV-2) is responsible for a pandemic due to our rapid globalization and urbanization [1]. Moderate to severe cases of SARS-CoV-2 patients have been linked to cytokine storms [2]. Our study looks through the lens of the novel coronavirus' antecedent, SARS-CoV-1, with the aim to find genetic connections for this unbalanced response and find possible target pathways.

Methods

We analyzed the NCBI GEO dataset, GSE30589, which consists of Vero E6 cells infected with SARS-CoV-1 (wild type) and with envelope gene knockout (SARS-CoV-1 ΔE). We compared 3 samples of SARS-CoV-1 and 3 samples of rSARS-CoV-ΔE at 24 hours past infection (hpi), checking for median value alignment and comparing the gene expression using GEO2R. After performing a t-test and sorting by lowest p-value and greatest magnitude log fold change (logFC), we narrowed our study to the top 250 differentially expressed genes. We input this subset into STRING for their connections, GeneCards for gene functions, and Kegg Gene Ontology database for overrepresented pathways.

Results

Heat shock protein genes HSPA1A, HSPA1B, HSPH1, and DNAJB1 are significantly overexpressed (logFC = 3.59, logFC = 3.39, logFC = 1.53, logFC = 1.80) in envelope knockout SARS-CoV-1. The first three of these heat shock protein chaperonins are connected in the heat shock protein binding Gene Ontology pathway, relating to DNAJB1 in the Hsp70 protein and chaperone protein domain, with both interactions having significantly low respective false discovery rates of 2.63×10^{-7} and 3.30×10^{-14}. HSPA1A and HSPA1B are needed to inhibit ubiquitination and degradation of FOXP3, a gene that inhibits cytokine production and T-cell effector function. HSPH1 acts as a nucleotide exchange factor for chaperone proteins HSPA1A and HSPA1B to trigger release of denatured protein. DNAJB1 negatively regulates heat shock-induced HSF1 transcriptional activity during the heat shock response.

Conclusion

The overexpression of HSPA1A and HSPA1B in SARS-CoV-1 ΔE regulate cytokine production, with HSPH1 clearing denatured FOXP3. This prevents uncontrolled cytokine production leading to a cytokine storm. Additionally, when not bound due to the upregulation of DNAJB1, heat shock protein transcription factor HSF1 can translocate to the nucleus and initiate a heat shock response that results in the production of Hsp70 proteins (HSPA1A, HSPA1B) and their activators. Drugs targeting cytokine receptors as treatment have been used on an extremely limited scale due to high cost [3]. However, recent studies have shown that the toll-like receptor 2 senses the SARS-CoV-2 envelope protein to produce inflammatory cytokines [4]. Since toll-like receptors have been shown to activate Hsp70 proteins, a study confirming the analogous nature of this interaction in SARS-CoV-1 and 2 with the importance of the envelope protein would be valuable to determine the feasibility of taking advantage of activating these receptors in healthy people in a vaccine adjuvant.

Microarray Analysis of Apoptotic Pathways in SARS-COV-1 versus SARS-COV-1-Δe: Regulation of Inflammation and Necrosis via TNF, IL-17, JUN and Others

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Introduction

COVID-19's deadly precursor, SARS-CoV-1, was responsible for an epidemic in the early 21st century. With a death rate over 10%, several SARS-CoV-1 patients died from respiratory shock during an inflammatory immune response (1). We studied the mechanism of one of the genes that confers virulence for SARS-CoV-1 hoping to better understand the viral pathway of SARS-CoV-2.

Methods

The NCBI GEO dataset GSE30589, contains microarray data for SARS-CoV infections of endothelial (lung) cells. Through GEO2R, we examined the difference in gene expression between endothelial cells infected with SARS-COV-1-e versus those infected with SARS-COV strains at 24 hours past infection. Based on functional enrichment analysis of the 142 most-upregulated genes, we found the TNF and IL-17 signaling pathways to be significantly more active in the cells infected with SARS-COV-1-e. Within both the TNF and IL-17 signaling pathways (0.0019 false discovery rate), we found the common upregulated genes of JUN, FOS, TNFAIP3,NFKBIA, JUNB, CEPB, and SOCS3. We used gene ontology servers to determine commonalities in gene function.

Results

Through functional enrichment analysis in STRING, we identified the TNF and IL-17 pathways as enriched for cells infected with r-SARS COV-E versus r-SARS-CoV (false discovery rate = 0.0019 < α level = .05). The TNF pathway regulates necrosis, or cell death from external stimuli, while portions of the IL-17 pathway regulate apoptosis, which during immune response is programmed cell death to reduce inflammation. We further explored some of the genes expressed heavily that are crucial in both pathways such as JUN and TNFAIP3.

Conclusion

We found associations between both signaling pathways and programmed cell death. The TNF signaling pathway normally regulates a passive form of cell death called necrosis, which normally results from environmental changes or inflammation. Apoptosis, which is regulated by portions of the IL-17 pathway including the JUN gene, is considered active cell death and in this case may be relevant to reducing inflammation. The JUN gene and TNFAIP3 both play a role in both signaling pathways, but JUN promotes inflammation as a response to viral stimuli while TNFAIP3 expression is known to calm inflammation via apoptosis (2). We hypothesize that the envelope gene of the SARS-COV confers virulence by affecting genes such as JUN in the TNF pathway. Transcriptional factors, like TNFAIP3, and other portions of the IL-17 pathway are active in the bodily effort to calm the immune system during a SARS-CoV-1 infection.

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The Role of the Cytoplasmic Pattern Recognition Receptor in COVID-19

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Introduction

According to the CDC, in the U.S. alone there have been 32,313,016 cases of COVID-19 and 575,491 deaths since January 2020. As of May 6th, 2021, there have been nearly 155 million cases worldwide according to the WHO. The pandemic created an urgent need for new, effective treatments against the virus. In our research, we analyzed the potential connections between COVID-19 infection and the downregulation of the cytoplasmic pattern recognition receptor pathway, specifically the retinoic acid-inducible gene I, to better understand not only the impacts this disease has on how the body functions but also develop potential treatments.

Methods

We used the GEO Dataset GSE47962 from NCBI which contained microarray expression profiling data from 134 samples of human airway epithelial (HAE) cultures that were mock-infected (controls), or infected with SARS-CoV(icSARS), SARS-dORF6, or SARS-BatSRBD at various time points. We used GEO2R to run a two-tailed t-test on our two comparison groups: icSARS at 72 hours post-infection (hpi) and mock at 72 hpi. Then we conducted enrichment testing using STRING-db on the top 280 differentially expressed genes to find enriched biological processes.

Results

We found that the cytoplasmic pattern recognition receptor signaling pathway was an enriched process among the icSARS group (false discovery rate=0.0022, count in gene=3). Genes IRF7, IFIH1, and DDX58 are involved in the pathway, with base-2 logarithmic fold change values of -2.94, -2.25, and -3.40 respectively. The p-values of these genes range from 8.74e-06 (DDX58) to 3.34e-05 (IFIH1). Furthermore, the gene DDX58 encodes for RIG-I, retinoic acid-inducible gene I, which is a cytosolic pattern recognition receptor responsible for activating the type-1 interferon (IFN1) response and recognizing viral infection in a cell.

Conclusion

Our results suggest that the lowered expression levels of the cytoplasmic pattern recognition receptor may be linked to COVID-19. Our research in this signaling pathway suggests a correlation between coronavirus infection and a decrease in the immune system's recognition response. In particular, the expression of the retinoic acid-inducible (RIG-I) receptor, which is encoded by the DDX58 gene, may be suppressed due to the downregulation of DDX58 expression. Since RIG-I is a type-1 interferon, its lowered expression levels in COVID-19 patients may lead to a decreased ability to induce T and B cell responses and increased coronavirus spread to other cells in the body. Potential treatments for COVID-19 could induce greater RIG-I receptor expression levels to stimulate the immune response against COVID-19 infection. A limitation of our research was small sample sizes for the control and COVID-19 groups. Further research could be done to determine whether the downregulation of the RIG-I receptor is present in other SARS or MERS strains. Another future research idea is measuring the change in expression levels of genes in the cytoplasmic pattern recognition receptor during recovery in COVID-19 patients and developing drugs or vaccinations that can mimic the increase in expression levels of these genes.

Progression of Cytokine-mediated Signaling Pathway Activity in the First 24 Hours of H1N1 Infection

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Introduction

Our research is centered around the orthomyxovirus H1N1, commonly known as Swine Flu, with a focus on specific gene families of the cytokine-mediated signaling pathway. By looking at the expression patterns of the IFIT and OAS gene families involved in the cytokine-mediated signaling pathway, we followed the progression of the human immune response against H1N1 during the first 24 hours post-infection.

Methods

We first analyzed gene expression in hour increments 0, 6, 12, 18, and 24 post H1N1 infection against the respective mock infection from the GSE47962 DNA microarray dataset on the NCBI GEO database. We found the top 100 common pathways among the top 150 genes with the lowest p-values. We studied the cytokine-mediated signaling pathway which was present in all hour groups and had a low false discovery rate. Among the top 150 genes in the cytokine-mediated signaling pathway, IFIT gene family and the OAS gene family were most prevalent in the STRING gene network map. We studied the function of both the IFIT and OAS gene families and their role in the immune response against H1N1 for the first 24 hours post-infection.

Results

At 0 hours, the IFIT gene family was downregulated in the H1N1 infected samples. We saw a continued increase in expression of IFIT genes from hours 6 to 18. From 18 hours to 24 hours, the expression of the IFIT1, IFIT2, and IFIT3 remained constant while there was an increase in IFIT5 expression. The OAS gene family was downregulated at 0 hours post H1N1 infection but similarly started to upregulate from hours 6 to 12. All genes in the H1N1 infected samples except for OAS3, reached their highest level of expression at 12 hours post-infection. OAS3 continued to increase in the H1N1 infected samples from hours 18 to 24 while the expression of the other genes of the OAS family declines.

Conclusion

In addition to analyzing the individual roles of the IFIT genes, further analysis of the gene complex formed by IFIT1, IFIT2, and IFIT3 may provide more insight into the interactions of the IFIT gene family. We also propose further analysis on the functions of OAS1, OAS2, and OAS3 when working together and how OASL may be included. Special focus should be given to OAS3 due to its necessity in activating the RNase L enzyme. Future studies that enhance focus on the gene families involved in the early viral immune response in the cytokine-mediated signaling pathway will provide us with a better understanding of how the human body combats viral infections at the molecular level.

Diagnosis of Colorectal Cancer Through Binary Computational Classification Models

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Introduction

One prominent type of cancer is colorectal cancer: the malignant invasion of the colon. Patient survivability can depend on quick diagnosis (at least in certain regions.)[2] Colorectal cancer is an especially deadly cancer killing 29 out of 1,000 people across all demographics; it is also one of the most common cancer diagnoses. Our initiative was to design a non-invasive diagnostic tool for colorectal cancer using mRNA expression values in hopes of accelerating the diagnosis time. We utilized genomic databases and programming languages to design machine learning models (ML) for this purpose.

Methods

Using R modules Biobase, GEOquery, and limma, we downloaded the expression values and patient descriptions from NCBI's GEO's GSE164191 dataset. GSE164191 characterizes the expression of 61 control and 59 colorectal cancer patients through profiling whole peripheral blood. Both expression value datasheet and patient descriptors were imported into our Python script. In Python, we used Pandas, Numpy, and google.colab to reduce the data into a single dataframe for ML implementation via Scikit-learn. We trained a Naive Bayes and K Nearest Neighbor model using 60% of the data for training and 40% for testing (60/40 split.) To optimize the results we used a random state of 7051 and 9200, respectively. To visualize our confusion matrices, we used Matplotlib to construct bar graphs.

Results

Our MLs were tested using the 40% of data each model wasn't exposed to for testing. The KNN model predicted 33 true positives, 37 true negatives, 0 false positives, and 3 false negatives. This is an overall accuracy rate of 95.89%. The Naive Bayes model garnered an accuracy of 98.63%. This correlates to 38 true positives, 34 true negatives, 1 false positives, and 0 false negatives.

Conclusion

Both models rank as "excellent" for medical implementation.[1] The Naive Bayes model out-performed the KNN: it had less bias and was more accurate. The Naive Bayes model operates on Bayesian principles which may have circumvented complex gene pathways due to mutual exclusivity. In the future, our results should be examined to elucidate how cancer stages impact the accuracy of predictions. Ultimately, these models could lead to faster patient diagnosis, which could improve prognosis, especially since testing data can be collected via a simple patient blood sample.

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A Bioinformatic Analysis of the Role of Heat Shock Proteins in MERS-CoV Infection

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Introduction

Middle Eastern Respiratory Syndrome (MERS), is a serious zoonotic respiratory illness caused by the MERS Coronavirus (MERS-CoV) with no available antiviral treatments or vaccines. Heat shock proteins (HSP) are a family of proteins that are synthesized in response to stress/infection. They are molecular chaperones, and they aid in protein folding/refolding (for misfolded proteins). This study investigated the role of HSP in MERS-CoV infection.

Methods

The public dataset GSE86529 from Gene Expression Omnibus (GEO) of RNA microarray data in human fibroblast cells was used. Using GEO2R, t-testing was performed to find the differential expression of the genes between 0-24 hours post-infection of MERS-CoV. The top 250 differentially expressed genes were inputted into String dB for enrichment testing. The GO molecular function of HSP binding was chosen for focus. Several HSP-coding genes were investigated to understand their potential correlation with MERS-CoV. Genes of interest were investigated using GeneCards.

Results

Two genes that code for HSP and 1 gene related to a HSP were studied (HSPA1A, HSP90AB1, and PPID). All three genes were upregulated between 0-24 hours post-infection of MERS-CoV. HSPA1A has various functions, including initiating proteolysis for misfolded proteins. During an infection with rotavirus A, the protein encoded by HSPA1A aids viral entry into the cell and may have a similar role in MERS-CoV infection. The protein encoded by HSP90AB1 has a key role in the body's immune response and is related to the pathway of “Antigen processing-Cross presentation”. Additionally, prior research has shown that quick build-up of viral proteins in cells causes viruses to rely on cellular chaperones. One study found that reduced quantity of Hsp90β (an alias for the protein encoded for by HSP90AB1) through siRNAs made replication of MERS-CoV far more difficult and stopped the spread of the virus. Finally, PPID is thought to be related to the replication and release of a RNA virus, hepatitis C (HCV), so similar functions may translate to MERS-CoV. PPID codes for a co-chaperone for Hsp90 complexes. It was previously found that Hsp90 is a host factor essential in the pathogenesis of three human coronaviruses (including MERS-Co-V) and that Hsp90 inhibitors could be adapted for use as an antiviral agent. 17-AAG, a specific Hsp90 inhibitor, inhibited MERS-Co-V propagation in cell lines and related human intestinal organoids.

Conclusion

The HSP genes are likely correlated with the negative effects of MERS-CoV on the human body between 0-24 hours post-infection. HSP encoded proteins can potentially serve as targets for antiviral therapies or biomarkers of infection. Further studies may include knockdowns of some of the investigated genes and any related genes in immune cell lines infected with MERS-CoV.

References

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Activation of Innate and Adaptive Immunity in Patients with COVID-19

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Introduction

Coronavirus disease 2019 (COVID-19), caused ~3.3M deaths worldwide with complications ranging from pneumonia to multi-organ failure. SARS-CoV-2 binds to host receptor, angiotensin-converting enzyme 2, and angiotensin II buildup activates the pro-inflammatory/pro-fibrotic innate and adaptive immunity. Innate immunity is the first line of defense via macrophages, neutrophils, dendritic cells and complement cascade; and B-/T-lymphocytes confer adaptive immunity. Immune signature in COVID-19 patients would better inform clinicians to monitor organ inflammation and related disease pathology. The objective is to examine the immunoprofile by gene microarray of peripheral blood mononuclear cells from mild and severe COVID-19 patients.

Methods

NCBI/GEO database (Accession:GSE164805) reported that peripheral blood mononuclear cells from mild and severe COVID-19 patients, and healthy controls (n=5/group), were used to isolate RNA, and then subjected to Arraystar Human LncRNA Microarray V5.0. Datasets were analyzed using GEO2R ($p<0.05$ after Benjamini and Hochberg adjustment was considered significant), and log fold-changes ≥ 0.5 and ≤ -0.5 were considered upregulation and downregulation, respectively. Innate immunity panel: interleukins (6, 17C/D), β-defensins (DEF121/133), complement regulators (CD46/55/59), C5, factor D. Adaptive immunity panel: B cells (CD19), T cells (CTLA4, IFNG/R2, HLA-DR), natural killer cells (NKG7, NKTR, granzymeB/H/A), and TLR9 (dendritic cells, macrophages, NK cells). Markers for migration (ENPP2/TIMP1), apoptosis (caspase 7, programmed cell death2/11), fibrosis (IL1B), and oxidation (NOX4) were examined.

Results

Of 29,106 transcripts, the differentially expressed (DE) genes unique to healthy versus mild (HvM): 2088, healthy versus severe (HvS): 8229, and mild versus severe (MvS): 1359. In HvS group, innate immunity panel demonstrated increased IL6, IL17C/D, DEFB, and CFD; reduced CD55/59. While MvS group showed suppressed CD46/59 and induced IL17D; HvM was similar to HvS group – exceptions were no changes in IL6 or DEFB121, and upregulated CD46/C5. Adaptive immunity was driven by all indicated genes in the HvS group. While MvS was similar to HvS group for B/NK cells, the only T cell-related increase was HLA-DR; and the difference in HvM vs. HvS groups was lack of CD19/CTLA4/IFNG signal. TLR9 and SRC (top 50 DE) was increased in all three groups, while IL1B (top 10 DE) was increased in HvM and HvS groups only. Markers for migration were increased in HvM and decreased in MvS, but only TIMP1 increased in MvS group. While all three markers for apoptosis were higher in HvS, only PDCD11 was induced in HvM, and CASP7/PDCD2 were induced in MvS groups. While NOX4 was upregulated in healthy or mild versus severe COVID-19 patients, it was downregulated in the healthy versus mild group.

Conclusion

This study shows a focused panel of markers that indicate unrestrained activation of adaptive and immune responses with increasing severity of COVID-19, and associated disease pathology markers which include robust pro-fibrotic signaling, and cellular apoptosis and oxidation.

Reference

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Allograft Rejection in SARS-CoV Patients

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Introduction

SARS-CoV is a strain of coronavirus which has continually evolved throughout the past year. Various factors influence how people respond to SARS-CoV, including the strain they contract and pre-existing health conditions. Current treatments target virus–host interactions, inhibit viral assembly, or use drugs that control host innate immune responses interfere with signaling pathways involved in viral replication[1]. Targeted gene therapies may provide more personalized treatment options that interfere with the virus on a person to person basis. This study focused on how the upregulation of a specific group of genes affects the response of the lung tissue to SARS-CoV.

Methods

I analyzed gene expression in mus musculus lung tissue samples using the NCBI GEO dataset GSE36016. GSE36016 contains 18 samples at 5 dpi, with 9 from mock-infected mice and 9 from SARS-CoV infected mice. Then, using GEO2R, I analyzed these samples to find significant differences in gene expression among the two sample groups. Using the String Database, I analyzed the top 250 genes with a p-value at or below 7.19e-05 to find connections between genes and their relevant KEGG pathways. The allograft rejection pathway, which had a low false discovery rate and is the subject of ongoing SARS-CoV research, and the genes related to it were further researched using GeneCards.

Results

Within the allograft rejection KEGG pathway in my dataset, there are 18 genes. Within this group, I focused on the upregulated genes of H2-Q2, H2-Q4, H2-Q7, H2-Q10, and H2-M2 with the lowest LogFC value being -2.28e-01 and the highest p-value being 9.37e-06. I found that these genes were upregulated in SARS-CoV patients, thereupon suggesting a link between the effects of SARS-CoV and allograft rejection.

Conclusion

Current research supports the relation of H2-Q genes to hypersensitivity to tissue transplants [2]. Allograft rejection is the rejection of a tissue graft from a donor of the same species as the recipient. Transplant patients often take immunosuppressive drugs in order to prevent rejection of the foreign tissue in their body by their immune system. Thus, they are more susceptible to having greater complications if they contract SARS-CoV. Furthermore, the cytokine storm which can occur in SARS-CoV patients may cause further tissue damage in transplant recipients, as too many cytokines being released may result in the attack of healthy tissue and transplant tissue. Evidence that the cytokine storm plays a relevant role in the progression of COVID-19 is growing and several anti-inflammatory agents have been studied [3]. Thus, an anti-inflammatory drug coupled with specific gene therapy for H2-Q genes would reduce the hyper inflammatory response caused by the cytokine storm more than an anti-inflammatory drug alone because of the relation between H2-Q genes and allograft rejection. A new treatment to downregulate these genes offers a personalized treatment for COVID-19 patients and could be used in addition to the anti- inflammatory drugs in place currently.

