Disrupting the HSP90/CDC37 Complex as an ALS strategy

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Introduction

Amyotrophic Lateral Sclerosis (ALS) is a deadly neurodegenerative disease characterized by misfolded protein buildup. The molecular chaperone HSP90 and its co-chaperone CDC37 are essential for protein folding and stabilization. Although HSP90/CDC37 complex disruption has been investigated concerning cancer, its ALS effects have not been examined. We hypothesize targeting HSP90/CDC37 interaction reduces misfolded protein buildup and neuroinflammation, providing a new, upstream ALS treatment.

Methods

Gene expression profiles from 508 controls and 233 ALS patients were found on Gene Expression Omnibus (GSE112681, platform GPL6947). GEO2R identified the top 200 differentially expressed genes (p-value <0.000007); a StringDB of protein-protein interaction networks was constructed with key pathways. The Aryl Hydrocarbon Receptor's WikiPathway (WP2586) and its Gene Ontology terms were chosen to discover CDC37's role in ALS.

Results

For ALS differential gene expression, the AhR WikiPathway's strength was 0.57 (moderate-strong) and false discovery rate 0.63%. 6 of 45 of AhR's genes were in the top 200 GEO2R differentially expressed genes, suggesting ALS dysregulates much of the AhR pathway. CDC37 was downregulated in ALS patients, (logFC=-0.224) decreasing HSP90 motility by disrupting N-terminal and middle domain binding sites. Downregulation correlates with decreased CDC37-HSP90 complex activation, crucial for stabilizing and maturing many protein kinases. Dsruption can lead to client kinase degradation, impairing critical downstream signaling pathways like MAPK (cell growth, differentiation, apoptosis) and PI3K/AKT (cell survival, metabolism). Downstream protein disruption could contribute to ALS's neuron death pathology. CDC37 underexpression also causes misfolded protein accumulation (ALS hallmark) by destabilizing proteostasis-regulating kinases. For example, HSP90 client kinases like CLK1 (logFC=0.662) help control RNA splicing; their dysregulation contributes to TDP-43 mislocalization observed in 97% of ALS cases. Also, the AhR pathway links environmental toxins to neuroinflammation via PTGS2 (COX-2), an inflammatory enzyme upregulated in ALS spinal cord tissue (logFC=0.453). CDC37 dysfunction may exacerbate ALS through proteostatic collapse and neuroimmune activation, which is seen in ALS patients with activated microglia.

Discussion

Current ALS therapies (Riluzole) fail to address upstream drivers. AhR findings suggest disrupting the HSP90/CDC37 complex with cancer drugs (Celastrol) could halt kinase dysfunction and protein aggregation, which resembles immunosuppressant use in Alzheimer's. AhR pathway's link to neuroinflammation connects ALS to autoimmune diseases, where comparable pathways contribute to disease spread. A single treatment of ALS and associated diseases may be possible by repurposing HSP90/CDC37 inhibitors optimized for brain delivery.

Keywords: ALS, HSP90, CDC37, protein misfolding, neuroinflammation, kinase regulation