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Ube3a deficiency inhibits amyloid plaque formation in APP^{swe}/PS1^{ΔE9} mouse model of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive decline in memory and cognitive function. Pathological hallmark of AD includes aberrant aggregation of amyloid beta (A β) peptide, which is produced upon sequential cleavage of amyloid precursor protein (APP) by β - and γ -secretases. On the contrary, α -secretase cleaves APP within the A β sequence and thereby prevents A β generation. Here, we investigated the role of ubiquitin ligase Ube3a (involved in synaptic function and plasticity) in the pathogenesis of AD using APP^{swe}/PS1^{ΔE9} transgenic mouse model and first noticed that soluble pool of Ube3a was age dependently decreased in AD mouse in comparison with wild type controls. To further explore the role of Ube3a in AD patho-mechanism, we generated brain Ube3a-deficient AD mice that exhibited accelerated cognitive and motor deficits compared to AD mice. Interestingly, these Ube3a-deficient AD mice were excessively obese from their age of 12 months and having shorter lifespan. Biochemical analysis revealed that the Ube3a-deficient AD mice had significantly reduced level of A β generation and amyloid plaque formation in their brain compared to age-matched AD mice and this effect could be due to the increased activity of α -secretase, ADAM10 (a disintegrin and metalloproteinase-10) that shift the proteolysis of APP towards non-amyloidogenic pathway. These findings suggest that aberrant function of Ube3a could influence the progression of AD and restoring normal level of Ube3a might be beneficial for AD.

References

[1] Singh, B.K., Vatsa, N., Kumar, V., Shekhar, S., Sharma, A. and Jana, N.R. (2017) Ube3a deficiency inhibits amyloid plaque formation in APP^{swe}/PS1^{ΔE9} mouse model of Alzheimer's disease. *Human Molecular Genetics* ddx295.
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