Analysis of MERS Infection Impact on Cell Function Over Time

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Introduction

The virus causing COVID-19 is biologically very similar to the virus MERS-CoV. The dataset used, (GSE100509)[1] looks at human microvascular endothelial cell transcriptome response to wild type MERS-CoV (icMERS). To study the dataset more in-depth, the data was split into two groups: 12 hours after infection and 48 hours after infection. We hypothesize that as infection progresses, we will see substantial alterations in normal cellular function.

Methods

We took the aforementioned gene set from GEO2R, and then set our comparison groups. GEO2R was used to analyze the chosen gene groups. The top 250 genes, with the most significant (most negative) P Values, were analyzed in STRING. STRING was used to determine relationships between genes as well as related KEGG Pathways. GeneCards was utilized to understand the functions of the genes yielded from our KEGG pathways.

Results

The analysis of STRING associations and resulting KEGG pathways revealed three groups of downregulated genes. These groups were divided into three related KEGG Pathways: Gap Junction, Protein and Antigen Processing, and Cell Cycle. The genes associated with the Cell Cycle KEGG pathway (CDK1, CCNA1, CCNB2, CCNB1, CCNA2) were significantly downregulated. This leads to abnormal cell behavior, as a cell that is infected with these genes downregulated, will not proceed through mitosis. The genes associated with the Protein and Antigen Processing KEGG pathway (HSPA1A, HSPA6, HSPA8) will lead to abnormal cell behavior as they are associated with protecting the cell against injury and thus protecting it from infection. When these genes are downregulated, they do not protect the cell against stress, inhibit the cell in proper protein folding/maintenance, along with repressing transcription. The final KEGG pathway, Gap Junction, with the genes EGFR and TUBA1A, also contribute to development of abnormal cell behavior. These genes are responsible for forming microtubules, which aid the cell in mitosis. When these genes are downregulated, they are unable to form microtubules and therefore the cell is prevented from normal behavior. As infection goes on, the cell sees a decrease in ability to protect from injury/infection and decreased ability for mitosis.

Conclusion

As noted in our results, with ongoing infection, normal cellular functions related to mitosis and DNA activity are significantly reduced. This decreased DNA function allows unregulated RNA transcription, which is necessary for viral production. We can conclude that activating the heat shock proteins, associated with genes HSPA1A, HSPA6, and HSPA8, has potential to mitigate the detrimental effects on cell function that furthering infection causes. In addition, to possibly negate the effects of infection on normal cell function, a possible treatment could consist of upregulating the genes associated with the KEGG pathways of Gap Junction and Cell Cycle. The findings deduced from this research have significance because they propose a further study on heat shock proteins and their relationship to infection.

Reference

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Correlating SNPs in Interferon-Pathway-Affecting Genes to Severe COVID-19 Comorbidities Through Candidate-Gene Association

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Introduction

Certain medical conditions can increase the risk for severe COVID-19. Studies have shown that gene mutations affecting the Type I Interferon Pathway increase the risk for severe COVID-19. I identified the following genes affecting the Type 1 Interferon pathway: IRF7, IRF9, TLR3, IFNAR1, IFNAR2, STAT2, UNC93B1, TRAF3, TBK1, IRF3, and STAT1. I also identified the following health conditions considered a high risk for COVID-19: high BMI, high blood pressure, Type 2 Diabetes, chronic kidney disease (CKD), and high red blood cell count (indicative of Chronic Obstructive Pulmonary Disease - COPD). The goal of my project was to draw a correlation by determining if single nucleotide polymorphisms (SNPs) in the interferon-pathway-affecting genes were significantly present in the genomes of patients with comorbidities of COVID-19.

Methods

I wrote a Python program to query a genome database, the Human Genetics Knowledge Portal database, to retrieve the minimum p-value of the SNPs in each of the genes for the health conditions I studied. A minimum p-value less than 5e-8 showed strong association.

Results

High BMI was correlated to the TRAF3 gene with a minimum p-value of 2.75e-23, high red blood cell count was correlated to STAT2 with 1.00e-10 and IRF3 with 6.40e-12, high blood pressure was correlated to STAT1 with 3.60e-10, and Type 2 Diabetes was correlated to TRAF3 with 2.82e-8, all showing strong associations. CKD, correlated to STAT1 with 1.34e-5, did not show significant association.

Conclusion

The gene association study conducted showed strong association between genes affecting the Type I interferon pathway and High BMI (indicative of obesity), high red blood cell count (indicative of low oxygen and COPD), high blood pressure and Type 2 Diabetes. The condition CKD, most correlated to STAT1, did not show strong association.

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Diabetic Upregulation of TNF and IL1B and the Effect on COVID-19 Severity

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Introduction

Throughout the COVID-19 pandemic, SARS-CoV-2 has disparately impacted people with underlying conditions, including type 1 diabetes. The purpose of this investigation is to discover and understand the genetic connections between COVID-19 and diabetes to identify the reason why severe cases of COVID-19 are more prevalent in individuals with diabetes.This way, we can categorize type 1 diabete patients of those who are at high risk, in order to prioritize these patients when distributing the vaccines to the public. Our research focuses on two main proteins of the cytokine storm in COVID-19, TNF (Tumor Necrosis Factor) and IL1B (Interleukin 1 Beta), which are both genes that play a vital role in diabetes.

Methods

This investigation relied on the use of published databases, literature review, and meta-analysis. We began with using GEO2R to analyze and find enriched proteins in diabetes patients from the two databases: Kaizer and Irvine. We then used string-db to construct a protein interaction map of the top identified proteins in order to identify proteins, as well as KEGG pathways, related to COVID-19. Then we analyzed the connections between those proteins and reinforced our conclusions using existing literature.

Results

Using our first GEO2R dataset, we found that TNF was expressed significantly more in patients with Diabetes Type 1 than in control patients ($p<0.0005$). The second GEO2R dataset showed that IL1B also had higher expression in Diabetes Type 1 than in the control group ($p<0.0005$). When we analyzed the proteins with string-db along with other proteins that we found to be highly expressed in diabetes patients, and proteins found in the Covid-19 KEGG Pathway, there were also strong associations between these two proteins expression and other proteins expression in the Covid-19 KEGG Pathway (such as ACE2). We also found that TNF is part of the cytokine storm pathway in the Covid-19 KEGG Pathway. IL1B also appears many times in the Covid-19 KEGG Pathway, especially in the cytokine storm.

Conclusion

Although there are a variety of studies expressing the connections linking COVID-19 and Type 1 diabetes, the genomic connections between them are still not yet entirely revealed. The auxiliary TNF and IL1B genes recognised in Type 1 Diabetes patients are also identified in the KEGG Pathway contributing in the cytokine storm which can increase the severity of the COVID infection by triggering the immune system to flood the bloodstream with inflammatory proteins called cytokines. While it has been well established that diabetes is a comorbidity for COVID-19, this study presents initial evidence for a mechanistic link between diabetes and the pathogenesis of COVID-19, and explains the role of gene expression in this process.

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Differential Gene Expression in Mers-Covid Infected Cells

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Introduction

In the midst of the ongoing Covid-19 pandemic, we have developed an analysis of the genomic sequences of the MERS-CoV-London strain, which still maintains a similar structure and genome to SARS-CoV and SARS-CoV2. The purpose of our research was to identify protein coding genes that could be targeted in the MERS-CoV-London strain. We hypothesize that MERS-CoV-London infected epithelial cells will show unique upregulation or downregulation as compared to uninfected cells that could allow for specific targeting for diagnostic or treatment purposes.

Methods

Genetic data from NCBI in the data set GSE56677 was analyzed using online tools such as GEO2R, String-db, and OMIM. GEO2R was used to run a comparison between our two groups: mock and infected. The data from GEO2R was sorted by p-value to determine the top 250 most significant genes. Analysis of those genes in String-db and looking at the LogFc values permitted analysis of the most significant genes, interactions, and Kegg pathways. String-db revealed that the dataset's genes had significantly more interactions than expected, and provided insight into how these genes connected to biological processes.

Results

In our analysis, we discovered several significant genes, including the SSX2 Gene with a LogFC value of 7.09818082. It was massively upregulated which implies a decreased rate of transcription, and it may play a role in the unregulated inflammatory responses seen by some COVID patients. This allowed us to identify SSX2 as a prime target for use as either a diagnostic, or potentially even as a treatment option. Decreased function in the HLA class one and two genes and the gene APP were also indicated by downregulation, implying that infected cells were less identifiable in the immune system. A third group of genes that included MAK16 and CDC25A among others showed decreased nuclear DNA function and decreased apoptosis.

Conclusion

SSX2 is a unique gene that is found expressed almost exclusively in cancer cells. Upregulation of SSX2 in virally infected cells could represent a unique target for diagnostic or therapeutic purposes. HLA genes, which are typically expressed in normal, healthy cells, are found downregulated in virally infected cells. Potential therapeutic options would require a method to upregulate HLA expression to help increase immune response towards infected cells. The third group of genes all had decreases in DNA function such as transcription, and apoptosis, indicating viral control of the cell for use in RNA processing. While this is a good marker for infection, with the exception of SSX2, these genes would be difficult to target therapeutically. Overall, more investigation into the SSX2 gene would likely prove to be the most therapeutically useful finding in this study.

Keywords: SSX2, Mers-CoV, Covid-19, HLA

Differential Gene Expression of Brain Cortex in COVID-19 Patients

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Introduction

The COVID-19 is associated with neurological complications, such as dementia. This presentation will delve into the less understood concept of how COVID-19 can infect brain cells and which molecular processes affects. The purpose of *the silico* study was to investigate these gene expression changes in COVID-19 brain degeneration, compare differential gene expression in various causes of dementia (Vascular dementia, Alzheimer's disease and COVID-19), and offer clues for future therapeutic direction.

Methods

The RNA sequencing and microarray datasets of postmortem frontal cortex samples from COVID-19, Vascular Dementia, Alzheimer's disease, and age-matched control subjects were collected from Gene Expression Omnibus (GEO) and analyzed the differential expressed genes (Deg) using GEO2R and Galaxy. Also, protein-protein interaction by String, and enriched function and pathway by DAVID were analyzed.

Results

In GEO-Deg analysis, KIAA0319, which plays a role in the development of the cerebral cortex by regulating neuronal migration and cell adhesion, is upregulated. While MYOF, which plays a role in membrane regeneration and repair by calcium-mediated membrane fusion, is downregulated in COVID-19. The protein-protein interaction analysis identifies the ribosome pathway-related genes including RPS11, RPL10A and COVID-19-related genes including NUP88, PSMC3. The functional enrichment analysis shows that the brain dysfunction in COVID-19 is closely associated with viral transcription, COVID-19, and structural constituent of ribosome pathway. It is different than Alzheimer's disease of synapse, neuron projection, neuroactive ligand-receptor interaction pathway, and Vascular dementia of G protein-coupled receptor signaling pathway.

Conclusion

These findings provide evidence that COVID-19 induced brain degeneration was not only associated with COVID-19 infection, also ribosome-related protein synthesis in cerebral cortex. And it could be utilized in the future as a therapeutic option for the preservation of brain function following COVID-19 infection.

Keywords: COVID-19, brain degeneration, gene expression

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Downregulation of ALAS2 in Human Coronavirus NL63 and Its Effect on the Porphyrin and Chlorophyll Metabolism and Red Blood Cells

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Introduction

The Human Coronavirus NL63, a transmissible, mutation susceptible, coronavirus, has caused over 10% of respiratory diseases in children and the immunocompromised. Understanding the hindrance this virus has on red blood cell function by targeting the cell's genes may aid in recognizing whether the same occurs in COVID-19 patients, as its root, SARs CoV 2, is a similar coronavirus. Our research aims to detect specific genes impacted by the virus to develop effective treatments for patients, to mitigate its severity and long term respiratory effects.

Methods

We analyzed the gene expression profiles for a female with human coronavirus NL63 using the NCBI GEO dataset GSE68310. Then, we utilized 7 samples from a patient infected with Human Coronavirus NL63 and 7 samples from the control group of a patient in which viruses were not detected. We studied these two groups using a String-DB analysis of the top 250 genes, sorted by statistical t-test of p values less than 0.008, of which both overexpressed and underexpressed genes were compared. We used this mapping to understand connections between the most prominently affected genes to investigate metabolisms, specifically the Porphyrin and chlorophyll metabolism, through Kegg Pathways, and subsequently the gene ALAS2 through GeneCards.

Results

We found that Gene ALAS2 is significantly underexpressed (logFC= -1.94) in chronic groups, and is present in the Kegg Pathway, Porphyrin and Chlorophyll Metabolism that has a fairly low false discovery rate at 0.013 and a count in network of 5 of 42. This gene is responsible for catalyzing porphyrin synthesis by activating the process that condenses glycine (Aminolevulinic acid synthase), an important step in the production of 5-aminolevulinic acid and 5'-aminolevulinate synthase 2, a precursor to porphyrin and hemoglobin respectively.

Conclusion

ALAS2 is an important gene in the construction of porphyrin, a component of a red blood cell's ability to carry oxygen from the lungs to the tissues. Coronaviruses however, target red blood cell structure, specifically the membranes where the products of ALAS2 are found, debilitating the cell from traveling through small capillaries. The downregulation of ALAS2 is attributed to the fact that coronaviruses saturate porphyrin, and in response, cells decrease the gene's expression. Novel treatments that may mitigate the virus' impact include pyridoxal phosphate, a form of Vitamin B that increases the activity of enzymes produced by ALAS2, gene therapy targeting ALAS2, and hydroxychloroquine (Plaquenil), which decreases porphyrin saturation. Understanding the role of ALAS2 demonstrates the effect of coronaviruses on red blood cells. Future studies may focus on the relationship between coronavirus and the bloodstream, specifically ALAS2, to denote whether a direct relationship exists. If so, the function of the pyridoxal phosphate may be examined to develop new treatment pathways.

Keywords: Human Coronavirus NL63, Red Blood Cells, Porphyrin

Downregulation of Cytosolic DNA-Sensing Pathway in Response to Coronaviruses

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Introduction

Coronaviruses are a common cause of infectious disease in humans. The coronavirus SARS-CoV-2 causes the current COVID-19 pandemic. Diseases caused by coronaviruses tend to increase in severity in the older population (those older than 65 years of age), while many other viruses, such as H1N1, cause more severe symptoms in those under 65. The general theory for this difference is that H1N1's prevalence since the early twentieth century has given the older population more exposure and a better immune response to the virus, while many coronaviruses are newer, not giving the weakened immune systems of the older population this same advantage. However, we wanted to determine if there are any specific differences regarding viral immune response pathways that contribute to this difference.

Methods

We used the NCBI GEO2R dataset GSE47961, which used microarray expression profiling to study the differences in gene expression in human airway epithelial cultures infected with SARS-CoV, SARS-ddORF6, SARS-BatSRBD, H1N1, and a mock infection at different time points. For our research, we compared four samples of H1N1-infected cultures and four samples of SARS-CoV-infected cultures, all at 24 h.p.i. We analyzed these two groups in GEO2R and found the top 250 differentially expressed genes with a significance level cut-off of $p = 0.05$. Then, we implemented STRING and its Analysis feature to find functional enrichments among these 250 genes, such as biological processes and KEGG pathways. We researched our STRING findings in scientific articles.

Results

In one of the KEGG pathways we studied, the Cytosolic DNA-Sensing Pathway, we found that genes in the pathway, including IRF7, CXCL10, and AIM2, are upregulated in the cultures infected with H1N1 compared to SARS-CoV. In further research using scientific articles, we found that the Cytosolic DNA-Sensing Pathway is involved in triggering senescence-associated secretory phenotype (SASP). SASP triggers active immune responses and releases inflammatory cytokines, which play a crucial role in combating viral infection. Also, we found that SASP develops during cellular senescence, which becomes more common as age increases.

Conclusion

The downregulation of Cytosolic DNA-Sensing Pathway genes in cultures infected with SARS-CoV compared to H1N1 suggests that this pathway triggers SASP less efficiently in response to coronaviruses, providing a plausible explanation for the increased severity of coronavirus diseases in the older population. SASP is one of the only immune response advantages that the generally weakened immune systems of the older population have since SASP coincides with cellular senescence. Further research could study defects in the Cytosolic DNA-Sensing Pathway as a predisposition to coronavirus diseases, which could help with the current COVID-19 pandemic and illness caused by coronaviruses in general.

Keywords: SARS-CoV, H1N1, Cytosolic DNA-Sensing Pathway

The Downregulation of HLA-c Gene in Covid Patients Leads to a Disruption in the Antigen Processing and Presentation Pathway

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Introduction

COVID-19 is caused by infection with a new coronavirus (called SARS-CoV-2). The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes. The COVID-19 virus has killed roughly around 3.44 million people worldwide. People can protect themselves from contracting the virus by getting vaccinated. My research is focused on the HLA-c gene and its effect on the antigen processing and presentation pathway. The HLA-c gene is associated with many diseases like viral infections. The purpose of this gene is to help the immune system differentiate proteins made by the body from proteins made by foreign bodies such as viruses and bacteria.

Methods

To begin, I found the COVID-19 samples in the data set GSE56677 through NCBI Geo Datasets. GEO2R was then used to compare two subgroups - Mock infected (control) and COVID-19 infected patient samples (experimental). The data was analyzed to locate a group of genes that possessed a specific
process behind them, and String-DB was further used to recognize the connections between HLA-c and other genes. Through KEGG pathways, I found the interactions between the HLA-c and other genes in the pathway.

Results

From my research, I found that there are multiple genes interrelated with each other but I chose to focus on one gene - HLA-c. I also found that this led to the downregulation in the COVID-19 group in comparison to the control group. When this gene is downregulated, more foreign invaders enter your body, causing a disruption in the immune system. For example, in COVID-19 patients, the HLA-c gene is downregulated, with a logFC value of -1.1935 and a p-value of 0.00000235. The p-value is statistically significant as it is less than 0.05. The p-value also shows that the data isn't random. Furthermore, the HLA-c gene is related to NK cells, a type of lymphocyte in the immune system that stops the spread of infections.

Conclusion

From the connection between the HLA-c gene and NK cells, I've come to a conclusion that their downregulation in COVID-19 patients leads to a disruption in the antigen processing and presentation pathway. This is related to COVID-19 because the coronavirus is an antigen and the immune system has to fight it off as a weaker immune system is more susceptible to COVID-19. Less expression of this gene in Covid than the control makes the immune system weaker. One way to combat this is to change the expression of the HLA-c gene to see if it has an impact on COVID.

Keywords: Coronavirus, Antigen Processing and Presentation, HLA - c

Downregulation of Immune System Process and Inflammatory Response in MERS-CoV Infection

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Introduction

The Coronavirus family is a large family of viruses which can cause respiratory illnesses in humans. Many of these viruses are zoonotic, which means that they are able to be transferred from animals to humans. The Middle East respiratory syndrome (MERS) is caused by the MERS coronavirus (MERS-CoV). It was first transmitted from an animal reservoir in camels in 2012. It is an acute respiratory illness which targets specific cells in the body. When a virus is detected, pro-inflammatory cytokines and interferons are expressed to fight off the infection. Understanding the limits of the immune system and inflammatory response can give insight into why a person may be more susceptible to a virus.

Methods

I used a publicly available dataset containing information on gene expression in patients affected with MERS-CoV. The NCBI GEO dataset GEO100509 consisted of 50 endothelial cell samples ranging from 0hrs to 48hrs after infection. In my analysis, I used samples of cells 0hrs after infection. I analyzed the dataset with GEO2R to find logFC and p-values, which I further used in the STRING database, where I found four biological processes affected by my genes of focus.

Results

Analysis through STRING showed that Positive Regulation of Immune System Process and Inflammatory Response were significant biological processes with a false discovery rate of 0.00057 and 0.0222 respectively. The genes involved in these processes included JUN, EDN1, BCAR1 and CXCL1 all of which were downregulated. Their logFC values were: 0.501, 0.403, 0.474, 0.7 respectively (they were downregulated in the MERS affected samples with respect to the control). The gene CXCL1, which had the greatest logFC value mentioned above, encodes for a member of the CXC family of Chemokines- which plays a role in inflammation as a chemoattractant for neutrophils. Neutrophils are the first cells to arrive at an infection site.

Conclusion

The downregulation of genes involved in immune and inflammatory response processes suggests that patients with lower expression of these genes are more susceptible to infection by MERS-CoV. By having a lower regulation of genes involved in these processes, the body cannot fight the virus as effectively. Upregulating these genes through gene therapy or other methods may decrease inherent susceptibility to the virus. Furthermore, similar treatment could be used to protect patients from SARS- CoV-2, which is the virus responsible for COVID-19.

