The ER-Resident Acetyltransferases: Novel Targets for Alzheimer’s Disease
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Abstract
Age-associated diseases are diseases that have a predilection toward persons of advanced age. Common examples of these types of diseases are cataracts, osteoporosis, arthritis, and certain types of dementia. One of the most common types of age-associated diseases is Alzheimer’s disease (AD), the leading form of dementia (1). The disease occurs through improper cellular protein processing, resulting in malformed bundles of non-functional proteins forming in the brain that reduce neuronal signal transduction and contribute to brain deterioration. Currently there are no known preventative or curative treatments for AD, so investigation into new targets for AD treatment is of high importance. One novel therapeutic approach is to use cellular autophagy, or the cells ability to stop protein production and to degrade and reuse malformed proteins, to prevent or slow AD progression. It has been determined that autophagy can be turned on by inhibiting the enzymes ATase1 and ATase2, components of the endoplasmic reticulum (ER) acetylation machinery. These enzymes, transfer acetyl from acetyl coenzyme A, a common metabolite in cells, onto properly folded proteins (2). Excitingly, when this inhibition occurs in an AD-mouse model there is no aggregation of Aβ, which is characteristic of AD (3). These findings lead to the investigation into new targets for AD treatment.

Objectives
• Identify potential areas of importance on ATase1 and ATase2 by:
  - Preparing an optimized protein homology model to identify potential areas of importance on the enzyme
  - Performing computational estimates on how inhibitors known to affect ATase1 and ATase2 function orient the structure
  - Assessing the strength of the predictions using hydrogen-deuterium exchange mass spectrometry, a method of determining protein structure by identifying the areas of the protein that are exposed to liquid

Preliminary hydrogen-deuterium exchange mass spectrometry studies gave some evidence of overall protein structure

Conclusions and future directions
1. Computational docking studies with the optimized homology models for ATase1 and ATase2 identified a subset of high-affinity binding compounds to be investigated further for ATase inhibition ability.
2. Structural studies with hydrogen-deuterium exchange mass spectrometry has the potential to characterize the hypothetical acetyl-CoA substrate binding pocket and further optimize our models.
3. Additional structural studies and inhibition studies on mouse animal models for protein aggregation diseases are underway. These could lead to novel therapeutics for age-associated protein aggregation diseases.

Acknowledgements and works cited
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