Amantha Thathiah

Center for human genetics
Laboratory for the Research of Neurodegenerative Diseases
Department of Molecular and Developmental Genetics, VIB
University of Leuven

B.Sc. of Science, Baylor University, 1998
Ph.D. in Biochemistry, Baylor University, 2005

Staff scientist at the University of Leuven, since 2009

E-mail: Amantha.Thathiah@cme.vib-kuleuven.be

Phone: +32 (16) 34 59 94

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Science

Alzheimer's disease (AD), the most common neurodegenerative disorder afflicting the elderly, is characterized by progressive memory and cognitive impairment and cerebral accumulation of amyloid plaques and neurofibrillary tangles. Although the specific molecular impetus of AD remains unclear, extensive research suggests that the amyloid β-protein (Aβ) plays an early and essential role in the disease pathogenesis.

Aβ is derived from proteolysis of the β-amyloid precursor protein (APP) following sequential cleavage by the β- and γ-secretases. The majority of cases of early onset familial AD (FAD) are attributed to mutations in the *Presenilin (PS)* and *APP* genes; however, FAD accounts for less than 10% of AD cases, and thus, the vast majority of late-onset AD cases are sporadic by nature. As a result, identification of the cellular mechanisms that regulate Aβ generation is believed to be important for understanding the pathogenesis of AD.

Utilizing a high-throughput functional genomics screen, we identified GPR3, a constitutively active orphan G protein-coupled receptor (GPCR), as an *in vitro* and *in vivo* modulator of Aβ peptide generation. In an AD transgenic mouse model, we determined that the absence of GPR3 alleviates Aβ peptide generation, whereas overexpression of GPR3 exacerbates Aβ accumulation in the absence of an effect on Notch processing. Moreover, we observed that GPR3 is abundantly expressed in areas of the normal human brain implicated in AD and is overexpressed in a subset of sporadic AD patients. Interestingly, modulation of APP processing by GPR3 does not affect Notch proteolysis. Consequently, these studies indicate that GPR3 is a putative therapeutic target for AD and suggest that drugs targeting GPR3 have the potential to be devoid of major Notch-

associated side-effects, a fundamental requirement for the development of a preventative therapy for AD.

Selected publications

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