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Downregulation of Nucleic Acid Binding Genes in the Measles Pathway Found in Patients Vaccinated for Influenza

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Introduction

Influenza is a common and occasionally fatal illness caused by an RNA virus. There are roughly 3 million cases of influenza a year in the US, which is partially preventable with a vaccine. 45.3% of adults and approximately 54% of pregnant women received the influenza vaccine from 2018 to 2019. The purpose of this study was to determine any potential irregularities in the genetic code of recipients of this vaccine.

Methods

We used the dataset GSE166545 (Geo Datasets [1]), which sequenced blood collected from 44 pregnant women zero (before), one, and seven days following influenza vaccination. We defined groups as vaccinated and unvaccinated, analyzed using Geo2r, and saved the results to a Google spreadsheet. We took the top 250 genes (defined by lowest p-values) and searched for enriched pathways in StringDB[2]. Finding the Measles pathway, we investigated the related genes found in subjects using KEGG Pathways [3] to identify placement and connection between genes and Genecards[4] to identify functions of genes.

Results

We identified nine genes in the measles pathway that were downregulated: OAS3 (logFC -0.669, RNA binding and transferase, oligoadenylate synthetase), OAS1(logFC -0.543, RNA binding and transferase oligoadenylate synthetase), IRF9 (logFC -0.249, DNA binding transcription factor activity), IRF7 (logFC -0.429, DNA binding transcription factor activity), STAT1 (logFC -0.484, DNA-binding transcription factor activity and protein homodimerization activity), STAT2 (logFC -0.429, DNA-binding transcription factor activity and identical protein binding), IFIH1 (logFC -0.48, nucleic acid binding and hydrolase activity), TNFSF10 (logFC -0.262, signaling receptor binding and tumor necrosis factor receptor binding), and TNFAIP3 (logFC -0.211, ligase activity and thiol-dependent ubiquitin-specific protease activity). Seven of these nice genes have molecular functions related to nucleic acid binding.

Conclusion

All nine genes corresponding with the measles pathway were downregulated, one of which does not appear in the influenza pathway that the vaccine targeted (TNFAIP3). Furthermore, seven genes appear in close proximity to each other in the measles pathway, and have a similar function of nucleic-acid binding. Given that these seven genes were present in both the influenza and measles pathways, and all shared a similar focus, it is possible that targeting these specific genes may produce a way to interrupt the genetic pathway of more than just one disease, and may present a method for working toward effective vaccines that could immunize against multiple, distinct diseases.

Keywords: Nucleic acid binding, measles, influenza vaccin

The Effect of Cocaine Use Disorder on the Gene Expression and Pathway of Glutathione Reductase

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Introduction

Cocaine use disorder (CUD) has been associated with several adverse health effects such as cardiovascular disease, respiratory illness, and neurological problems.[1] Furthermore, the presence of reactive oxygen species (ROS), which are highly reactive oxidative molecules, can damage cellular organelles and processes and lead to the development and progression of these CUD-induced health conditions.[2] Enzymes such as glutathione reductase are capable of preventing cellular damage resulting from ROS and serve in detoxification metabolism.[3] This research investigated if patients with CUD experience a downregulation of genes responsible for glutathione reductase activity leading to ROS-induced conditions. Understanding the effect of gene regulation on biochemical processes is vital for the development of treatments for disorders associated with drug addiction.

Methods

A sample of 30 human subjects with CUD and 30 control non-cocaine users were selected from GeoDataset GSE54839 to compare the gene expressions and the pathway of glutathione reductase activity. Using the GEO2R database, data for gene expression was gathered and 250 significantly expressed genes were identified based on p-values <0.05. Interactions between the genes were then mapped in the String database to identify relevant pathways and processes. The most relevant pathway, glutathione metabolism, was then analyzed using the KEGG pathway database.

Results

A significant correlation between CUD and glutathione metabolism was found in the GSTO1 and MGST3 genes. The data showed that the GSTO1 and MGST3 genes, that play a significant role in the regulation of glutathione reductase activity, were downregulated in people with CUD; GSTO1 (LogFC= -0.33) and MGST3 (LogFC= -0.234), whereas normal gene regulation was observed in non-cocaine users. This indicates that patients with CUD experienced less glutathione reductase activity which may have led to more ROS-induced adverse reactions.

Conclusion

The findings revealed that CUD can lead to the downregulation of genes related to glutathione reductase activity. Reduced glutathione reductase activity increases the risk of ROS-induced conditions such as inflammation, hyperoxia induced lung injury, and hypertension which are common in patients with CUD.[2] This newfound correlation between CUD and ROS can potentially lead to targeted drug therapies which may improve glutathione reductase activity in patients with CUD and prevent health complications induced by cocaine use.

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Effect of IL-17 and TNF Pathways on Cytokine Storm in COVID-19

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Introduction

Having caused millions of deaths worldwide, the COVID-19 pandemic has profoundly impacted people around the world. With over 150 million cases globally, the pandemic has led to social and economic difficulties for many families. The COVID-19 disease is caused by the coronavirus SARS-CoV-2 and can result in varying symptoms as well as death. Individuals with more severe symptoms can often exhibit a condition known as a cytokine storm, in which the body's immune system goes into overdrive. The interleukin-6 (IL-6), an inflammatory cytokine, plays a significant role in the cytokine storm. The cytokine storm leads to oxidative stress, which has been shown to increase the severity of COVID-19, which in turn leads to the cytokine storm again. Although treatments do exist, there exist few effective methods of both treating and preventing this cycle.

Methods

We used the dataset GSE30589 from GEO Accession viewer, then analyzed the data with GEO2R. We then compared the SARS and mock groups at 0hpi, 7hpi, 15hpi, 24hpi, and 65hpi, then downloaded the volcano plot created by these comparisons. After finding the genes with both a low p-value and significantly upregulated logFC, we used STRING-db to find pathways the majority of these genes were associated with. The pathways we found were then analyzed using KEGG and the Gene Ontology Resource.

Results

Using the results from the dataset, we found that the biological pathway cellular response to oxidative stress as well as the TNF and IL-17 signaling pathways consisted of many of these significantly upregulated genes. By using KEGG, we found the IL-17 and TNF signaling pathways contribute to the cytokine storm in COVID-19 by leading to the expression of cytokines such as IL-6 that play a role in the cytokine storm. TNFR1 and IL-17, receptors for the TNF and IL-17 pathways respectively, can induce oxidative stress.

Conclusion

These results suggest the NFKB1 gene in the TNF and IL-17 signaling pathways as a target of treatment to prevent excess cytokine expression of IL-6. To regulate oxidative stress to prevent the cytokine storm cycle, we could target the IL-17 gene from the IL-17 pathway or regulate the activation of ROS species in the TNF pathways, affecting the amount of oxidative stress and thus cytokine expression as well as the presence of a cytokine storm.

Keywords: COVID-19, cytokine storm, oxidative stress

Effect of MERS-Coronavirus Infection Progression on Genetic Pathway Expression in Microvascular Endothelial Cells

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Introduction

SARS-CoV-2, the cause of the COVID-19 virus, is closely related to Middle East respiratory syndrome coronavirus (MERS-CoV). The study of MERS-CoV progression can elucidate the progression of current and future coronaviruses. In a study by Pacific Northwest National Laboratory[1], human microvascular endothelial cells were infected with wild-type MERS-CoV (icMERS). We hypothesized that gene expression differences between infected cells at different time points would reveal how the genes respond based on infection progression.

Methods

We investigated the progression of icMERS infection in early (12 hr) versus late (48 hr) stages of the infection. We analyzed our groups using GEO2R, which returned genes sorted by decreasing p-value. Using STRING, we analyzed the top 250 differentially expressed upregulated genes, and found that many of these genes interacted with each other. We used KEGG to analyze the significant pathways from our STRING results.

Results

Analysis showed that the downregulated genes in the 48 hour group had few to no associated KEGG pathways or interactions. The upregulated genes had more interactions and were linked to three KEGG pathways: Cellular Senescence, Pathological Escherichia Coli Infection, and Antigen Processing and Presentation. The most notable genes in the Cellular Senescence pathway were IL6 and IL1 (participants in several infection pathways, including COVID-19), and HLA-A, which is part of the Antigen Processing and Presentation pathway and many viral infection pathways.

Conclusion

The upregulation of IL6 and IL1 is linked to promotion of virus survival and exacerbation of clinical disease[2]. HLA has been shown to affect susceptibility to COVID-19 infection and may apply to MERS-CoV[3]. Previous research on virus interaction with cellular senescence has shown that, while cells trigger senescence to restrict virus replication, viruses can also exploit this process to improve replication[4]. The E. coli infection pathway is upregulated, which likely means that even though senescence is increasing, infection still increases over time. This suggests that MERS-CoV is likely exploiting the process of senescence as infection progresses.

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Effects of IL23A Upregulation and Functional Enrichment of T-helper Cell Differentiation in Coronaviruses

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Introduction

Carried by the SARS-CoV-2 coronavirus, COVID-19 has been contracted by 162 million people and has led to the deaths of over three million worldwide as of May 2021[1]. This study aimed to identify and explore the changes in genetic expression instigated by a similar coronavirus, which would be analogous to the changes instigated by SARS-CoV-2, in order to explore their practical implications.

Methods

The NCBI dataset we analyzed is GSE45042. The data comes from 6 replicates of Calu-3 2B4 cells, 3 infected with HCoV-EMC and 3 that were mock infected. Expression data was taken at multiple times past infection. We then used GEO2R to find both the top differentially expressed genes at 24 HPI and generate visuals for the data. The top 150 differentially expressed genes were fed into STRING-db, which revealed functional enrichments in the infected cells. AmiGo allowed us to further explore the gene ontology of those functional enrichments, including related genes and further information on their functions.

Results

The main functional enrichment in the infected cells was the regulation of T-helper 17 cell differentiation, with a false discovery rate under 0.05 and a strength over 1. The main genes in the dataset which contributed towards this enrichment were IL23A, RC3H1, and ZC3H12A. IL23A is significant in that it plays a role in the JAK-STAT signaling pathway. Specifically, IL23A activates JAK, the kinase central to the JAK-STAT signaling pathway.

Conclusion

Our results show that the upregulation of genes in the regulation of T-helper 17 cell differentiation, specifically in the JAK-STAT signaling pathway, is associated with cells infected with human coronavirus EMC (MERS). Coronaviruses are positive-stranded RNA viruses that negatively affect the respiratory, digestive, and nervous systems of humans, possibly leaving fatal or long-term effects[2]. Currently, the crucial process of detecting the disease is through genomic and immunoglobulin detection-based testing, but these methods can lead to false positives[3]. By examining omics data for the upregulation of IL23A and heightened activity of other certain elements in the JAK-STAT pathway, it is possible that the virus could be detected more expeditiously than with current tests. Further research into this method could lead to a more accurate and improved test for COVID-19 diagnosis.

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Evaluating the Role of Certain Genes and Cytokines in TNF-α and IFN-γ Induced Cytokine Storms

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Introduction

Organ failure and lung damage caused by a cytokine storm is a defining factor of severe COVID-19 infection, and treatment is difficult. Production of the cytokines TNF-α and IFN-γ have been pinpointed to the induction of inflammatory cell death and other processes in infection. The IRF1 gene (Interferon Regulatory Factor 1) was found to be a central part of the immune response to cytokine activation. By knocking out the gene while stimulating cells with the cytokines, it is possible to deduce the role that other genes play in cytokine storms, as well as further understand the causes of cytokine shock, which could help in the treatment of severe COVID and other diseases.

Methods

We used a publicly available dataset on NCBI containing the gene expression of wild type and IRF-knockout mice stimulated with cytokines TNF-α and IFN-γ. We compared the gene expression of wild type and IRF-ko (stimulated) using GEO2R to find the top 250 differentially expressed genes between the two groups. We then input those 250 genes into STRING to investigate prominent biological processes and KEGG Pathways related to them, as well as their interactions. For further insight into gene expression and connections, we repeated the entire process using the same dataset, this time comparing all six groups.

Results

The comparison of wild type and IRF-ko mice (both stimulated with both cytokines) found that the chemokines CCl7, CCl5, CCl2, CCl3, CCl22, CCl12 and chemokine receptor CCr7 were among the top differentially expressed genes with $p<.05$ as well as Nos2, Il27, Il6 and Il12rb1. Most of the genes are associated with the cellular response to TNF-α and IFN-γ, which are regulated by CCr7, Il27, and Il12rb1. CCl7, CCl2, CCl3, and CCl12 were upregulated in IRF-ko mice, while CCl5, CCl22, and CCr7, Il27, Il6, Il12rb1, and Nos2 were downregulated.

Conclusion

Although CCl2 has been independently correlated with COVID severity and viral load, expression is lowest when stimulated with both cytokines, meaning that the immune dysregulation associated with COVID may be uncorrelated to the cellular response to infection itself, opening up new possibilities for treatment of patients that are already infected. This partially explains the small changes in expression value between WT and IRF-ko of several genes such as Il6 when stimulated. Nos2, which is induced by cytokines, is downregulated in the IRF-ko group showing a connection between the IRF1 axis and production of nitric oxide. Nos2 has antiapoptotic and proapoptotic properties and its downregulation correlates with more control of damage. Since CCr7 and CCl5 are involved in the positive regulation of macrophage migration, downregulation in IRF-ko led to an impaired chemotactic response, which is essentially the goal in lessening cytokine storms.

Keywords: chemokines, cytokine storm, IRF1

Gene Expression in SARS-CoV-2 Infected Cells

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Introduction
As of June 2021, the coronavirus SARS-Cov-2 has infected over 170 million people worldwide. Gene expression studies can help to unravel the molecular mechanisms enabling coronavirus infection of normal or cancer cells. The aim of this study was to determine genes that are differentially expressed in SARS-Cov-2 infected cells.

Methods
We analyzed gene expression changes in a lung normal epithelial cell line (NHBE) and a cancer cell A549 infected with SARS-CoV-2 using published microarray dataset GSE147507. We further performed pathway annotation analysis to determine the potential function of these genes.

Results
We found 906 upregulated genes and 748 downregulated genes in SARS-CoV-2 infected NHBE cells, whereas in A549, there were 1074 upregulated genes and 605 downregulated genes (P<0.05). We identified 125 genes, including *CXCL5*, *CCL20*, *IL6*, *IFI27*, and *XAF1* genes that were upregulated, and 21 genes including the *WNK1*, *TNFRSF10D*, *BTBD11*, *ABHD2*, and *HIPK2* genes that were downregulated in both cell lines. In addition, 1654 genes were differentially expressed only in NHBE, whereas 1679 were altered in A549. Pathway annotation analysis showed that signatures of viral infection (e.g., Herpes, Hepatitis B, and Hepatitis C pathway) were altered in NHBE cells while Spliceosome, RNA transport, and RNA degradation pathways were altered in A549.

Conclusion
Our preliminary results suggest a pattern of expression differences between normal and cancerous lung cell lines, which could be important in understanding and disrupting SARS-Cov-2 infection.

Keywords: Coronavirus, COVID-19, cancer, microarray

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Genes: a COVID-19 Vaccine Study

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Introduction

The COVID-19 pandemic has resulted in a complete 180 of the world's conditions. Within just a year, it has taken the lives of over 3,000,000 people [1]. The race to a safe and efficient vaccine is essential in overcoming this pandemic. At least 70% of the population must be vaccinated to achieve herd immunity. A smallpox vaccine has been found to be effective against respiratory pathogens such as COVID-19, when administered by skin scarification. Thus, this paper aims to establish the relationship between gene expression and production of T-Cells to analyze how such a vaccine works.

Methods

I chose the GSE150190 dataset from the National Center for Biotechnology Information, which compared the genes in OTI-cells that were activated by a smallpox vaccine and their effect in reducing respiratory pathogens. Out of 33 samples, I used 6 that administered the vaccine by skin scarification and 12 that administered the vaccine by intra-tracheal administration or intra-tperitoneal injection. All samples were studied 60 hours post treatment. I then used GEO2R to compare the 2 groups. The p-value cutoff was <0.001 to ensure statistically significant results. I defined genes with a positive logFC value as under-expressed in the s.s. sample and those with a negative value as over-expressed. I put the most significant 650 genes into the STRING database to observe the first-shell, experimentally-detected interactions and looked for the most densely connected genes.

Results

My two genes of interest were SIL1 and RPL7, which both had negative logFC values: -0.414 and -0.277, respectively. Thus, they were both over-expressed in the s.s. samples. Using GeneCards, I learned that SIL1 is involved in protein processing and translocation in the endoplasmic reticulum and that the RPL7 gene is involved in the inhibition of cell-free translation.

Conclusion

The production of CD8+ T-cells is crucial in fighting off viruses. Therefore, the increased production of receptor proteins (to transform naïve cells into specialized killer T-cells) and interleukins (proteins that create a cascading immune response) is vital. When there are more OTI cells, the immune response is stronger, thus the overexpression of genes such as SIL1 aid in the production of such proteins and consequently enhance the performance of killer T-cells against pathogens like COVID. Viruses use ribosomes to transform their mRNA into harmful proteins. When the RPL7 gene was overexpressed, it aided in the inhibition of this translation. This research establishes a relationship between genes and their effect on translation of specific proteins and allows us to realize which genes we should target to get maximum immune response. Overall, the joint effort of increasing the genes that aid the translation of proteins for immune response whilst increasing the genes that limit the translation of mRNA of foreign bodies has resulted in fighting off the COVID-19 virus. Now that we have found ways to limit its spread with mask use and proper sanitization, this study will allow us to develop ways to fight it off.

HLA Class I Genes in Coronavirus Antigen Presentation

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Introduction

Coronaviruses are agents of various severe respiratory illnesses, including Middle Eastern Respiratory Syndrome. In such viral infections, the HLA system of genes plays a central role in the immune system by presenting peptides to be recognized by cytotoxic T cells. HLA genes contribute to varying immune responses, including those in patients infected with MERS-CoV and SARS-CoV-2, both of which are caused by spike protein coronaviruses. Effective host response against the virus largely depends on HLA restricted T-cell responses [1]. Our research investigates the genetic pathways that affect the expression of HLA genes in cells infected with MERS-CoV. Through researching MERS-CoV and the HLA genes we can understand the workings of similar viral infections such as SARS-CoV-2.

Methods

This study used a publicly available NCBI dataset, GSE56677, which measured gene expression in human epithelial cells. Using GEO2R, 18 loCov (MERS-CoV-London) infected samples and 15 mock samples were analyzed. We input the 250 genes with the lowest p-values into STRING-db and identified enriched KEGG pathways. We found that the MHCI pathway within the antigen processing and presentation KEGG pathway contained HLA class I genes that were discovered to be downregulated in cells infected with MERS.

Results

From STRING-db, we found a group of HLA genes that were a part of the top six enriched KEGG pathways. They were all downregulated (logFCs from -1.007 to -0.482) in the MERS-infected human epithelial cells. The most prominently downregulated was the HLA-A gene (logFC = -1.007). HLA-A is a HLA class I molecule, which play a central role in the immune system by presenting viral peptides to be recognized by cytotoxic T cells. HLA class I genes were downregulated in the antigen presentation pathway in the cells affected with MERS.

Conclusion

Cells infected by the MERS-CoV virus show a downregulation of HLA genes, which causes less presentation of MERS peptide antigens to the body's T cells. This results in the body's inability to recognize this disease, leading to an immune response that is less effective. Existing SARS-CoV-2 treatment studies show that HLA class I gene therapies may be effective [2], and the injection of artificial antigen presenting cells have been shown to be able to activate T-cells [3]. We believe that further experiments involving the overexpression of HLA genes can be used to assess the validity of our hypothesis, and develop treatments targeting the HLA system in cells infected with MERS and SARS-CoV-2.

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Identifying Pathways That Promote Host-Virus Response to MERS

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Introduction

MERS or Middle East Respiratory Syndrome is a contagious and sometimes fatal respiratory syndrome caused by the MERS-coronavirus. MERS-CoV spreads in close proximity through airborne droplets. There is no MERS-CoV vaccine or specific drug treatment. In microvascular endothelial cells infected with MERS-CoV compared to uninfected microvascular endothelial cells, inflammation and host-virus response are increased. It is possible to identify the pathways that promote inflammation and increase host-virus response by determining the genes that are strongly upregulated or downregulated in MERS-CoV infected cells.

Methods

We used the publicly available dataset GSE100509 which contained samples from 50 human microvascular endothelial cells -- 25 infected with MERS-CoV and 25 mock-infected -- at different time points post-infection (hpi). Using GEO2R, we analyzed differential gene expression between 10 samples at 24 hours post-infection. We selected the top 250 genes with the lowest p-values using a two-tailed student's t-test. This aided in identifying potential biomarker genes that are highly correlated with the virus's efficacy. We then investigated the interactions between the proteins coded by these genes using STRING. This gave us insight into pathways, functions, and cellular components affected by those genes, which we utilized as we analyzed pathways of interest using KEGG.

