**Investigating the Role of HDAC6 in Protection Against Alzheimer’s Disease**

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**Summary**

Tau protein is the main component of accumulated waste proteins, often referred to as tangles, responsible for neuronal death in Alzheimer’s Disease (AD) patients. As AD progresses, tau becomes modified in a way that ultimately leads to significant cognitive decline. Strong evidence suggests that a deacetylase enzyme can alter tau modification. Therefore, elevation of deacetylase activity could retain tau in an unmodified state, and thus be a potential therapeutic approach against AD. Dorens of kinases were proposed to regulate deacetylase activity and some are known to be impaired in AD. Understanding how these kinases operate may provide alternative strategies for AD intervention.

**Background**

Alzheimer’s Disease (AD) is the most common neurodegenerative disease (affecting > 6 million Americans) and is the 6th leading cause of death in the U.S. AD patients generally suffer from neuronal loss and atrophy, memory loss, and significant cognitive decline. Currently, there is no known cure to stop progression.

As AD progresses, tau becomes modified and forms tangles that strongly correlate with the cognitive dysfunction characteristic of AD. Strong evidence suggests that a deacetylase enzyme known as HDAC6 can alter this modification when activated via phosphorylation and thus, serve as a potential protecting agent against AD pathology.

**HDAC6 serves as a potential modifier for AD pathogenesis**

**Results**

**Kinase activity influences HDAC6 activation**

**Binding affinity to HDAC6 may be activity-dependent**

**Kinase candidates do not facilitate nuclear HDAC6 shuttling**

**Visualization of Nuclear HDAC6**

**Conclusion**

This study shows that kinase activity influences both binding affinity and activation of HDAC6. We concluded that LRRK2 and GSK-3β exhibit strongest affinity for HDAC6, but do not seem to mediate nuclear shuttling of HDAC6. Therefore, downstream effects of translocation of HDAC6 may not be of concern and elevation of HDAC6 activity via phosphorylation could serve as a potential therapy against AD pathology. Our future steps will include analysis of identified kinases in different disease models, investigations of interactions between kinase candidates and HDAC6 or tau in in vitro environments, and analysis of human brain tissue.

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