The Role of DLG5 in Alzheimers Disease

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Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common form of dementia in the elderly featuring progressive memory loss and cognitive decline. Compelling evidence suggests that soluble Aß oligomers are responsible for early synaptic disruption and cognitive decline in AD. In contrast to Aß-derived synaptic loss, the takusan domain family member a1-takusan enhances synaptic integrity and synaptic activity through interactions with PSD95 as demonstrated in our previous publication in Neuron. In our recent publication in the

Journal of Neuroscience, we have shown that overexpression of a1-takusan can alleviate Aß-induced synaptic loss including decreased synaptic PSD-95 clustering, loss of dendritic spines, and depressed synaptic activity mediated by AMPA-type glutamate receptors. Interestingly, D2 is the most conserved sequence among all takusan family members, including human DLG5. For suitability purposes in downstream clinical applications (such as intranasal delivery) and simplified protein synthesis/purification, we generated a shorter DLG5-derived fragment hD2b comprising the human DLG5 D2 sequence and C-terminal PDZ-binding motif. Like a1-takusan, DLG5/hD2b alleviated Aß-induced synaptic loss in cultured neurons as demonstrated in our previous publication. In preliminary studies, we have found that DLG5/hD2b overexpression reduced Aß levels in conditioned medium from cultured N2a/APPswe cells expressing human APP harboring amyloidogenic Swedish mutations. We further found that DLG5/hD2b interacted with ßSGT, a co-chaperone protein and a negative regulator of HSP70, raising the possibility that DLG5/hD2b overexpression reduced Aß levels and alleviated Aß-induced synaptic loss at least in part through its ability to enhance HSP70-mediated Aß-degradation. mRNA levels of the Aß-degrading component insulin degrading enzyme (IDE), was consistently elevated by DLG5/hD2b overexpression. These results suggest an alternative mechanism underlying DLG5-mediated synaptic protection in addition to previously identified PSD-95-mediated synaptic protection. This hypothesis will be carefully tested in this project. In specific aim 1, we will determine the correlation between the level of DLG5 reduction and severity of dementia in AD patients and investigate the molecular mechanism underlying DLG5-mediated Aß-reduction and synaptic protection. The role of ßSGT/HSP70 chaperone proteins and Aß-degrading enzymes in these actions will also be examined. In specific aim 2, we will determine the in vivo role of DLG5 as well as DLG5-mediated SGT/HSP70 chaperone activity in reducing amyloid pathology and cognitive deficits by performing immunoblotting, histochemistry, electrophysiology, and behavior tests in Tg2576 AD mice. If successful, our work will provide valuable information on the role of DLG5/hD2b against AD pathogenesis and establish groundwork for future development of DLG5-based therapeutics in AD.

Further information available at:

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