Results

Significantly upregulated genes in the transcriptional misregulation in cancer pathway and TNF signaling pathway include CEBPB, BIRC3, IL6, and TNFAIP3. CEBPB regulates genes involved in immune/inflammatory response and BIRC3 modulates the NF-kB transcription factor which in turn stimulates apoptosis and inflammation-inhibitory genes. IL6 is required in the adaptive immune response to differentiate B cells into immunoglobulin-secreting cells. This gene is also an inducer of the acute phase response, which is vital for host defense against MERS. This could also potentially indicate elevated levels of plasma proinflammatory cytokines/chemokines.

Conclusion

From analyzing the differentially regulated genes in the transcriptional misregulation and TNF pathways, CEBPB, BIRC3, TNFAIP3, and IL-6 were most significantly upregulated. These results indicate that inflammatory response in the host cells could be activated by the inhibition of the acute-phase response of the MERS-CoV infection. Analyzing the function of acute-phase response is relevant in MERS-CoV and can aid in finding possible treatments for MERS.

Keywords: MERS, transcriptional misregulation

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The IL-17 Pathway in MERS-CoV Samples

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Introduction

Middle East Respiratory Syndrome (MERS), is a respiratory illness caused by MERS-CoV, a coronavirus similar in structure and function as SARS-CoV-2. [1] SARS-CoV-2 triggers the onset of COVID-19, a more widespread disease with over 157 million cases and 3 million deaths worldwide.[2] Research on how MERS-CoV affects the human immune response can provide a greater understanding of coronaviruses in general, essential in developing more effective treatment for MERS and COVID-19 alike.

Methods

I used a dataset GSE81909 containing samples of human airway epithelial cells infected with MERS-coronavirus and control cell samples. From the 50 samples provided, 25 were infected with MERS- coronavirus and 25 were control samples. I analyzed the 250 genes with the lowest p- values in GEO2R and used Stringdb to identify enriched pathways, one of the most relevant being the IL-17 signaling pathway. I then used OMIM and GeneCards to identify significant genes involved in the IL-17 signaling pathway.

Results

Several genes significant to the IL-17 pathway exhibited an upregulation or downregulation in expression, including IL6, CXCL8, CXCL3, CXCL2, CXCL1, CSF3, and IL17C. The IL17C gene in particular was upregulated with a logFC value of 0.534 and $p<0.05$. When expressed, the IL17C gene activates T cells that release cytokines known to stimulate the release of tumor necrosis factor (TNF) alpha and interleukin 1 (IL-1) beta from a monocytic cell line. CXCL1 (LogFC = 0.452 and $p<0.05$) and CXCL3 (LogFC = 1.43 and $p<0.05$) were also upregulated and assist in this process by encoding for chemokines that are part of the CXC subfamily; the cytokines function as a chemoattractant for neutrophils and induce inflammation.

Conclusion

The upregulation of genes involved in the IL-17 pathway induce an inflammatory response while signalling T cells and neutrophils to the site of infection. Targeting the downregulation of genes involved in the IL-17 signaling pathway may be useful in lessening inflammation and other symptoms of infection, while still ensuring that the body is effective in eradicating the virus and infected cells. Understanding how the IL-17 pathway is activated and regulated is essential in treatment and managing symptoms for MERS-CoV, SARS-CoV2, and related coronaviruses.

Keywords: coronavirus, MERS, IL-17 signaling pathway, IL17C

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Inflammatory Responses in H1N1 Compared to SARS

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Introduction

Coronaviruses are a family of viruses that have been a significant cause of infectious diseases in humans. The SARS, COVID-19, and MERS pandemics all resulted from their respective coronaviruses and had a large impact on our society. These coronaviruses have been found to have a more severe effects on people above the age of 65, while other viruses such as H1N1 tend to affect the younger population. We investigated genetic differences between H1N1 and coronaviruses that account for their variation in effects on people of different age groups.

Methods

We analyzed the microarray expression profiling data of NCBI GEO dataset GSE47961 specifically for 4 samples of H1N1-infected human airway epithelial cell cultures and 4 samples of SARS-CoV-infected cultures, all at 24 h.p.i. We used GEO2R analysis to identify the top 250 differentially expressed genes between the two groups. We used the String database to find fundamental enrichments between these differentially expressed genes.

Results

We found that symptoms resulting from upregulation of inflammatory responses were more prevalent in SARS and COVID-19, another significant coronavirus, compared to H1N1. Cases of severe SARS and COVID-19 can both lead to pneumonia, a condition in which the alveoli of the lungs become inflamed. COVID-19 KEGG map showed that SARS-CoV-2 cell entry lead to a cytokine storm, a state of excessive release of pro-inflammatory cytokines, whereas the Influenza A KEGG map does not. However, when comparing the String and GEO2R data, important genes involved in inflammatory responses, such as DDX58 (logFC= 5.96073) and CXCL10 (logFC= 12.51606), were upregulated in H1N1 rather than SARS. However H1N1 also had more anti-inflammatory genes expression, such as PARP14, which negatively regulates production of pro-inflammatory cytokines; SOCS1, which suppresses cytokine signalling; and CD274, which inhibits cytokine production.

Conclusion

While human airway epithelial cells had a more proinflammatory response to infection with H1N1, there was a significantly decreased anti-inflammatory response to SARS and SARS-CoV-2 infections. Since individuals above 65 are more likely to be experience more inflammation, upregulation of suppressors to inflammatory responses in H1N1 allows inflammation to be much better controlled and therefore less prevalent in the symptoms compared to SARS and the other coronaviruses. By understanding how treatments can be better tailored to patients using the relative levels of baseline inflammation indicated by age and by the type of virus causing a disease (ex: increasing expression of pro-inflammatory cytokine suppressors for older COVID-19 patients), disease treatment may be able to become more effective, thus reducing the huge global impacts that these viruses cause for the future.

The Intersection of the Biological Processes Cellular Response to Oxygen Levels and Regulation of Cell Death in Wild Type MERS-CoV

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Introduction

Middle East respiratory syndrome (MERS-CoV) is a viral respiratory disease, and a variant of the coronavirus. It affects the respiratory system, specifically the lungs and lymph nodes. A symptom of shortness of breath correlates to the biological process “cellular response to oxygen levels”, which is the change in cell state or activity due to a change in oxygen concentration. Mers also induces apoptosis in the lungs, leading to the biological process “Regulation of Cell Death”. Some genes of intersection of the processes are ICAM1, CAV1, SIRT4, and EGLN3. Their expressions over three periods of time are analyzed to identify their significance.

Methods

Using NCBI’s GEO dataset finder, the data set on Wild Type MERS-CoV, GSE81909, was explored. The data was separated into 3 groups of 0 hour, 24 hour, and 48 hours. Using the GEO2R analyzer, the genes of the dataset were sorted by log fold change from smallest to largest. The top 250 of these genes were then analyzed in String db to identify connections. The biological processes Cellular Response to Oxygen Levels and Regulation of Cell Death were both explored to find the common genes: ICAM1, CAV1, SIRT4, and EGLN3; additionally, genes in only cellular response to oxygen levels (PDK1 and BACH1) and only regulation of cell death of the two biological processes (MYB and PLK1) were selected. These genes’ expressions were then analyzed using the GEO2R data and graphs.

Results

ICAM1 mers samples are downregulated then upregulated(logFC = -0.147, 0.129, -0.018). CAV1 mers samples are downregulated then upregulated (logFC = -0.044, 0.043, -0.0). SIRT4 mers samples are upregulated then downregulated(logFC = 0.176, -0.098,0.078). EGLN3 mers samples are downregulated then upregulated(logFC =-0.370, 0.033,-0.338).

Conclusion

ICAM1 and CAV1 have similar expression patterns for mers samples and are also involved in “regulation of cell communication”. EGLN3 follows a similar pattern to the genes of “cellular response to oxygen levels”, while SIRT4 expression is similar to “regulation of cell death”. Using further analysis, scientists can improve treatment by understanding Mers mechanisms.

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Investigating Significant Genes and Biological Processes in SARS-CoV and MERS-CoV to Predict Key Biomarkers in SARS-CoV-2

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Introduction

The recent global outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has wreaked havoc on the world, infecting at least 167 million and killing 3.48 million as of May 25, 2021. Though numerous prevention and control measures have been established to suppress further infections, with a mortality rate of 1 in 50 patients, health professionals are limited in their responses to treat hospitalized patients. The current predominant treatment for symptoms of SARS-Cov-2 include providing supplemental oxygen and mechanical ventilatory; remdesivir, a class of antiviral medications, can also be given to patients with extreme symptoms. Aside from these two treatments, there exist no reliable common alternatives. This is, in large part, due to the novelty of SARS-CoV-2. More research regarding the mechanisms behind the virus may shed valuable light on how it could be treated, and through which biological processes it makes patients ill. Unfortunately, there is limited data about the SARS-CoV-2. Thus, to better understand key biomarkers and processes in SARS-CoV-2, this project investigated differentially expressed genes and significant biological processes involved in other coronaviruses like SARS-CoV-2, namely SARS-CoV (2003) and MERS-CoV (2012).

Methods

Through the public database NCBI (National Center for Biotechnology Information), two datasets studying the gene expressions in patients of control and diseased groups were discovered for SARS-CoV and MERS-CoV. The unique GSE codes for these datasets were GSE17400 and GSE100509 for SARS-Cov and MERS-CoV, respectively. Using the interactive gene analysis tool, GEO2R, gene expressions of patients in the control and diseased groups were examined. logFC, P-value, and adjusted P-values were extracted for each gene. These values were used to sort the data in a Google Spreadsheet, to ultimately obtain the top 50 upregulated and downregulated genes for each disease. These 50 genes were input into the molecular biology database string-db.org, to identify key biomarkers and shared biological pathways within genes.

Results

In SARS-CoV, the most significant biological processes were the positive regulation of interleukin-1 and the regulation of ketone. These processes involved the upregulated genes EGR1, CCL20, and DKK3. In MERS-CoV, the most significant biological processes were the regulation of nucleotide-binding oligomerization and the negative regulation of bone resorption. These processes involved the upregulated genes BIRC3, TNFAIP3, and IL6.

Conclusion

As the results indicate, the regulation of interleukin-1, ketone, nucleotide-binding oligomerization, and bone resorption may be significant in coronaviruses. These findings are interesting and unexpected, to a degree. Yet, there exist previous studies supporting the relations of these biological processes on SARS-CoV-2, such as the interconnectedness of bone metabolism and infection. The results of this study set the stage for further research regarding these biological processes in SARS-CoV-2. Ultimately, further research may lead to novel treatments to improve health outcomes of hospitalized SARS-CoV-2 patients.

IRF1 Knockout Is Associated with the Downregulation of Leukocyte Apoptosis Regulatory Genes in COVID-19

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Introduction

The COVID-19 pandemic caused by the SARS-CoV-2 virus has emerged as the most catastrophic global health crisis since the 1918 influenza pandemic. Upon infection, the virus triggers a response from the human host's immune system: the body's white blood cells (WBCs) release elevated levels of pro-inflammatory cytokines, such as TNF-α and IFN-γ, to coordinate an immune response with other immune cells. However, many COVID-19 patients experience a "cytokine storm" in which these cytokines reach extremely high levels, causing tissue damage. Our study focuses on the significance of the regulation of WBC apoptosis in COVID-19's cytokine storm and its implications for treating COVID-19.

Methods

We used the publicly available NCBI GEO dataset GSE160163, which analyzed the transcriptional profiles of bone marrow-derived macrophages from IRF1-/- and wild-type (WT) mice that were stimulated with the cytokines TNF-α and IFN-γ. We compared cells infected with SARS-CoV-2 and stimulated with both cytokines from WT mice (n=2) and IRF1-/- mice (n=2). Using GEO2R, we verified value distribution normalization and performed a t-test to determine the top 200 differentially expressed genes (DEGs) (adj. p-value < 0.01). After converting the probe IDs to gene names, we entered the list of genes into STRING-db (181 nodes). Then, we studied enriched Gene Ontology processes, noting patterns in upregulation and downregulation as determined by log2 fold change (logFC) values.

Results

Our STRING-db map of the top 200 DEGs showed several enriched functions involved in the apoptotic process of WBCs. These functions included the regulation of leukocyte apoptotic process (false discovery rate: 0.0172), the regulation of myeloid cell apoptotic process (FDR: 0.0256), and the regulation of neutrophil apoptotic process (FDR: 0.0256). The significant DEGs CCL5 (logFC: -2.55), HCAR2 (logFC: -1.53), and FCGR2B (logFC: 1.98) were each involved in several of these processes, while MERTK (logFC: -1.58) and CCR7 (logFC: -1.84) were each involved in only one process. With the exception of FCGR2B, all of the five genes above were downregulated in IRF1-/- samples.

Conclusion

We hypothesize that the downregulation of biological processes that regulate WBC apoptosis in IRF1-/- mouse macrophages indicates a lower incidence of apoptosis. However, we believe that future studies should clarify the role of apoptosis and IRF1 in the cytokine storm to determine whether either could serve as genetic therapeutic targets. Since apoptosis has anti-inflammatory effects, perhaps the introduction of cells undergoing apoptosis should be studied as a possible treatment for the COVID-19 cytokine storm.

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Locating Pathways that Promote Necroptosis of SARS-CoV

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Introduction

SARS stands for Severe Acute Respiratory Syndrome and is caused by the SARS-CoV. The virus has affected over 150 million people worldwide. SARS-CoV is transmitted through airborne droplets through the nose/mouth when coughing or sneezing. The envelope (E) protein plays a strong role in the SARS-CoV life cycle and is involved in modulation of inflammation and apoptosis. In recombinant SARS-CoV with the E protein (rSARS-CoV) compared to recombinant SARS-CoV without E (rSARS-CoV ΔE) infected cells, inflammation increases and apoptosis decreases. Identifying genes that are differently regulated in rSARS-COV makes it possible to locate pathways that promote inflammation and cell death in SARS.

Methods

We examined the publicly available dataset GSE30985 which contained samples from 33 MA-104 cells: 12 rSARS-CoV ΔE infected, 12 rSARS-CoV infected, and 9 mock-infected, at different time points post-infection (hpi). We selected 3 samples that were rSARS-CoV ΔE infected and 3 samples infected with E, all 24 hpi. Using GEO2R we identified differentially expressed genes between the 6 samples. We selected the top 300 genes with the lowest p-values. We then investigated the interactions between the proteins coded by these genes using STRING. This gave us insight into pathways, functions, and cellular components affected by those genes, which we utilized as we analyzed pathways of interest using KEGG.

Results

We focused on the necroptosis pathway responsible for programmed cell death and response to inflammation. In that pathway, TNFAIP3 (A20), SQSTM1 and HSP90AA1 were upregulated while HMGB1 and FTL were downregulated. HMGB1 is released from cells that undergo necrosis and FTL regulates nanoparticle-triggered necrosis. Additional gene analysis showed that RIPK 1-3 were upregulated. These proteins regulate signaling downstream of tumor necrosis factor (TNF). Necroptosis requires RIPK3 and its substrate MLKL. Inhibition of radicicol shifted cellular response to TNF from necrosis to apoptosis. TNFAIP3 inhibits TNF-mediated apoptosis; since the TNF gene is involved in inflammatory response but is toxic to cells, TNFAIP3 is necessary to prevent cell death. TNF signaling stimulates apoptosis and activation pathways, requiring the NF-kB transcription factor to induce apoptosis-inhibitory genes such as NFKBIA. SQSTM1 regulates the activation of NFKB1 by TNF-α.

Conclusion

From analyzing the differentially regulated genes, we observed that TNFAIP3, SQSTM1 and HSP90AA1 in the necroptosis pathway were upregulated. The results indicated that necroptosis could be triggered in host cells due to infection by SARS-CoV. It is possible that host cells resort to necroptosis due to the inhibition of apoptosis. Determining the role and mechanism of necroptosis in SARS-CoV can provide insight to finding possible treatments.

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MHC-I Glycoprotein Function in Viral Myocarditis Pathogenesis

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Introduction

The emergence of the Middle Eastern Respiratory Coronavirus (MERS-CoV) demonstrates the extent to which coronaviruses can permanently disrupt the human immune system and epigenome. MERS-CoV presents a litany of symptoms ranging from pneumonia and multiorgan failure triggered by respiratory complications. Despite the prevalence of MERS-CoV, researchers lack an understanding of the ways in which it modifies genetic expression crucial to immune health. This investigation seeks to identify key genes and their related pathways in order to determine the underlying mechanisms by which MERS-Cov infections manifest in innate immune systems.

Methods

We analyzed gene expression profiles from human epithelial cell lines using dataset GSE56677 from NCBI GEO. In total, we examined a total of 18 samples, 9 samples from human Calu-3 2B4 cells infected with MERS-CoV-EMC (HCoV-EMC or EMC) and 9 Calu-3 2B4 samples infected with MERS-CoV-London (LoCoV). Using GEO2R, we checked for appropriate value distribution, and then compared genes with positive and negative logFC values to distinguish genes by expression. We selected the top 250 genes for both overexpression and underexpression with adequate p-values (<0.05). Data from these genes were put through STRING.db to investigate the connections between selected genes and their functions. Genetic relations identified in the STRING.db were then assayed through the Kegg Database to further explore the link between expressional regulation and pathway changes.

Results

In LoCoV-infected isolates, HLA-G and HLA-F genes were substantially overexpressed, with logFC values of 1.21 and 1.08 respectively. These genes, belonging to the MHC class I family, are linked by the viral myocarditis pathway with a trivial false discovery rate of 1.44×10^{-6}. Both HLA-G and HLA-F play crucial roles in the presentation of foreign antigens within the immune system; HLA-G serves in protein homodimerization and peptide antigen binding, while HLA-F has shown to be involved signaling receptor binding and stabilization that promotes antigen processing.

Conclusion

Through an analysis of two distinct MERS-CoV isolates in humans, we pinpointed two genes with a considerable influence on the viral myocarditis pathway. As parts of the MHC class I gene network, overexpressed HLA-G and HLA-F genes encode for MHC molecules in the sarcolemma of human myocardium involved in T-cell antigen binding. Viral antigen binding with MHC II stimulates CD8+T-cell activation through the T-cell receptor signaling sub-pathway. Cytotoxic T-cells remain dependent on MHC-I complexes because of their role in recognizing pathogens. Uncontrolled T-cell activity prompts the overproduction of perforin-1 protein. High perfornin saturation, in addition to overproduction of virus-specific and autoreactive antibodies, induces immune-mediated myocyte damage and cardiomyopathy. Thus, despite the importance of T cell immunity, overactive immune response can ultimately lead to inflammation and viral myocarditis. The nature of MHC-I glycoproteins demonstrates the potential for therapies targeting HLA-G receptors and HLA-F stabilization mechanisms to ensure regulated T-cell activity. Future studies could prioritize structural assays within HLA-G especially in order to determine the optimum target approach. With further research, gene therapies identified for this viral infection could be utilized to treat other coronaviruses including COVID-19.

Mirror Concept of SARS-CoV-2 in Organismal Epithelial Colon Cells

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Introduction

The disease SARS-CoV-2, more commonly referred to as coronavirus or COVID-19, is a raging infection that causes a number of fatalities from its various methods of conquering and tainting the immune cells, or more specifically in this study, epithelial cells located in the colonic area of the human body. Further examining these effects, a certain mirroring system is used by the virus to locate itself within the previously uninfected organismal colon cell. Mirroring a cytokine with the name IFN gamma (IFN-χ) with the aid of the ACE-2 receptor protein is one of the main methods used by the virus to enter and infect cells. The main focus of this study was to comprehend how the virus was able to lodge itself into the epithelial cell and nominate a remedial treatment used to cure COVID-19 symptoms and infection.

Methods

In this study, the GEO dataset GSE156544 from NCBI was used, and this dataset came from a series of expression profiling by array datasets specifically personalized for homo sapiens. The data set consisted of 6 non-infected samples and 2 COVID-19 infected homo sapiens. Studying through GEO2R conceded the information that there were over 250 different genes were positively different from one another. The pathways between a set number over these genes yielded to show that the genes were tightly in cohesion with one another through the STRING-db database.

Results

Through deep research and analysis through the STRING database, the pathways between all infected and non-infected proteins and genes are extremely significant in terms of contributing to the importance of these research findings. Representative genes that were utilized from the GSE156544 database were COL6A3, COL4A2, SERPINH1, COL12A1, COL5A1, COL6A2, COL3A1, COL1A2, COL5A2, COL6A1, and COL1A1. Genes were predominantly upregulated, especially infected genes like COL6A2, which are directly linked to the SARS-CoV-2 infection.

