EGFR Amplification May Downregulate miR-133b to Activate MET Expression in Lung Cancer

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Introduction

Lung cancer causes more deaths than any other cancer. Like all cancers, it is characterized by uncontrolled cell division. There are three major subtypes: small cell lung cancer, non-small cell lung cancer (including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma), and lung carcinoid tumor. Recent studies have focused upon the gene EGFR (epidermal growth factor receptor) and its role in various cancers. Also, the potential for competition between mRNAs for their regulating miRNAs has been shown in the case of competing endogenous RNAs (ceRNAs)[1]. This study looked for potential ceRNA activity in lung adenocarcinoma (LUAD) in an attempt to learn more about disease pathways.

Methods

The Cancer Genome Atlas, a collaborative project between the National Cancer Institute and the National Human Genome Research Institute, offers data from many different cancers. The data for LUAD had 551 tumor samples; of these, 50 patients had EGFR Copy Number Variation (CNV) amplification. Fifty-six patients were used as the no CNV group. The TCGA mRNA and miRNA expression data for the selected 106 samples were separated into upregulated and downregulated mRNAs and miRNAs. Using a database of experimentally validated miR-target genes from miRTarBase, the upregulated genes and downregulated miRNAs with p-values of less than 0.05 were checked to see if any were paired targets. Heatmaps of select genes and miRNAs were made to visualize correlations of the data.

Results

EGFR expression was upregulated for the CNV group. After the upregulated mRNAs and downregulated miRNAs were compared using miRTarBase, 19 pairs were discovered. Among them, EGFR and MET shared a common regulating miRNA: miR-133b. Heatmaps allowed visualization of the correlations between EGFR, MET, and miR-133b present in certain patient subgroups in the TCGA data. The subgroups with amplification of both EGFR and MET as well as downregulated miR-133b had low survival compared with other subgroups. It was confirmed that the MET activation was not due to CNV amplification. MET, like EGFR, is a growth factor receptor that leads to several signaling cascades including those within the RAS-ERK pathway, which is often targeted by cancer drugs. When functioning normally, MET is essential to such processes as angiogenesis, wound healing, and liver regeneration.

Conclusion

As EGFR mutation is commonly found in lung cancer patients, there have been targeted therapies for those with this mutation. Gefitinib and Erlotinib are two of the drugs used to target the EGFR overexpression. This therapy, though successful in some, has encountered drug resistance in many cases. In 20% of resistant tumors, there is MET amplification present[2]. The gene correlations described above may lead to new therapies available to those in the subgroup with EGFR and MET upregulation as well as miR-133b downregulation. It seems possible that EGFR and MET act as ceRNAs. Further investigation seems necessary and reasonable.

Keywords: EGFR, MET, ceRNAs, miR-133b, LUAD, CNV amplification

References

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