ABSTACT

THE ROLE OF MICRORNA AND SERINE PALMITOYLTRANSFERASE IN ALZHEIMER'S DISEASE

By

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The mechanism by which early-on-set Alzheimer's disease (AD) manifests is well understood. However, little is known about the molecular mechanisms contributing to late-onset AD, which accounts for >95% of AD cases. Research thus far invariably suggests that elevated ceramide, a sphingolipid, may be a risk factor for AD. Serine palmitoyltransferase (SPT) is not only the first rate limiting enzyme in the de novo synthesis of ceramide but varying SPT levels are consistently associated with varying ceramide levels. I observed that increased ceramide levels in AD are directly regulated by increased SPT levels. I also observed that SPT directly regulates amyloid beta (Aβ) levels through the post-transcriptional regulation of miR137,-181c,-9 and -29a/b, suggesting SPT and the respective miRNAs are potential therapeutic

targets for AD. Therefore, I investigated the use of SPT inhibition as a potential therapeutic strategy for AD. I administered a SPT inhibitor subcutaneously through surgically implanted osmotic pumps into an AD mouse model. I observed that the inhibition of SPT and thus ceramide, reduced cortical Aβ and hyperphosphorylated tau levels, major hallmarks of AD, with statistically significant correlations between SPT, ceramide and Aβ levels. With nominal toxic side effects observed, inhibition of SPT is suggested as a potentially safe therapeutic strategy to ameliorate the AD pathology. In addition, I have identified that the afore mentioned miRNAs are reduced in the blood sera of probable AD and amnestic mild cognitive impaired patients,

suggesting a potential use for these circulating miRNAs as non-invasive diagnostic biomarkers. In the AD mouse model studied, I observed that these miRNAs show positive correlations between their expressions in the brain cortices and presence in the sera, further suggesting a potential diagnostic role for these circulating miRNAs. A positive correlation was also observed between cortical and sera Aβ levels, providing further insights into the search of blood biomarkers.