Conclusion

The relationships between the various genes and the general upregulation trend amongst the genes represents how SARS-CoV-2 is so easily able to enter and infect a healthy colonic immune cell and submit the infectious disease. Using the mirroring method similar to the one done by the IFN−χ cytokine to develop an immune response to COVID-19 with its ACE-2 receptor protein attaching to the outermost part of the cell, the cell becomes increasingly susceptible and prone to infection due to the ease with which the virus can trick the cell into believing its doing no wrong and is only there in the hopes of being of help to the confused cell.

Keywords: SARS-CoV-2, COVID-19, epithelial colon cells, IFN-χ cytokine, ACE-2 receptor

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Novel Diagnostic Method for SARS-CoV-2 Delta E-gene Strain Using JUN and FOS Genes

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Introduction

COVID-19 has infected over 140 million people worldwide, 3 million of whom have died. Since the virus is relatively new, scientists have utilized the original SARS-CoV virus to conduct research. The E-gene is one of the most frequently tested gene targets for the detection of SARS-CoV-2 in present testing methods.[1] However, some strains of COVID-19 do not contain the E-gene, which poses potential problems for testing. The objective of our study was to identify certain genes that can be utilized to diagnose the SARS-CoV-2 Delta E virus strain.

Methods

We used GEO Dataset GSE30589 from the NCBI database, which consists of microarray expression profiling data from 3 SARS-CoV infected samples without the E-gene and 3 mock-infected SARS-CoV samples. GEO2R database analysis uncovered that 250 genes significantly differed in SARS-CoV infected samples compared to control cells. StringDB, KEGG Pathways, GeneCards, and Gene Ontology databases were then utilized to identify the enriched pathways and biological processes that these genes are involved in, along with how these pathways and biological processes are connected and related to one another.

Results

We inputted our top-250 genes into STRING to find biological processes and KEGG Pathways relevant to COVID-19, and we selected KEGG pathway hsa04668 (the TNF signaling pathway) to research. We found strong connections between genes JUN and FOS. Both genes were found to be upregulated among the infected cells, with logFC values of 1.87 and 3.75 respectively. JUN encodes a protein that interacts directly with target DNA sequences to regulate gene expression. FOS encodes leucine zipper proteins that can dimerize with proteins of the JUN family, and are regulators of cell proliferation, differentiation, and transformation.

Conclusion

The TNF signaling pathway plays an important role in physiological and pathological processes, such as the modulation of immune responses and induction of inflammation. TNF-α contributes to the secretion and activation of IL-6, a pro-inflammatory cytokine that releases at a high level in critical patients of COVID-19.[2] These secretions from pro-inflammatory cells lead to an uncontrolled inflammatory response that plays a key role in the pathogenesis of COVID-19.[2] Since the JUN and FOS genes are highly active in the TNF signaling pathway, they can be utilized as indicators of COVID-19 induced increased inflammatory response. The abundant expression of these genes can be detected through PCR, a simple tool already used for COVID-19 diagnosis.

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nvH1N1 Virus Affect on the Cell Cycle

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Introduction
The nvH1N1 virus shares similarities to SARS-CoV-2, the cause of the current health crisis around the world. There is also currently no cure for the nvH1N1 virus. The main focus of this abstract is to observe the effects of the nvH1N1 virus on the cell cycle with a specific focus on how it impacts the G1, S, and G2 phases of the cycle. Understanding how viruses like nvH1N1 affect a person's body is essential in being able to properly treat COVID-19.

Methods
Data from the NCBI GEO dataset GSE21802 analyzed plasma, serum and RNA samples collected from 19 patients affected by nvH1N1. Four control blood samples without the virus and four blood samples from positive critical patients under mechanical ventilation in the late period (after day 9) were chosen. The GEO2R tools compared gene expression of specific genes. Using STRING.db, the top 250 overexpressed and underexpressed genes were analyzed with p-values <0.0014 in order to determine their interconnected biological processes and prominent KEGG Pathways. By utilizing the KEGG database, it was discovered that genes involved in the cell cycle were significantly overexpressed in the experimental group.

Results
In this study of the Cell Cycle, genes CDC25A and CCNA2 were significantly overexpressed, with logFC values 1.535 and 2.091 respectively, in groups relating to the G2/M process. These findings have a false discovery rate of 0.0020, 0.0112, and 0.0025 respectively. CDC25A is required for progression from phase G1 to S phase in the cell cycle and activates the cyclin-dependent kinase CDC2 by removing two phosphate groups. The gene is present in research when DNA damage is present in the cell, as the gene is degraded to make way for a greater preparation for the S phase to make up for DNA damage. CCNA2 also controls the G1/S and G2/M transitions in the cell cycle by forming specific serine/threonine protein kinase holoenzyme complexes with the cyclin-dependent protein kinases CDK1 or CDK2. Both genes are related to cyclins and the progression of the cell cycle effectively at normal levels.

Conclusion
Knowing the effect of nvH1N1 is important in treating it, specifically by using targeted gene therapy to introduce genetic material to counter genes CDC25A and CCNA2 when they mutate. The method used in collecting data effectively displayed how the overexpression of these genes caused by the nvH1N1 virus disrupts the cell cycle and causes damage to the DNA. The KEGG pathway named Cell Cycle (homosapiens) further connects to this outcome as the degradation of CDC25A protein phosphatase is crucial to intra-S-phase checkpoint activation. As CDC25A is overexpressed in the infected patients, it shows that degradation did not occur effectively, leading to the cell skipping the checkpoint. This allows the virus to take over defenseless cells.

Keywords: DNA damage, cell cycle, nvH1N1 virus

Opioid Addiction May Lead to Downregulation of RNA-splicing in the Brain

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Introduction

Every day, 91 to 130 people die as a result of opioid use. Opioid deaths were responsible for the lives of 60,039 people in 2019. Access to resources and adequate healthcare could cost up to $2 billion per person in total (NIH). $78 billion is spent on opioid care per year in the United States. While it is well understood that going to rehab and leaving the medication will help deter relapse, people may not yet have a good enough understanding of the triggers and consequences of opioid addiction to create biomedical approaches or formulate alternative therapies, which is research towards the disease is critical.

Methods

Our dataset GSE87823 was found from the NCBI database. The human nucleus accumben study consisted of 49 samples, 27 non heroin and 22 heroin users. Using GEO2R we found the 230 most significantly downregulated genes out of the top 500 and took and put them into STRING-db, where we looked at gene interactions. We found two significant clusters involved in RNA splicing (14 genes) and ribonucleic proteins (26 genes). We then looked at gene ontology terms related to our clusters of interest. Finally, we looked at prominent Reactome Pathways and KEGG Pathways through our STRING analysis.

Results

Our KEGG Pathway results found that RNA Spliceosome was prominently downregulated in heroin addicts. From looking at the KEGG Pathways we found that the genes downregulated in heroin users were a part of Spliceosome Components. It is possible that opioids may alter the RNA Components of the human Spliceosome. From our Reactome Pathway results, we found an mRNA splicing pathway prominent on our data set. This supports our data found through the KEGG results. Though both the Spliceosome Pathway and the Reactome Pathways are highly expressed in our data, both are incomplete pathways. They need further research to conclude our research.

Conclusion

To back our conclusions, further research is needed to determine if spliceosome and ribonucleoprotein downregulation are linked to opioid addiction. There are a combination of environmental, genetic, and developmental factors that influence risk for addiction that could be confounding factors. Additionally, it is possible spliceosome downregulation is simply a general toxic response. It could be that toxic things (opioids, alcohol, etc) cause death by changes in splicing. Seeing if these changes are just because opioids are toxic or if they are special to opioids is important. A future experiment to differentiate toxic response from impact specific to opioids could be to use alcoholic mouse brains, and see if we get similar results. Ultimately, to better confirm our results, further research is needed.

Keywords: opioid addiction, heroin, heroin user disorder, RNA-splicing, spliceosome

Pathways and IcMERS

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Introduction

Today the world is overtaken by a rapidly spreading virus called SARS-CoV-2. It is most commonly recognized by the name “Covid-19” or “coronavirus”. The Centers for Disease Control and Prevention (CDC) reports that COVID-19 is thought to spread mainly through close contact from person to person, including between people who are physically near each other (within about 6 feet). The virus affects different people in different ways, but it mainly affects people with weaker immune systems. Covid-19 is the third leading cause of death in 2020 taking over a thousand people's lives last year in the US. Being a new virus, researchers are trying the best they can to figure out what this virus is and what it does so that they can start producing better vaccines.

Methods

Using the GEO2R database the dataset “GSE65575” to begin our research. The two virus samples used were “d4b MERS” and “icMERS” with the time of 24 hours. Collecting the top 250 samples to run through STRING DB where we chose our gene of focus (EGFR). Later, the KEGG database was used to find how this gene is related to the work of Covid-19.

Results

A diagram made by Kanehisa Laboratories on January 19 this year shows the signaled genes when the coronavirus enters the body. The first step of the process shows that when coronavirus enters through the cell using endocytosis it signals the gene ACE2 that signals to two other genes MAS1 and AT1R to start tissue protection. When AT1R is signaled it signals to ADAMI7 which then signals to three other genes (TNFa, HBEGF, IL-6Ra) that break apart into different pathways. When IL-6Ra is signaled, it passes the indirect effect or state of change to SII-6R that in the end falls into a Cytokine storm, when a body releases too many cytokines into the bloodstream, that leads to overactivated inflammatory cells that causes stroke and tissue damage along with Acute lung injury (ALI), Severe Acute Respiratory Distress System (ARDS), Macrophage Activation Syndrome (MAS), Acute Kidney Syndrome (AKI).

Conclusion

It is important to study pathways such as these because these can help researchers create new discoveries, vaccines, or other creations that save people’s lives.

Patients with Middle Eastern Respiratory Syndrome Exhibit Decreased Autophagy Function

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Introduction

The widespread COVID-19 pandemic has caused substantial mortality rates resulting in millions of deaths worldwide. Although patterns of the severity of the illness have already been associated with increased age, the wide range of symptoms across all groups cannot solely be explained by this factor. Genetic risk factors may also have a role in disease progression, which may bring up relevant evidence about younger people having severe symptoms. We investigated the relationship between genes and biomarkers related with symptomatology of infectious clone of Middle Eastern Respiratory Syndrome (icMERS) coronavirus and mutant viruses.

Methods

The dataset GSE65574 contained information on human Calu-3 cell transcriptome response to a wild type icMERS coronavirus and icMERS mutant viruses. icMERS is one of the four β-coronaviruses along with SARS-CoV, OC43, and HKU1. GEO2R and gene expression of the mock virus (11) vs icMER (12) subjects after various lengths of time revealed both up and down regulation of various genes. The interactions and relations between the top 250 genes, String, and Kegg, revealed that autophagy is the most common pathway.

Results

We were able to identify 2 upregulated genes that demonstrated abnormal expression in the cell autophagy pathway: ATG101, ATG16L1, and GABARAP. The autophagy pathway functions to remove harmful or surplus items in the cell, such as protein aggregates, dysfunctional organelles, and storage nutrients. ATG101 is located in the cytoplasm, and interacts with ATG13 in the ULK1 complex. Both ATG101 and ATG16L1 are important factors in activating phagophores, which in turn mature into autophagosomes. In icMERS patients, ATG101 and ATG16L1 are downregulated, meaning that patients with the virus do not have as many functioning autophagosomes to clean out damaged cells. GABARAP is important for autophagosome-lysosome fusion. A part of the autophagy process is the fusing of the outer membrane of the autophagosome and the lysosome membrane, which then allows for the autophagosome formation.

Conclusion

The icMERS coronavirus is correlated with the down-regulation of genes involved in the autophagy pathway. The results of this research indicate that icMERS coronavirus interferes with the fusion of autophagosomes and lysosomes. Interference with lysosomes can lead to lysosome de-acidification, altering immune system functions. This provides insight into the immune system abnormalities seen with patients suffering from the icMERS coronavirus or other forms of the coronavirus.

Potential Inhibition of Cytokine Surge in SARS-CoV-2 Patients

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Introduction

The contagious SARS-CoV-2 virus has led to an ongoing pandemic with a death toll of over three million. Transmission occurs through virus-containing respiratory droplets and airborne particles causing symptoms ranging from cough, fever, respiratory difficulties. Approximately 5% of infected patients suffer critical symptoms of respiratory failure, shock, and multiorgan dysfunction with an overwhelming inflammatory cytokine response observed. My objective was to find causes of the inflammatory cytokine surge in critical SARS-CoV-2 patients

Methods

To find causes of the cytokine surge, I used the NCBI dataset GSE30589 of SARS-CoV researching cell stress responses and apoptosis. This dataset uses Affymetrix microarrays to compare gene expression between SARS-CoV-infected, mock-infected and SARS-CoV-ΔE-infected cells. GEO2R was used to identify differentially expressed genes and String-db to note protein associations between genes. Gene Cards and String-db's Gene Ontology was used to research the biological pathways related to those genes.

Results

The genes MAPK1, JUN, and TNFAIP3 were identified to affect the cytokine surge experienced by critical SARS-CoV-2 patients. Gene MAPK1 is less expressed in infected patients with a p-value of 4.24e-07, whereas genes JUN and TNFAIP3 were more expressed with p-values of 2.74e-06 and 9.07e-09 respectively. MAPK1, JUN, and TNFAIP3 were found to be associated with the IL-17 signaling pathway and TNF signaling pathway.

Conclusion

The upregulation of genes involved in the IL-17 signaling pathway triggers inflammation seen in the severe symptoms of SARS-CoV-2 infection such as fatal pneumonia and sever respiratory failure with dyspnea. This triggers the activation of proinflammatory cytokines, chemokines, and antimicrobial peptides. Additionally, multi-organ failure seen in critical SARS-CoV-2 patients caused by intravascular coagulation mediated by inflammatory cytokines. These findings open the possibility for therapeutic inhibition of the IL-17 pathway through suppressing MAPK1, JUN, and TNFAIP3 gene activity which can help prevent SARS-CoV-2 symptoms which lead to fatalities. One preclinical study has already shown positive results in MAPK1 inhibition in SARS-CoV mouse model.

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The Potential of Chemokine-targeted Therapeutics in the Treatment of Virus-associated Cancers

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Introduction

The vast devastation caused by the SARS-CoV-2 virus highlights the importance of research into the genes and pathways associated with high mortality in patients. Patients afflicted with certain cancers, such as Kaposi's sarcoma-associated herpesvirus (KSHV), could be more susceptible to virus-associated cancers. Further research into the processes involved in this oncogenic reactivation can be immensely helpful to at-risk patients. This study focused on the analysis of human epithelial cells infected with MERS-CoV; both MERS-CoV and SARS-CoV-2 are closely related beta coronaviruses and cause high mortality in patients.

Methods

Analysis was performed on the GSE81909 dataset from NCBI, consisting of human epithelial cells infected with wild type MERS-CoV and time-matched mocks. The data was split into two groups: infected cells at 36 and 48 hours post infection (10 samples) and mock cells at 36 and 48 hours post infection (10 samples). GEO2R was used to determine the top 250 differentially expressed genes (DEGs) between these two groups, with p-values ranging from 8.26e-27 to 2.91e-06. In order to further explore DEGs and identify enriched pathways, the top 250 DEGs were run through STRING-db. Genes and pathways of interest were then examined using the KEGG and GeneCards databases.

Results

The tumor necrosis factor (TNF) signaling pathway and the IL-17 signaling pathway were among the top enriched KEGG pathways (FDR: 4.11e-10, 6.67e-8 respectively). They were both upregulated in infected cells and have been shown to play direct roles in the hyperactive immune response characterized by cytokine release syndrome. Additionally, two virus-associated cancer pathways, KSHV infection and Human T Leukaemia Type-1, were found to be significantly upregulated in infected cells (FDR: 5.55e-6, 0.0038 respectively). The genes involved in the KSHV pathway were members of the CXCL family, specifically CXCL1 and CXCL8. The overexpression of these chemokines can cause increased angiogenesis and tumorigenesis, which can trigger KS progression.

Conclusion

This study identified the KEGG pathway of KSHV infection to be upregulated in cells infected with MERS-CoV; this supports preliminary research regarding the impact of SARS-CoV-2 and some COVID-19 treatments on the lytic reactivation of KSHV and virus-associated cancers. Gaining a deeper understanding of the chemokines involved in this reactivation can assist in the creation of targeted therapeutics which inhibit the replication of KSHV and lower the risk of virus-associated cancers, thus reducing overall mortality.

Potential Pathway Connecting G0/G1 Cell Cycle Arrest with Delayed Apoptosis in MERS Infections

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Introduction

The Middle East Respiratory Syndrome (MERS) and COVID-19 are both deadly infections caused by coronaviruses, and an increased load of the SARS-CoV-2 virus that causes COVID-19 has been linked with increased mortality rates. Therefore, research into reducing the viral load during an infection could help improve patient outcomes. This study investigated the link between cell cycle arrest and apoptosis, and their role in increasing viral replication.

Methods

The dataset GSE45042 contains 32 microarray gene expression profiles of Calu-3 cells, with 15 samples taken from mock infected cells and 17 samples taken from cells infected by MERS coronavirus EMC/2012. Out of these, 3 samples from each of the following groups were selected for differential gene expression analysis in GEO2R: mock infected cells at 0 hours past infection (hpi); mock infected cells at 24 hpi; MERS-infected cells at 0 hpi; and MERS-infected cells at 24 hpi. Genes with an adjusted p-value of under 1E-10 were inputted into String. From there, biological processes of interest were investigated in GeneCards and Gene Ontology.

Results

The String analysis revealed a p-value of 0.048 for the negative regulation of G0 to G1 transition biological pathway, and the involvement of three interlinked genes in the dataset: E2F6, PHC3, and EPC1. GEO2R analysis revealed that all of these genes were upregulated in the MERS-infected samples 24 hpi. E2F6 is an inhibiting transcription factor that regulates genes required to enter the cell cycle from a G0 state. PHC3 is part of a polycomb group complex, which maintains transcriptional repression. As for EPC1, it acts as an enhancer of polycomb.

Conclusion

SARS-CoV and MHV, which are other coronaviruses, have stalled the cell cycle of infected cells at the transition from the G0 to G1 phase [1]. One of the potential effects of cell cycle arrest is a delay of apoptosis in infected cells, allowing for maximized viral replication [1]. Notably, the EPC1 gene has been previously linked to the prevention of apoptosis in acute myeloid leukemia (AML) [2]. Thus, the genes I investigated in my research could provide a potential pathway for future research to investigate whether apoptosis is directly linked to cell cycle arrest in coronavirus infections. If such a link can be made, these genes could become targets for therapies that could reduce the severity of coronavirus diseases.

Keywords: cell cycle arrest, apoptosis, coronavirus

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Promoting the Regulation of Metabolic Processes Pathway to Increase Resistance to SARS-CoV-2

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Introduction

SARS-CoV-2, a type of coronavirus, causes symptoms varying greatly in severity, ranging from a mild fever to being unable to breathe. According to the World Health Organization, there have been over 140 million confirmed cases of COVID-19 and 3 million of those have resulted in death [1]. This study aims to find genes associated with the metabolic process pathway, which controls virus replication, in order to find more precise and safe treatments for SARS-CoV-2.

Methods

We chose the dataset GSE100509, which studied the gene expression of cells both affected and unaffected by wild-type MERS coronavirus. Using GEO, we compared 10 samples from human endothelial cells infected with icMERS; 5 of these samples were obtained 0 hours post infection, while the other 5 were obtained 24 hours post infection. Using tools in GEO2R, we checked the median value alignment and compared how genes were expressed in these two groups. We identified genes with positive logFC values as overexpressed in the 24 hour group and genes with negative logFC values as underexpressed in the 24 hour group. The top 250 overexpressed and top 250 underexpressed genes with statistically significant p-values ($p<0.05$) were analyzed with the STRING database in order to explore their interconnected functions. We used GeneCards to determine the more specific functions of each gene involved in the regulation of metabolic processes pathway.

Results

4 genes in our top 500 most significantly underexpressed were found to be related to the metabolic pathway: HSPA1A, HSP40, BAG3, and PPID. Each had a p-value <.05. We found the HSPA1A, HSP40, BAG3, and PPID genes code for proteins part of the heat shock protein family and are involved in protein folding, transport, and anti-apoptotic function with their logFC values being -5.17, -5.6, -4.82, and -2.89 respectively. In relation to SARS-CoV-2, these genes are involved in viral replication, intracellular immunity, and often cooperates with viruses to promote survival.

