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A role for SPT and miRNA as therapeutic strategies and biomarkers for alzheimer's disease

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Abstract

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-on-set AD, which accounts for >95% of AD cases. Research thus far invariably suggests that elevated ceramide, a sphingo lipid, may be a risk factor for AD. Serine palmitoyltransferase (SPT) is the first rate limiting enzyme in the *de novo* synthesis of ceramide.It was observed that increased ceramide levels in AD are directly regulated by increased SPT levels. It was also observed that SPT directly regulates amyloid beta (Aβ) levels through the post-transcriptional regulation of miR-137,-181c,-9 and -29a/b, suggesting SPT and the respective miRNAs are potential therapeutic targets for AD. A SPT inhibitorwas administered into an AD mouse model to investigate the use of SPT inhibition.The inhibition of SPT and thus ceramide, reduced cortical Aβ and hyperphosphorylated tau levels, the 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, the afore mentioned miRNAswere identified to be 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. These miRNAs show positive correlations between their expressions in the brain cortices and their presence in the seraof the AD mouse model studied, further suggesting a potential diagnostic role for these circulating miRNAs.

Biography

Hirosha Geekiyanage has received her PhD from Michigan State University. She is a post-doctoral fellow at Mayo clinic. She has peer reviewed articles published in Journal of Neuroscience (2011), Experimental Neurobiology (2012) and Neurobiology of Aging (2013). Her article in Journal of Neuroscience was featured on "This week in Journal", Journal of Neuroscience 31(41): 14820-30; Alzheimer's research forum: Micromanaging Aβ—Small RNAs Control Peptide via Lipids (ttp://www.alzforum.org/new/detail.asp?id=2935); and Nature.com: Science-Business Exchange, Distillery: Therapeutics – Neurology: MicroRNA-137 (miR-137); miR-181c; serine palmitoyltransferase long chain base subunit 1 (SPTLC1; LBC1); β-amyloid (Aβ) (http://www.nature.com/scibx/journal/v4/n42/full/scibx.2011.1186.html).

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