Conclusion

Controlled metabolism is crucial for recovery from COVID-19. Here, we use gene expression comparison between icMERS 0 hours after infection and icMERS 24 hours after infection to identify genes and pathways involved in COVID-19. We hypothesize that the underexpression of genes that regulate metabolism, HSPA1A, DNAJB1, BAG3, and PPID, increase the replication of SARS-CoV-2 which causes the deadly effects of COVID-19. Thus, upregulating the HSPA1A, DNAJB1, BAG3, and PPID genes can strengthen an organism's metabolism, increasing resistance to COVID-19. Upregulation of these genes can be achieved through epigenetic therapy, regulating expression of a gene without altering the gene itself through the use of transcription factors [2]. Linking cellular metabolism to SARS-COV-2 offers a solution for the therapy of the symptoms of COVID-19 and could potentially save millions of lives.

Reduction of Cytokine Storm by IDO1/AhR Pathway Suppression in SARS-CoV-19 Patients

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Introduction
Cytokine storms occur when cytokines proliferate excessively and attract cytotoxic T-cells. They can be devastating in many common diseases, including SARS-CoV-19 and cancer. Recently, some of the most severe cases of COVID-19 have been caused by SARS-induced cytokine storms and it has been suggested to be a leading cause of death. The cytokine storm often induces acute respiratory distress syndrome, which can be fatal. In this paper, we investigate targeting the IDO1/AhR cytokine pathway as a potential treatment of COVID-19.

Methods
We analyzed a publicly available GEO2R dataset, GSE163529, containing specimens of COVID-19 patients and a control set of healthy lung tissue to find genes involved in the cytokine response. We used Kegg Pathways and String-DB to view the significant involved genes and pathways. We consulted OMIM for further information on the gene functions. Finally, we performed a t-test to view the statistical significance of our chosen gene.

Results
The two-tailed P value was less than 0.0001, highlighting its extreme statistical significance. From the unpaired t-test, we concluded that there was an absolute difference of 0.74379 in average IDO1 expression between the control patients and the COVID-19 infected samples, with the infected samples expressing IDO1 in greater amounts. The virus stimulates the AhR gene, which creates cytokines, such as IL-1β, IL-6, and TNFα. These cytokines activate IDO1, a heme enzyme, which metabolizes tryptophan into kynurenine, which further activates AhR. This overproduction of cytokines from the positive feedback loop results in a cytokine storm.

Conclusion
Due to its significant role in the cytokine response, we conclude that AhR and IDO1 can be repressed to inhibit deleterious cytokine storms. Prior research by Endo et al., concluded that siRNA can successfully be used to silence the IDO1 gene, which decreases negative immune responses and enhances cell-based cancer immunotherapy. Based on this research, we suggest targeting the IDO1/AhR pathway with siRNA to alleviate cytokine storms and improve the survival rate in diseases such as H5N1 flu, streptococcus, variola, COVID-19, and cancer.

Keywords: SARS-CoV-2, Cytokine Storm, Cytotoxic T-cells, IDO1, AhR, siRNA

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The Response to Cytokine Stimulus in SARS-MA15

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Introduction

COVID-19 is a respiratory disease most vulnerable to weakened immune systems, spread primarily through respiratory coughs and sneezes. The fatal virus has nearly affected 165m people and contributed to almost 3.42m deaths globally. The COVID-19 virus predominantly influences the release of Cytokine cells to target the infected area in a host. COVID-19 precipitates the up-regulation response to Cytokine Stimulation or Cytokine Storm. Cytokine Storm has been associated with causing organ failure, tissue damage, and chronic pain.

Methods

Using the GSE50879 dataset from NCBI to distinguish three samples of SARS-MA15 strain infected mice with three samples of MOCK infected mice. All six samples were taken from lung tissue 2 days post-infection. After analyzing the dataset using GEO2R, I examined the top 250 differentially expressed genes in String. From the enriched pathways found in String, I further researched the response to Cytokine Stimulus biological pathway, along with the genes corresponding within it such as Irgm1. Irgm1 is linked to the pro-inflammatory production of Cytokine cells leading to the initiation of nociceptive sensory neurons causing pathological pain[2].

Results

The response to the Cytokine Stimulus pathway had a false discovery of 8.42e-05. Seven genes from the top 250 (Zbp1, Ddx58, Irf7, Irgm1, Parp9, Parp14, Ifih1) were linked to the pathway, and all were up-regulated in the infected group (2.11+ LogFC values). The up-regulation of these genes suggests a higher expression of Cytokine production is linked to the cellular response to infection from SARS-MA15 strain, and possibly other coronaviruses.

Conclusion

The possible connection of Irgm1 to Cytokine storm and other research has suggested of Dpp4, a gene also involved in a cell's inflammatory process through Cytokine Storm, can be targeted in Diabetes patients to reduce Cytokine inflammation. Given this connection, if there was a drug that included Dpp4 inhibitors, it could help with immunization of the gene Irgm1 in the positive regulation of response to cytokine stimulation, and down-regulating of over-expressed inflammatory responses, thereby decreasing the risk of tissue damage, organ failure, and pain in patients infected with a coronavirus.

Keywords: Cytokine Stimulus, SARS-MA15, Cytokine Storm

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Rheumatoid Arthritis Flares Caused by COVID-19's Upregulation of Prostaglandins

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Introduction
The WHO estimates there have been over 161.5 million cases of COVID-19 worldwide. The elderly population is more symptomatic for COVID-19 and also suffers from inflammatory diseases, like rheumatoid arthritis (RA). We studied COVID-19 patients' risk for more frequent episodes of RA and investigated the biosynthesis of prostaglandins to better understand the biological mechanisms behind this association and develop more effective treatments.

Methods
The dataset GSE30589 consists of microarray gene expression data from Vero E6 (African Green Monkey) cells infected by SARS-CoV. We determined gene expression differences between three samples of mock-infected cells and three samples of SARS-CoV-infected cells at 7 hours post infection using GEO2R. In order to identify enriched biological pathways and interactions, the top 250 genes with the lowest p-values were input into STRING. Due to the limited data for Chlorocebus sabaeus, the analysis was conducted assuming a human sample, considering their genomic similarity. We further investigated the biological processes shared by genes of interest using resources such as Gene Ontology and GeneCards.

Results
The STRING analysis revealed a p-value of 0.0482 for the regulation of prostaglandin biosynthetic process pathway. The analysis included two genes in the pathway, ANXA1 (logFC = 1.48, p-value = 5.14E-08) and FABP5 (logFC = 2.03, p-value = 5.95E-09). ANXA1 acts as a regulator of inflammation, while FABP5 is a fatty acid binding protein that modulates inflammation by regulating PTGES, a Prostaglandin E synthase.

Conclusion
Previous studies show that some COVID-19 patients experience episodes of RA after infection, due to COVID-19-related inflammation[1]. Prostaglandins are directly involved with inflammation, and are a major contributor to RA[2]. Our analysis shows that SARS-CoV upregulates prostaglandin biosynthesis through the FABP5 gene. Because the pathology of SARS and COVID-19 share properties like inflammation, we can extrapolate our results from SARS-CoV to understand COVID-19. We propose that the upregulation of prostaglandin synthesis is the mechanism that links COVID-19 to the onset of RA. As a result, genes involved in prostaglandin synthesis, such as FABP5 and ANXA1, may offer potential therapeutic targets to reduce risk of RA following COVID-19 or similar diseases. We suggest future studies examine the role of prostaglandins as a link between coronavirus infection and other inflammatory diseases.

Keywords: COVID-19, coronavirus, rheumatoid arthritis, prostaglandins, inflammation

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The Role of ATG5 and ATG12 in Autophagy and COVID-19

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Introduction

The epidemic of the recent coronavirus has created dire effects on the global population. The coronavirus disease (COVID-19) is a highly contagious respiratory illness. The symptoms include shortness of breath, coughing, headaches, and nausea, and severity can range from mild to severe. Identifying the causes of COVID-19 is critical in the development of treatment. Thus, our research addresses the question of autophagy and its contribution to COVID-19.

Methods

We used the NCBI GEO dataset GSE164805, which featured the transcriptional profile of severe COVID-19. This study determined the transcriptional expression in 10 severe and mild COVID-19 patients as well as 5 healthy controls. GEO2R analysis was used to compare the two groups, which revealed that 250 genes exhibited different expressions between these groups. We identified enriched pathways among two of these genes using the STRING database and used GeneCards to analyze the functions of such genes.

Results

From our analysis, we identified two main autophagic genes: ATG12 and ATG5. The ATG5 gene plays a key role in autophagic vesicle formation, such as double-membrane vesicles (DMVs) [1]. The presence of double-membrane bound vesicles within coronavirus cells suggests that COVID viral cells utilize DMVs for viral replication and propagation [2]. In addition, overexpression of both ATG5 and ATG12 genes can form the ATG5-ATG12 conjugate, which inhibits antiviral immune response against the coronavirus.

Conclusion

From our research, we found that the ATG5 gene and ATG5-ATG12 conjugate plays a key role in the autophagic pathways. Since the upregulation of autophagy increases virus replication, within the DMV, we can conclude that the ATG5 gene and ATG5-ATG12 conjugate act as proviral factors and apply to viruses such as SARS-CoV-2.

Keywords: COVID-19, autophagy, viral replication, double membrane vesicle, SARS-CoV-2

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Role of Hematopoietic Cell Lineage in SARS-CoV-1

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Introduction

Levels of lymphocytes, white blood cells that protect against infection, and blood platelets, colorless blood cells that help blood clot, are both commonly low in patients with Severe Acute Respiratory Syndrome (SARS-CoV-1)[1]. This study aims to understand the role of hematopoietic cell lineage in SARS-CoV-1, a 2002 virus that targets the epithelial cells of the respiratory tract while also infecting and damaging other cell types and organs, and propose a targeted drug therapy based on hematopoietic genes.

Methods

I used the NCBI GEO dataset GSE1739 consisting of microarray data from 10 normal peripheral blood mononuclear cell samples and 4 samples of peripheral blood mononuclear cells from SARS-CoV-1 infected patients. GEO2R analysis revealed the top 250 genes with significantly different expressions between infected and healthy samples ($p \leq 2.33 \times 10^{-3}$). The STRING database then identified enriched pathways amongst the top 250 genes.

Results

Analysis through STRING identified hematopoietic cell lineage as significantly enriched (false discovery rate = 0.0152), and genes in this pathway from dataset GSE1739 were ITGA6 (logFC = -1.75), IL1R2, MS4A1 (logFC = -3.011), CR2 (logFC = -3.053), ITGAM (logFC = 1.398), GP1BA (logFC = 1.424), and IL7R (logFC = -2.115). Some hematopoietic genes were downregulated while others were upregulated such as GP1BA which initiates signaling events that lead to amplified platelet activation. Downregulated IL7R plays a critical role in lymphocyte development as does MS4A1 that encodes a B-lymphocyte surface molecule which develops and differentiates B-cells into plasma cells.

Conclusion

The upregulated enhanced platelet activation of GP1BA indicates that the low blood platelet levels of SARS-CoV-1 patients may likely be due to the increased consumption of platelets in the damaged lungs and less likely due to a decrease in production of platelets[1]. The downregulation of IL7R and MS4A1 involved in developing and differentiating white blood cells is consistent with the lowered levels of lymphocytes in SARS-CoV-1 patients[1]. As IL7R and MS4A1 are both involved in the pathway developing hematopoietic stem cells into B cells, hematopoietic growth factors such as G-CSF might be used to target the immune system's low lymphocyte levels putting the body at risk of infection[2].

Keywords: SARS-CoV-1, hematopoietic, targeted drug therapy, lymphocytes, platelets

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The Role of Inflammatory Cytokines in MERS-CoV Infection

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Introduction

Coronaviruses are a group of viral agents that affect the upper-respiratory system, causing symptoms that range from mild to lethal. The more lethal strains include MERS, SARS, and SARS-CoV-2. Their symptoms can be attributed to the inflammatory response triggered by infection. As of April 2021, an average of over 8,000 people die every day due to coronaviruses [1]. Due to the current COVID-19 pandemic, it is especially important to research potential treatments for coronaviruses, including research specific to the inflammatory response.

Methods

We used the NCBI dataset GSE81909, which measured mRNA expression in primary human airway epithelial cells infected with wild type MERS-coronavirus (MERS-CoV) (icMERS). With GEO2R, we grouped all the MERS-infected samples together (excluding the 0-hour samples) and all the mock samples together (excluding the 0-hour samples) and analyzed for significant upregulation or downregulation of genes. We input the 250 genes with the lowest p-values into STRING-db to identify enriched pathways. The IL-17 signaling KEGG pathway was among the top enriched pathways and included the genes TNFAIP3, multiple CXCL's, IL6, JUN, and FOS.

Results

The enriched IL-17 pathway has proinflammatory functions. Within the pathway, there were a number of significantly upregulated genes related to the inflammatory response: TNFAIP3 (logFC = 1.306), CXCL2 (logFC = 2.751), CXCL1 (logFC = 0.881), CXCL3 (logFC = 1.553), IL6 (logFC = 0.927), JUN (logFC = 2.513), and FOS (logFC = 5.032). TNFAIP3, the CXCL's, and IL-6 encode inflammatory cytokines, which are induced by viral proteins [2]. JUN and FOS proteins are important parts of the transcription factor AP-1, which is initiated by viral infection and cytokines [3] and induces the expression and secretion of inflammatory cytokines [4].

Conclusion

The upregulation of inflammatory cytokines TNFAIP3, CXCL1, CXCL2, CXCL3, and IL6 seen in the MERS-infected cells could trigger a cytokine storm. The viral infection and production of cytokines would initiate the transcription factor AP-1 (consistent with the upregulation of FOS and JUN seen in the infected cells), which would then continue to feed into the cytokine storm. In short, infection by the MERS virus would cause a detrimental inflammatory response, which accounts for common MERS symptoms as well as those common to other coronaviruses such as SARS-CoV-2. Further experiments should be conducted to explore the underexpression of inflammatory cytokines as treatment for coronavirus symptoms.

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The Role of the Graft-versus-Host Disease Pathway in the Inflammatory Response of SARS

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Introduction

COVID-19 is a highly contagious disease that has infected almost 168 million people across the globe, in which the virus SARS-CoV-2 replicates by infecting human lung cells via the ACE2 receptor. Symptoms generally include a fever, cough, and severe breathing difficulties. The Graft-versus-Host Disease (GvHD) pathway, a significantly enriched pathway in individuals infected with SARS, typically involves donor stem cells targeting recipient cells after an allogeneic stem cell transplantation. The object of the study was to identify the role of the GvHD pathway in the inflammatory response of Calu-3 human lung cells infected with SARS.

Methods

We used the NCBI GEO dataset GSE37827 with data from microarray profiling. It consists of 87 samples, though we only looked at 57, 30 of which were mock infected and 27 were SARS Bat SRBD infected. Comparing these two groups, GEO2R analysis revealed the top differentially expressed genes. We used the top 250 upregulated genes in String-db to identify enriched pathways in SARS, one of which was the GvHD pathway.

Results

String-db identified the GvHD pathway as significant with a false discovery rate of 1.15e-10. Important upregulated genes from the GSE37827 dataset that are involved in GvHD include HLA-C, HLA-B, HLA-E, and IL-6. HLA-C (logFC=0.622) and HLA-B (logFC=0.592) are homologous paralogs that present peptides from the endoplasmic reticulum lumen to identify between host proteins and foreign proteins in the inflammatory response. HLA-E (logFC=0.485) is involved in self-nonself discrimination and functions as a ligand for natural killer cells. IL-6, the most upregulated gene (logFC=1.064), encodes the cytokine that promotes inflammation and the maturation of B cells, and induces a transcriptional inflammatory response through the interleukin-6 receptor.

Conclusion

The significant upregulation of these protein-coding genes in the GvHD pathway is consistent in the inflammatory response in patients with SARS. During parts of the GvHD pathway, the upregulation of these genes can induce severe inflammatory responses, leading to cell death in both transplanted and host tissue. Both GvHD and COVID-19 target stem cells (GvHD targets skin cells and COVID-19 targets lung cells), which leads them to display a similar inflammatory response that may explain the age-severity of both diseases[1]. Drugs that are used to treat GvHD by targeting the upregulated gene IL-6 can also be repurposed for COVID-19, like tocilizumab, an anti-IL6 monoclonal antibody. Since tocilizumab inhibits the expression of IL-6, it can also be used to treat COVID-19.[2]

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Role of ZAP70 and the CD Molecules Gene Family in the Progression of COVID-19

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Introduction

COVID-19, a virus targeting the respiratory system, threatens people who have compromised immune systems. The MA15 virus is a strain of SARS-CoV. The T-cell receptor signaling pathway, which relates to the MA15 strain, plays distinct roles in the immune system during the different stages of life [1]. This dataset provides a potential coronavirus treatment that was inspired by the immune system's flaw of underreacting.

Methods

Using dataset GSE68820 in NCBI, lung tissue from four samples of mock-infected wild type mus musculus were analyzed seven days post-infection. Four samples of strain-infected wild type MA15 mus musculus, also at seven days post-infection, were analyzed. The top 250 differentially expressed genes were inserted into String-db; then, it was found that 15 of the genes were related via the T-cell receptor signaling pathway.

Results

Of these 15 genes (ICOS, PDCD1, ZAP70, ITK, CD8B1, CD247, CD3G, CD28, CD3D, CD8A, GRAP2, LCP2, LAT, VAV1, IFNG), several are part of the CD molecules gene group. These fifteen genes all had a LogFC value of -5.208 or higher. CD247 is important for T-Cell differentiation and creating homodimers. It is a docking site for ZAP70 [1], which is impactful in T-Cell activation. The CD8B1 gene is the coreceptor for MHC in T-Cells. Collectively, these genes stabilize the immune response through their connection to T-Cells.

Conclusion

The body is so selective about its cellular processes that, sometimes, the immune system underreacts towards viruses. This is due to an initial insufficient sense of alarm towards a virus. Fortunately, a drug can stimulate the immune system to recognize viruses as more threatening, thereby amplifying the attack on the virus. The virus will cause less overall damage because of this earlier, more vigorous attack against it. The body does not already work hard enough to eliminate viruses because it does not seek to fatigue itself, through defending itself. So, a healing element to repair damaged proteins and enhance regrowth can be incorporated in the drug. The drug would down-regulate the CD247 and ZAP70 genes, as they are connected to the immune system. This drug will safely encourage the immune system of MA15 strain-infected patients. It can make the wishful thinking of an upgraded immune system into reality, especially since extra bodily work is a factor that can be countered through the drug's healing element.

Keywords: MA15, T-Cell, immune system, virus elimination, ZAP70, CD molecules

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Stress Response and TLR3 in MA-15 SARS Coronavirus

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Introduction

COVID-19 has affected over 136M people and has caused 2.9M deaths worldwide. A SARS-CoV virus adapted for mice, called MA15, has been created and used for research about SARS-CoV-2 -- the virus that causes COVID-19. In mice, MA15 has spike proteins that bind to its receptor -- mouse ACE2 -- in order to infect its host and attack the immune system. Inoculation with MA15 has many similar aspects to the human SARS. There has been little research done about the role of the TLR3 gene in SARS-CoV-2 or other SARS related viruses, and how it in turn affects the disease COVID-19. The purpose of this study was to research how the TLR3 gene affects MA-15 inoculated mice, and what implications that has for the human-affected disease, COVID-19.

Methods

The NCBI GEO dataset GSE68820 was used, which consisted of a microarray expression comprising data from 9 lung tissue samples of MA15-inoculated mice. Five of the lung tissues were examined from mice without the TLR3 gene, while the other four were examined from wild-type mice with the TLR3 gene. GEO2R analysis revealed that the expression of many genes involved in response to stress were different in the wild-type mice compared to mice with the TLR3 gene. Further, with analysis of the top 250 genes in the STRING database, we found enriched pathways in genes responsible for response to stress.

Results

From analysis on STRING, the “response to stress” pathway was found to be enriched in TLR3- mice, with a false discovery rate of 0.0494. Genes we found of importance in this pathway were Cxcr2 (logFC = -1.296), Cnot7 (logFC = -1.216), and Saa2 (logFC = -1.793) -- all of which were all downregulated. Cnot7, a part of the CCR4-NOT complex, plays an important role in the first step of mRNA degradation, often determining the rate of degradation; as well as general regulation of transcription. Saa2 codes for a major acute phase protein, which is expressed significantly more in response to inflammation. Cxcr2 codes for a protein receptor called IL-8, which upon binding activates neutrophils to migrate to sites of inflammation and lead immune response.

Conclusion

The downregulation of genes in the stress response pathway in mice lacking the TLR3- gene demonstrates that the TLR3- gene is crucial in the body’s immune response when combating viruses. The gene is key in the reception of viruses and other pathogens and the activation of cytokines. This information can be critical in treating patients who are infected with viruses like MA15. One possible solution could be gene therapy with a TLR3 agonist, such as the drug Imiquimod. This may result in an upregulation of the genes linked with an absence of TLR3, and may bolster the stress response pathway in patients. Identifying this link between stress response and TLR3 in MA15 could pave the way for future research into SARS-Cov-2 virus and COVID-19 treatment.

Keywords: SARS-Cov-2, gene therapy, MA-15, TLR3

Targeting Symptoms Caused by Proinflammatory Cytokines

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Introduction

Coronaviruses have made a large global impact in the last few decades, causing pandemics and changing the way people experience their daily lives. SARS, caused by the coronavirus SARS-CoV, has no current preventative treatments, only supportive treatments that ease adverse symptoms of viral infection. These are varied in type and effectiveness depending on the patient, so examining treatments more universal in method, yet still are personalized to the patient, may be beneficial. Thus, we studied how the optimal amount of proinflammatory cytokines needed for an immune response against SARS-CoV could be achieved by regulating the cytosolic DNA sensing pathway, since these cytokines are important in immune responses yet can be responsible for severe physiological reactions when levels are too high.

Methods

We used NCBI GEO dataset GSE17400, which contained a gene microarray of SARS-CoV infected, DOHV infected, and uninfected (mock) human bronchial epithelial cells. We selected the SARS-CoV infected and mock infected cells 48 hours-post-infection to compare. We used GEO2R analysis to sort the genes by most differentially expressed, and used the top 250 of them ($p \leq 8.14E-07$) to identify enriched pathways using the STRING database.

Results

We took a look at the enriched cytosolic DNA sensing KEGG pathway and the functions of this pathway: it plays a major role in immune defences against double-stranded DNA viruses. One specific gene in this pathway is DDX58, which is upregulated in the SARS-infected group compared to the mock-infected group and has a logFC value of 1.95. DDX58 is used as an immune receptor and plays an important role in the activation of antiviral responses, including production of type 1 interferons and proinflammatory cytokines. DDX58 also encodes a RIG-I-like receptor that recognizes short double stranded viral RNA and is used in the RIG-I-like signaling pathway. The RIG-I-like signaling pathway is used in bigger pathways like the RIG-I/MDA5 mediated induction of IFN-alpha/beta pathways. RIG-I is a gene that recognizes cells infected with a virus and is responsible for the type-1 interferon response. MDA5 is a gene that can detect double-stranded viral RNA.

Conclusion

The DDX58 gene's major function in the cytosolic DNA sensing pathway is aiding production of proinflammatory cytokines, which can lead to cytokine storms that worsen symptoms of severe SARS infections. To prevent this, we can first allow normal DDX58 expression after a SARS infection, then downregulate or inhibit the gene, potentially through downregulating RIG-I signalling using the ISG15 protein, if a cytokine storm is sensed. Using this method, we can reduce damage caused to the patient by SARS-CoV infection without hindering the patient's initial immune response. Furthermore, regulating the cytosolic DNA sensing pathway may reduce the risk of other cytokine-induced inflammatory diseases and have implications in treating other coronavirus infections as well. However, inhibiting this pathway may lead to negative side effects, such as a lacking immune response for future viral infections.

Tissue Remodeling in Lung Adenocarcinoma and Idiopathic Pulmonary Fibrosis

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Introduction

Lung Adenocarcinoma (LA) is a type of non-small cell lung cancer. Idiopathic Pulmonary Fibrosis (IPF) is a disease characterized by the buildup of scarred tissue in the lungs. These findings may be used to improve patient health which targets the specific genes or proteins, by showing the outcome when the contradictory gene expression is elevated or present in a greater amount.

Methods

Two data sets done by expression profiling by array, GSE 140797 for LA and GSE 73395 for IPF, were analyzed using GEO2R. Samples were sorted for adjusted p-values less than 0.05 and sorted based on logFC values. String-db, Genecards, and Kegg were used to find correlations between the two diseases.

Results

LA has an upregulated expression of MMP1, MMP9 and ANLN. IPF has an upregulated expression of MUC20 and a downregulated expression of ANLN. MMP1 is involved in proteolysis of the extracellular matrix, tissue remodeling, and breaks down collagen of type I, II, III, VII and X. MMP9 is involved in the breakdown of proteins into amino acids in the extracellular matrix, tissue remodeling and breaking down collagen of type IV and V. MMP9 is activated when it is split by extracellular proteinases. MUC20 inhibits the HFG-induced proliferation of MMP1 and MMP9. ANLN is a protein involved in cell growth, migration, and cytokinesis. Cancer is a mutation which does not have a functioning cell cycle, meaning that ANLN is accordingly upregulated, leading to quick growth with quick tissue remodeling involving MMP1 and MMP9.The ANLN levels in IPF are accordingly downregulated as scarred tissue cells do not grow, being as MMP1 and MMP9 would remodel the tissue but are inhibited by the increased amount of their inhibitor MUC20.

Conclusion

As LA expresses genes that are inhibited in IPF, the ANLN expression follows the same pattern of being more present in LA. If the ANLN gene was to be targeted using radiation, a risk occurs where the patient may show signs of IPF after treatment potentially because of the body producing excess MUC20 to counteract the no longer needed excess MMP1 and MMP9. Additionally, MMP1 has shown signs of being an inflammatory cytokine for COVID-19. These are genes which are involved in lung diseases and are potential drug targets.

Keywords: Lung Adenocarcinoma, Idiopathic Pulmonary Fibrosis, tissue remodeling

TLRs May Drive Inflammation in SARS-CoV

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Introduction

Like COVID-19 caused by SARS-CoV-2, SARS caused by SARS-CoV is a highly contagious and sometimes fatal respiratory disease. The Envelope (E) protein in SARS-CoV has previously been shown to interact with the host cell in mice to activate the immune system causing inflammatory cytokines resulting in severe SARS disease and subsequent death [1]. Locating additional inflammation-causing pathways triggered by the interaction of the host with E could result in drug development that can target these pathways to prevent inflammation. Since the E proteins found in the membranes of SARS-CoV and SARS-CoV are approximately 94.74% similar [2], drugs targeting inflammatory pathways caused by SARS-CoV may provide a foundation for the study of potential drugs to reduce inflammation in COVID-19 and vice versa.

Methods

We selected 3 MA-104 (*chlorocebus sabaeus*) cell line samples infected with recombinant SARS-CoV without E (rSARS-CoV ΔE) and 3 samples infected with SARS-CoV wild type with E (SARS-CoV) at 24 hours post-infection from the NCBI GSE30589 dataset. Using GEO2R we identified the top 250 differentially enriched genes between the two, with the lowest p-values. We then analyzed these genes in STRING for the organism *homo sapiens* to determine any interactions and to identify Gene Ontology (GO) and KEGG enriched processes and pathways.

Results

We found that GO pathways that regulate toll-like receptors TLR2, TLR3 and TLR4 and the TNF signaling KEGG pathway were enriched in our top-250 differentially enriched gene set. Further analysis showed TLR and NF-Kappa B signaling pathways were also enriched. Key upregulated genes and their LogFC were FOS-1.28, TNFAIP3-1.08, MAP2K3-0.803 and NFKBIA-0.627. TLR2 had the lowest p-value of all TLRs in the dataset (p-value = 0.00109).

Conclusion

These TLRs, especially TLR2 may sense the E protein in SARS-CoV as TLR2 does in SARS-CoV-2 [3]. Regulators of TLRs and TLR pathway genes are then upregulated in response to the activity of the TLRs. In addition to activation by TNF-α, the NF-KB pathway is also stimulated by TLRs to generate proinflammatory cytokines and chemokines which may lead to cytokine storms, drugs that inhibit NF-KB could prevent this. Further study of the role of TLRs is needed.

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Transcriptional Enrichment of TNF Pathways and Related Processes from MERS and SARS Coronaviruses

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Introduction

The Middle Eastern Respiratory Syndrome (MERS) is heavily related to Severe Acute Respiratory Syndrome (SARS) in that they are both similarly caused by coronaviruses, being responsible for severe outbreaks in 2012 and 2019 respectively. SARS-CoV-2 (COVID-19) is a current scientific urgency that has caused over 3 million deaths worldwide. While we know of several similarities in viral mechanisms between MERS and SARS coronaviruses, the linkage in genetic response to the coronaviruses is a lesser studied topic. This leads us to specifically question: how does enriched gene expression in cells exposed to the MERS coronavirus compare to control samples post-infection, and what can this tell us about similarly affected processes in SARS coronaviruses? Based on our analysis of enriched functions in MERS samples, we hypothesize that the Tumor Necrosis Factor (TNF) signaling pathway and associated processes will be enriched in SARS.

Methods

Using public GEO data set GSE65574, which contained microarray data for Human Calu-3 cell responses to MERS, we compared gene expression in control cell samples to infected samples at 24 hours post-infection. We then used STRING-db to pinpoint several enriched processes and pathways corresponding to the 250 most enriched genes determined from GEO2R. In KEGG and GO, we further researched the mechanisms of enriched pathways. We utilized similar resources and methodology to analyze the GSE30589 SARS dataset from GEO—which contained data on *Chlorocebus aethiops* cells exposed to SARS-CoV-1—to verify our hypothesis.

Results

Based on functional enrichment analysis of the top 250 most enriched genes, we identified a prominent, upregulated pathway in the infected MERS samples: the Tumor Necrosis Factor (TNF) signaling pathway. Five significantly upregulated genes present in the pathway include TNFAIP3, TRAF3, IL6, NFKBIA, and JUN. In the SARS sample, we found the same genes to be similarly upregulated, and the TNF signaling pathway to also be highly upregulated.

Conclusion

TNF, the signaling protein in the TNF signaling pathway, coordinates apoptosis in post-infection inflammatory episodes. Upregulation, as seen in MERS and SARS, creates irregular signaling which inhibits the pathway's ability to deliver an appropriate immune defense towards a virus and creates imbalance between cell survival, proliferation, differentiation, and programmed cell death—a weaponizing mechanism in the coronaviruses. Hence, it is likely that the severity and immune dysfunctionality resulting from coronaviruses is associated with the abnormal upregulation of TNF. For COVID-19, various medications can be proposed to provide a valuable treatment for symptoms after infection. TNF inhibitors—such as adalimumab and other 'TNF blockers'—would be highly useful in suppressing some of the post-infection effects. In conclusion, drugs inhibiting the TNF can play a meaningful role in treating coronaviruses like COVID-19, and will lessen its hindrances to immune responses. More research and clinical trials of specific drugs targeting its suppression after infection is encouraged, for it can help mitigate a part of the virus' symptomatic severity.

Upregulated Genes in SARS-CoV-DeltaE Samples Found to Play a Role in TNF Pathway and Gene Expression

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Introduction

Since the beginning of the outbreak in 2019, COVID-19 has emerged as a major global concern resulting in an increasing number of deaths. Early on in the pandemic, lack of knowledge about the disease made it difficult to treat and cure. Fortunately, with the help of physicians' efforts, scientists and researchers have come up with numerous vaccines. This prompts us to wonder which aspects of COVID-19 scientists could next target to develop more effective vaccines.

Methods

We began by selecting the dataset GSE30589 from NCBI, which consisted of microarray expression profiling data from 9 samples of mock-infected cells and 12 samples of cells infected with SARS-CoV-DeltaE, then analyzed it using GEO2R. This provided us our top 250 genes that we inputted into String-db to observe pathways and biological processes that connected the genes. We selected the TNF-signaling KEGG pathway and three closely-connected genes from the pathway—JUNB, JUN, and FOS. Using GeneCards, we identified that these three genes code for basic leucine zipper proteins (bZIP) which make up transcription factors used in gene expression.

Results

Through our GEO2R analysis, we were able to determine the logFC values of our three genes—JUN, JUNB, and FOS—which were -1.53, -1.45, and -2.81 respectively. JUN functions as a protein encoder similar to the viral protein and a regulator to gene expression. JUNB exerts dual action on the cell cycle to act as a cell proliferation inhibitor and tumour suppressor. FOS is involved in gene expression, proliferation, and apoptosis. Consequently, we concluded that all three of the upregulated genes played a role in gene expression in the cell cycle, especially since all genes are members of the transcription factor activator protein (AP)-1 family, and the observed pathway was the Tumor Necrosis Factor (TNF) Signaling Pathway, which is involved in physiological and pathological processes, including proliferation, apoptosis, and modulation of immune responses and induction of inflammation.

Conclusion

The genes JUN, JUNB, and FOS all made up transcription factors that played a role in gene expression, which prompted the question of whether a correlation existed between the two. Additionally, these genes were also found within the TNF pathway which made us wonder whether there existed a correlation between the pathway and COVID-19. Further research can be conducted on these specific genes as well as the TNF pathway, which may help scientists to potentially identify how these genes might play a key role in pathogenesis of COVID-19. Hence, if a connection is identified, scientists can find a way to target these genes to increase the effectiveness of the vaccine and alleviate symptoms of the disease in general.

Keywords: TNF Signaling Pathway, JUN, FOS, and JUNB, gene expression

Upregulation in TNF Signaling Pathway in MERS- CoV

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Introduction

MERS- CoV is an infectious respiratory disease with a case fatality rate of 37.5% in Saudia Arabia in 2020. It is similar in pathogenesis to SARS-CoV-2, a disease that has resulted in 3 million deaths worldwide. The TNF signaling pathway is essential in physiological and pathological processes: immune responses, inflammatory responses, cell proliferation. TNF is a cytokine with effects on endothelial function and is considered an anti-cancer agent. An upregulation in this pathway heightens inflammatory responses and the increase of TNF in a patient's bloodstream increases susceptibility to insulin resistance. We hypothesize that there exists a positive correlation between the Coronavirus infection and increased insulin resistance in diabetic patients. This relationship could lead to the possibility of developing new drugs to combat coronavirus and a better understanding of the long-term effects.

Methods

We downloaded gene expression values and volcano plots from the dataset GSE100509 through NCBI GEO. The GSE100509 dataset focused on the endothelial cell transcriptome response to wild type MERS-CoV and consists of 25 control expressions and 25 icMERS expressions that were collected at 5 different periods through expression profiling by an array. After separating the samples into control and icMERS groups, we used GEO2R to find the top 250 genes with the lowest p values (range was set to < 0.01). Next, we separated these genes into upregulated and downregulated groups according to the logFC value (positive log FC signifying upregulated, negative logFC signifying downregulated). Finally, we ran the upregulated genes through STRING-DB and analyzed the correlating KEGG Pathways. Gene Cards aided in identifying gene functions and drugs related to the genes.

Results

After inputting the upregulated genes into STRING-DB, we noticed one of the enriched KEGG Pathways was the TNF Signaling Pathway. TNF and IL6 initiate inflammation as well as control immunity through different mechanisms. This pathway also had the lowest false discovery rate (0.0029). The 5 genes related to the TNF signaling pathway are IL6, CEBPB, BIRC3, BCL3, and TNFAIP3. IL6 and CEBPB are significant in the human immune system and play an important role in how the system readily responds to infectious diseases. In addition, BIRC3, BCL3, and TNFAIP3 have relations to functions that contribute to apoptosis's automatic response.

ConclusionWild type MERS-CoV depicts an upregulation of genes in the TNF signaling pathway. This upregulation results in an intensified inflammatory response. While TNF is a necessary component of human function, abnormally high levels of TNF require stabilizing inhibitors. Insulin resistance becomes more likely due to the high levels of TNF. 1 in 10 Americans have type 2 diabetes and our study provides insight into future consequences of SARS-CoV-2 for diabetic patients. Further investigation into TNF related genes, especially IL6, could test drugs like methotrexate to inhibit TNF upregulation.

Keywords: TNF signaling pathway, MERS-CoV, insulin resistance

Upregulation of Collagen Coding Genes in Cells Infected with Coronavirus

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Introduction

Typical patients infected with COVID-19 will have relatively mild flu-like symptoms and recover without any special treatment. The body usually does a sufficient job of fighting and killing the virus by itself. However, around 1 in 6 of cases will have more severe symptoms that require hospitalization [1] due to the body's immune system targeting its own healthy cells and destroying tissue, which can lead to death. Some triggers for this autoimmune response are certain types of collagen, a protein that is found nearly everywhere in the body.

Methods

I used the NCBI GEO DataSet GSE45042. This dataset has 3 Calu-3 2B4 cells infected with Human Coronavirus EMC 2012 and 3 Calu-3 2B4 mock infected. Samples were taken from these cells at 0, 3, 7, 12, 18, and 24 hours post infection. Analysis of the 24 hpi group of cells using GEO2R, a website that can compare 2 or more sample groups and show different expressions of genes, showed that there were significant differences between the infected cells and the mock infected cells. Using STRINGdb, an online database that can look at and highlight connections between proteins, I looked at the pathways of the top 250 genes with p value ≤ 4.27 x 10-7 and found a cluster of significant genes from the collagen family which were tightly connected.

Results

Analysis using the STRING database showed a cluster of genes from the collagen family. The 5 genes in this cluster are COL3A1, COL23A1, COL20A1, COL9A1, and COL9A2 and are all a part of the collagens gene group, COL. All 5 genes are upregulated and significant(logFC ≥ 2.6486698; p-value ≤ 3.46 x 10-7), and COL9A2 was the second most upregulated (logFC = 4.9154569). This gene gives instructions for making type IX collagen, which is found in joint or cartilage areas like the trachea and the larynx. These tissues can be attacked and damaged from an autoimmune response [2].

Conclusion

An upregulation of the protein coding genes COL9A1 and COL9A2 could trigger an immune response in the body. Part of the response is a cytokine storm, where the body produces too many cytokines and they attack the body's cells. A cytokine storm could occur due to an infection or an autoimmune response from certain collagen types [3]. Discovering a way to prevent or treat a cytokine storm could alleviate symptoms and prevent death from viruses or diseases like COVID-19. Some immunosuppressive drugs are already in use: Tocilizumab, for instance, reduces the risk of death by 45% [4]. However, it also doubles the risk of another infection due to its effects on the immune system overall. Further research and experimentation will be required to find an effective treatment.

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Upregulation of Leukocyte Migration Related Pathways in Autism Spectrum Disorder Patients

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Introduction

Autism spectrum disorder (ASD) is a developmental disability that is known to cause social and behavioral issues. It is estimated that about one in 68 children are affected by ASD. Unfortunately, no single allele is common amongst all of those who share the disorder, and no single gene has emerged to be the root of it either. However, it was recently discovered that white blood cell data recorded from toddlers showed a critical network that is disrupted in infants suffering from Autism spectrum disorder.

Methods

A superset on NCBI (National Center for Biotechnology Information) Expression Omnibus (GSE111176, made up of GSE42113 and GSE111175) which consisted of 288 samples of blood samples with leukocytes was taken from developing infants and toddlers. Of those 288 samples, 24 blood samples from ASD patients, as well as 24 samples from healthy infants were selected to be analyzed with GEO2R. Downregulated genes were separated from the upregulated genes found in ASD patients, and were ordered by P values less than 0.05, as well as LogFC values. StringDb was used to find pathways between downregulated and upregulated genes, while KEGG (Kyoto Encyclopedia of Genes and Genomes) was used to analyze these pathways.

Results

Important upregulated genes in ASD were found to be ITGB2, MMP9, ITGAX, PTPN6, CX3CR1, and LEP. They were part of the biological pathway linked to leukocyte migration. Using KEGG, these pathways were soon identified to play roles in cytokine-cytokine receptor interaction, leukocyte transendothelial migration, complement and coagulation cascades, proteoglycans in cancer, and natural killer cell mediated cytotoxicity. PTPN6 was discovered to be a product of inhibition of cell migration, proliferation, and survival. Matrix Metalloproteinase 9 (MMP9) held roles in two of the mentioned pathways, which were proteoglycans in cancer, and leukocyte transendothelial migration. ITGB2 held multiple roles in the pathway of leukocyte transendothelial migration, as well as working together with ITGAX in complement and coagulation cascades to induce phagocytosis. LEP and CX3CR1 are related in the cytokine-cytokine interaction pathway, although they are part of different families (CX3C subfamily and Prolactin family).

Conclusions

Leukocyte migration and its related pathways are upregulated in ASD patients when compared to non-ASD patients, and can be used to better determine how Autism Spectrum Disorder is caused. An upregulation of leukocyte activity in the blood could eventually be a method of detection and act as a test of diagnosis for ASD, as no efficient diagnosis test exists currently.

Upregulation of p53 Genes in Colorectal Cancer Pathway to Affect Tumorigenesis

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Introduction

The Middle East Respiratory Syndrome (MERS) is closely linked to the SARS-CoV-2 virus, which causes the disease COVID-19. SARS-CoV-2 has infected nearly 32 million people globally, but due to its novelty, the lasting effects and consequences of those who suffered from the virus are still widely unknown. Our research concerns the genetic overlap between MERS and colorectal cancer. Specifically, we examine what effects a pathogen similar to SARS-CoV-2 can have on inducing genetic predispositions to colorectal cancer. Both diseases primarily affect the same age group (74+), so discovering links between colorectal cancer and COVID-19 could help prevent the risk of developing cancer in COVID-19 survivors.

Methods

We analyzed the NCBI GeoDataset GSE100509 (5 icMERS vs 5 mock at 36 hours post-infection) to investigate the effects that diseases like SARS-CoV-2 may have on the genetics of our immune system. The samples were derived from Homo sapiens and were analyzed using expression profiling by array. Using STRING-DB, we entered the top 250 differentially expressed genes in our dataset, sorted by a statistical t-test ($p<0.05$) to determine enriched biological processes and pathways shared among the genes. To help us define the roles of the specific genes and pathways of interest, we used Gene Ontology and GeneCards. Lastly, we used KEGG to further understand associated pathways in our dataset.

Results

Through a STRING analysis, we found the Colorectal Cancer pathway to be enriched in our dataset, which had a false discovery rate of 0.04 and a count in network of 5 of 85. The genes MYC, JUN, and GADD45G are involved in the pathway and are significantly upregulated in the icMERS group, with logFC values of 3.06, 3.41, and 6.00, respectively. MYC acts as a proto-oncogene by activating the p53 signaling pathway. JUN plays a role in colorectal tumorigenesis while also binding to the USP28 gene, which is involved in MYC stability. GADD45G is an inhibitor of the CDC1 gene, which promotes cellular senescence, leading to the inhibition of cessation of cellular division.

Conclusion

The upregulations we examined in our target genes may lead to cell-cycle disruptions including extended cell-life cycles and increased cellular proliferation in COVID-19 survivors. Infection by a coronavirus such as MERS or SARS-CoV-2 may render older age groups more vulnerable to risky diseases such as colorectal cancer. It is also especially concerning that COVID-19 and colorectal cancer primarily affect the same age group. The upregulation of the GADD45G gene and its involvement in the inhibition of cellular senescence within the p53 signaling pathway indicates that targeted gene therapy for GADD45G can be utilized in survivors to prevent colorectal cancer tumorigenesis. Similar preventative treatments for the genes JUN and MYC may be effective in cancer prevention. Identifying the link between coronaviruses and cancers may be key in reducing mortality rates as the long-term effects of COVID-19 begin to take hold.

Upregulation of the TNF Signaling Pathway as a Potential Pharmacological Target for Heroin-Addicted Individuals

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Introduction

Cocaine is a highly addictive stimulant that acts on the dopamine neurotransmitter system in the brain. Overdose deaths related to cocaine have been steadily increasing since 2014, with existing addiction treatments having limited capabilities. Therefore, the purpose of this investigation was to identify a specific set of genes that had the potential to become genetic biomarkers or targets for pharmaceutical treatments, with the hopes of improving and expanding upon current cocaine addiction recovery options. Identifying groups of enhanced or diminished genes in cocaine users may provide viable targets for pharmaceuticals designed to curb the addictiveness or the health effects of cocaine.

Methods

We used the dataset GSE54839 from the NCBI database to investigate the genetic differences between groups of chronic cocaine abusers and drug-free subjects. The dataset consists of 60 samples, 30 per test group, and has Homosapien participants. GEO2R identified and separated 370 significant genes into groups of upregulation or downregulation. We then analyzed these genes using String-dB, which provided information about prominent KEGG pathways and biological (GO) processes. We chose the tumor necrosis factor (TNF) pathway, which had the lowest false discovery rate out of both downregulated and upregulated groups.

Results

Out of all the 48,760 probes, only 369 were identified $p < 0.000001$ and analyzed in this paper. Cell surface signaling was the most notable GO process related to the KEGG TNF Signaling Pathway, with 7 out of 8 genes shared with the pathway. We also looked at the response to the cytokine GO process in which 6 out of 8 genes related to the pathway. This indicates that the TNF KEGG pathway is related to cell signaling and the cytokine pathway. Additionally, the degradation of certain nuclear receptor transcription factors, such as Retinoid-X-Receptors (RXRs), was found to be induced by the expression of the TNF signaling pathway.

Conclusion

In previous studies, the TNF signaling pathway's upregulation due to cocaine use had been linked to neuronal degradation and inflammation. RXRs, in particular, play a central role in dopaminergic signaling, dopamine-mediated locomotor activity, and reward processing in the striatum. Thus, the TNF pathway holds a crucial position in inhibiting a person's natural dopamine response, increasing the addictiveness of cocaine and a person's dependency on the substance. We believe that it has the potential to become a biomarker or a pharmaceutical target.

Keywords: cocaine addiction, TNF, dopamine

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Upregulation of the Type 1 Interferon Signaling Pathway in HIV

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Introduction

Although HIV and SARS-CoV2 are largely unrelated viruses (besides their destructiveness and contagion) they share similarities in that they infect a wider variety of tissues than most people think they infect, and they cause brain damage from inflammatory responses such as encephalitis. Although current antiretroviral therapies decrease the effects of HIV, brain damage is not completely avoided. The object of this study was to understand the role of the type 1 interferon pathway in HIV and SARS-CoV2 associated brain damage and propose a targeted drug therapy.

Methods

We used the NCBI dataset GSE155352 and compared control vs HIV associated inflammation or dementia not differentiating the various neural tissues involved in the data. We then analyzed the top 250 with STRING (pval <=1.39E-04) and then with GO and various scientific articles.

Results

Functional enrichment analysis in STRING identified the Type1 Interferon Signaling pathway as significant (false discovery rate =2.34e-05). Members of the pathway from GSE
Were HLA- A,B,C,E,F, STAT1, XAF1, IFITM1, and PSMB8. The most upregulated gene, XAF1 (logFC=1.53) is an interferon induced tumor suppressor gene that leads to apoptosis. HLA genes code for major histocompatibility proteins, cell surface proteins that are on almost every cell and increase in expression due to most infections, due to their function being to signal immune cells that there is an infection. STAT1 triggers various oxidative stress-related proinflammatory genes to be transcribed and is currently a target for research on drugs to decrease its expression in patients with chronic inflammation. All genes mentioned were upregulated in the HIV encephalitis and dementia samples.

Conclusion

This is notable because it is a held belief in medicine that less interferon and STAT1 signifies a compromised immune system (and often it does); however, findings from studies on COVID patients show that upregulated from normal t1 interferon pathways lead to higher mortality rates and severe inflammation-related complications-- even more than the patients who have lower than normal INF-beta levels. AG-490, a chemical inhibitor of JAK (enzyme upstream of STAT1) has decreased STAT1 activity, so this could be a potential treatment for patients with HIV encephalitis and COVID, as well as other inflammatory diseases (autoimmune and caused by viruses). High baseline INF-beta levels could also be used to predict the severity of inflammation if a patient were to get COVID.

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CPA3 Is a Potential Biomarker for COVID-19 Severity

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Introduction

The world is currently confronting a COVID-19 pandemic caused by the SARS-CoV-2 [severe acute respiratory syndrome coronavirus 2] novel coronavirus, which begins as a lower respiratory airway illness like asthma but progresses in severity to clinically manifest as severe difficulty with breathing. As with asthma, emerging research shows that human mast cells contribute to the pathophysiology of COVID-19 severity. Mast cells infiltrate the lung and undergo granulation releasing bioactive mediators into the lung including cytokines and the carboxypeptidase A3 (CPA3) enzyme, which is expressed exclusively by mast cells. Because the severity of COVID-19 illness can quickly progress from mild symptoms (excluding troubled-breathing) to severe (blood oxygen levels < 94 percent, a high breathing rate > 30 breaths/min, and signs of severe lung disease) which is life threatening, identifying a biomarker for monitoring severity of COVID-19 illness is highly sought after by both clinicians and researchers. The findings of this research strongly support CPA3 as that potential biomarker**.**

Methods

To identify any differentially regulated genes that could provide insight into pathophysiological differences between mild and severe COVID-19 illness, gene expression data in the **GSE164805** dataset in the **GEO database** containing 5 mild and 5 severe COVID-19 patients was analyzed as a comparison group using the site available GEO2R statistical analysis program.

Results

The proteolytic enzyme carboxypeptidase A3 (CPA3) was significantly over-expressed in patients with severe COVID-19: **adj. P.Val:** 0.00000164, **P.Val:** 2.94E-11, **t-stat:** 26.29193, **B-stat:** 15.33391, **logFC:** 5.241725. CPA3 is well known to be elevated in persons with asthma and is an accepted biomarker for the inflammatory status of human airways.

Conclusion

Results support CPA3 as a biomarker that informs about the severity of COVID-19 illness, thus should be clinically monitored. The logFC of 5.241725 indicates CPA3 is expressed at least 30 times more in severe COVID-19 patients. CPA3 levels should also correlate with the number of lung mast cell infiltrates because it's exclusively expressed in mast cells. Mast cell abundance in the lungs might also be a contributing factor for the well reported cytokine storm occurring in severe COVID-19 patients because granulation also releases cytokines. This hypothesis can be tested by graduating K18-hACE2 mice (model for severe COVID-19) intake of Nerita versicolor carboxypeptidase inhibitor (NvCI) then monitoring the severity of COVID-19 illness. NvCl is a strong natural CPA inhibitor highly specific for CPA3. If curtailing CPA3 expression also reduces COVID-19 severity, a new targeted treatment is identified.

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miRcore Volunteer Program and GIDAS History

Early 2011

- A small group of students meets Saturdays as miRcore volunteers to advocate for personalized medicine.
- Volunteer students vote Alzheimer's as their disease of focus.

2011-2012 School Year

- Huron GIDAS (Genes In Diseases And Symptoms) founded in 2011.
- Huron GIDAS spreads awareness of Alzheimer's disease through posters, assemblies with invited speakers, videomaking, and a fundraiser for Alzheimer's research.

2012-13 School Year

- Half-day Computational Biology summer camp for high school students offered through Ann Arbor Rec&Ed in 2012.
- Community, Pioneer, and Skyline high school GIDAS chapters founded in 2012.
- Diseases of focus: autism (Huron and Skyline), breast cancer (Pioneer), type 1 diabetes (Community).
- Saturday volunteer students start to analyze gene expression data using GenePattern tools.
- Two students participate in the DREAM (Dialogue for Reverse Engineering Assessments and Methods) 7 challenge subsection and earn an unofficial ranking of 6th and 16th competing with 43 professional computational teams.
- The first Genes and Health contest in February 2013 with the sponsorship of the University of Michigan WISE (Woman In Science and Engineering), Janssen, and Zingerman's.
- Fundraised over $13,000 for microgrants to support researchers in autism, breast cancer, and type I diabetes.

2013-14 School Year (Disease of Focus: Alzheimer's Disease)

- Computational biology summer camp for high school students held in the University of Michigan in 2013 with the help of WISE.
- University of Michigan GIDAS becomes active.
- Milan and Farmington high school GIDAS chapters founded in 2013.
- Students begin to use command line computations for gene expression data analysis.
- The second Genes and Health contest in February 2014 with the sponsorship of WISE and Janssen.
- Music and dance performances for Alzheimer's patients in 2014.
- The first high school GIDAS research conference at the University of Michigan with the sponsorship of WISE, Janssen, and Hyundai.
- Fundraised $8,000 for a microgrant to support Alzheimer's disease research.

2014-15 School Year (Disease of Focus: Parkinson's Disease)

- Computational biology summer camp for high school students and R programming camp for middle school students and above held in 2014 with the help of WISE.
- A team of "Those Kids without PhDs" participated in the Alzheimer's Disease Big Data DREAM Challenge #1, subsection 2, ranking 11th in competition with professional computational biologists.
- Mercy and Bloomfield Hills High School GIDAS chapters founded.
- Half-day camps were offered throughout the school year.
- The third Genes and Health contest in February 2015 with the sponsorship of WISE.
- miRcore volunteer committees were formed for specific activities, including GIDAS support.
- Students perform group research on Parkinson's and prepare papers for the *Journal of Emerging Investigators*.
- The second high school GIDAS research conference at UM with the sponsorship of WISE, the Prechter Family Fund, and Hyundai.
- Fundraised $5,000 for a microgrant to support Parkinson's disease research.

2015-16 School Year (Disease of Focus: Lung Cancer)

- Summer camps using TCGA (The Cancer Genome Atlas) datasets and R were offered at the University of Michigan.
- Student papers published in the *Journal of Emerging Investigators*.
- GIDAS chapters founded outside of Michigan.
- Online meeting attendance available.
- Pilot "Lab on Wheels" program for Huron high school biology classes with the sponsorship of the Ann Arbor Area Community Foundation and New England BioLab.
- Volunteer meeting invited speakers: David Beer, Ph.D. (Professor, University of Michigan), Yuanfang Guan, Ph.D. (Assistant Professor, University of Michigan), Philip Maini, Ph.D. (Professor, University of Oxford).
- WISE-sponsored events: The fourth Genes and Health Contest in February and the third High School Research Conference in June.

2016-17 School Year (Disease of Focus: Depression)

- Summer camp extended to La Jolla, California, sponsored by Scripps Translational Science Institute.
- A biotechnology summer camp was added to the UM site with the sponsorship of the Michigan Institute for Computational Discovery and Engineering (MICDE) and WISE.
- "Lab on Wheels" program extended to Huron, Pioneer, Skyline high schools, engaging with 14 teachers, 44 classes, 1100 students, and 34 teaching assistants from UM (ranging from freshmen to PhD lab managers), sponsored by the Prechter Family Fund.
- A student paper was accepted for publication at the Pacific Symposium on Biocomputing, a professional bioinformatics society.
- Received the Constellation Award from the Genes in Space contest as a Midwest region institution.
- Volunteer meeting invited speakers: Michael Boehnke, Ph.D. (Professor, UM), Huda Akil, Ph.D. (Professor, UM), Robert Thomas, Ph.D. (Research Associate Professor, UM).
- WISE-sponsored events: The fifth Genes and Health Contest in February and the fourth High School Research Conference in May.

2017-18 School Year (Disease of Focus: Brain Cancer)

- The Cancer Genome Atlas Camp was added to the Scripps Summer Camps, La Jolla, California, sponsored by the Scripps Translational Science Institute.
- Collaborative efforts began with Scripps Research Summer Internship programs.
- Field trip to Illumina, Inc. was offered at the Scripps Summer Camp.
- Extended Flux (high performance computing cluster at UM) usage for Biotechnology Summer Camp with MICDE support.
- Scaling up of the "Lab on Wheels" program was successfully tested, running parallel sessions at both Huron and Pioneer high schools, engaging 900 students in one week, sponsored by the Prechter Family Fund.
- Recruited UM students to facilitate the Saturday volunteer meetings.
- Private miRcore YouTube channel for recorded meetings
- GIDAS leadership student committee independently led and trained all GIDAS leaders.
- Students in Arizona, Michigan, Virginia received multiple student research project awards.
- Volunteer meeting invited speakers: Carl Koschmann, M.D. (Assistant Professor, UM), Maria Castro, Ph.D. (Professor, UM), Jungsoo Chang (miRcore Alumni, UM Biomed Engineering graduate, Washing Univ at St. Louis Med School student).
- WISE-sponsored events: The sixth Genes and Health Contest in February and the fifth High School Research Conference in May.
- Fundraised $10,000 for a microgrant to support brain cancer research

2018-19 School Year (Disease of Focus: Pancreatic Cancer)

- Two volunteer students started research internships at Scripps Research Translational Institute.

- Scripps Community Lab experiments were introduced at the Scripps Summer Camp.
- Southern California volunteer students started meetings on the University of California at San Diego campus.
- Collaborative efforts began with UM Rogel Cancer Center outreach program.
- UM GIDAS trained members to become TAs for the “Lab on Wheels” program and piloted the program with Ann Arbor public school biology teachers
- The “Lab on Wheels” program was piloted at Ypsilanti Community High School, MI and at Mission Bay High School, CA, after running sessions at Huron, Pioneer, Skyline, and Community High Schools in Ann Arbor, MI, sponsored by the Prechter Family Fund.
- Advanced research sessions to analyze RNAseq data was piloted for multi-year volunteer students.
- Student teaching became a part of volunteer meeting program.
- Huron GIDAS helped our pilot afterschool biology enrichment teaching (led by Dr. Valarie Thomas) to promote STEM knowledge to the general student body.
- Six volunteers became finalists at the Intel International Science and Engineering Fair in 2019, two of them using the R summer camp materials.
- Students in California and Michigan received multiple student research project awards using computational biology research camp materials.
- Volunteer meeting invited speakers: Harold Crawford, Ph.D. (Professor, UM), Marina Pasca Di Magliano, Ph.D. (Associate Professor, UM), Iván Godinez, Ph.D. (Project Manager, Illumina, Inc.), Laura Nicholson, M.D., Ph.D. (Associate Professor, Scrips Research Institute), Gregory Botta, M.D., Ph.D. (Assistant Professor, Scrips Research Institute).
- WISE-sponsored events: The seventh Genes and Health Contest in January and the sixth High School Research Conference in May.

2019-20 School Year (Disease of Focus: Opioid Addiction)

Before the pandemic

- Volunteer students continued to participate in research internships at Scripps Research Translational Institute.
- 2019 Summer camps were run on campuses of the Georgia Institute of Technology, University of Michigan, and Scripps Research Institute, all with wet-lab teaching components.
- Bi-weekly southern California volunteer student in-person meetings on the University of California at San Diego campus were established.
- miRcore volunteer program (MVP) officers started online weekly officer meetings to plan for the main meetings.
- An online support committee was established to support distant and out-of-state MVP students.
- MVP alumni at other universities also actively helped MVP meetings.
- UM GIDAS prepared and led the Eighth Genes and Health Contest on UM campus in January. The contest was also run simultaneously on the UCSD campus, while two campuses were virtually connected and coordinated with the help of UCSD graduate students.
- UM GIDAS trained members to serve as TAs for the “Lab-on-Wheels” program at Pioneer High School in Ann Arbor, MI, sponsored by the Prechter Family Fund.

- A small research group analyzed small RNAseq data and generated results as a research project.
- Volunteer students initiated “Amazing World of Genes, Biology, and Me,” a workshop targeting middle school students and supported by UM GIDAS.
- Volunteer meeting invited speakers: Michael Englesbe, M.D. (Professor, UM), Shelly Flagel, Ph.D. (Associate Professor, UM).
- WISE-sponsored events: The Eighth Genes and Health Contest in January.

After the pandemic

- MVP meetings changed to all online meetings.
- Mid-week MVP meetings were added to support connections with peers.
- Added weekly material on COVID-19 facts and research related to SARS-CoV-2.
- Developed virtual summer camps and ran them with many returning MVP alumni.
- Opened all invited speaker talks during any camps to all summer campers, MVP students, and GIDAS members.
- Developed a virtual conference format including Slack poster sessions and added workshops on “Healthy Minds” and “Pseudocode.”

2020-21 School Year (Disease of Focus: COVID-19): All-virtual pandemic year

- 2020 summer camps were run all virtual, accommodating additional students who could not have attended on-site camps at the Georgia Institute of Technology, University of Michigan, and Scripps Research Institute.
- Volunteers participated in all-virtual weekly meetings enthusiastically, building friendships in the pandemic era.
- Five parents of volunteers formed a research group, met each weekend with Dr. Valarie Thomas, and wrote a research abstract on COVID-19.
- More programs are connected with UM GIDAS:
  - UM GIDAS members actively participated in the weekly volunteer meetings and directly guided volunteer group research.
  - In addition to the normal volunteer meetings, some multi-year volunteers met with UM GIDAS research leaders and performed novel small RNA research on COVID-19 (paper in progress).
  - The UM GIDAS invited speaker series includes miRcore-related high school students in the audience.
  - The 9th Genes and Health Contest was fully prepared and run virtually by UM GIDAS.
  - UM GIDAS leaders volunteered to prepare for the 8th High School Research Conference
- UM faculty members got more involved in the miRcore programs:
  - As invited speakers for the summer camps.
  - Providing research advice to volunteer groups during April-May before groups finalized their research projects.
  - Serving as judges for abstract scoring and poster presentation evaluation.
- More scientists helped miRcore programs than in previous years:
  - NIH principal investigators.
  - Scripps Research Institute connections (UCSD, Scripps, and CSL Behring).

- Supported BuzzOnline with the Spring 2021 5-week course “Mutations in Cancer,” teaching middle school students.
- Volunteer students ran our second annual biology workshop for middle school students with the title “Genes, Computational Biology, and Cancer,” generating funds to support Dr. Shelly Flagel’s research (Associate Professor, UM).
- The GIDAS support committee in the miRcore volunteer program ran a second GIDAS seminar series. New GIDAS chapters brought their members to the G&H Contest and helped members submit research abstracts!

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