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"Investigate whether Bri2 loss of function in CNS is pathogenetic mechanism of familial dementia."

by
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Cancer Center H 1196
Friday, October 7th, 2022
11:00 A.M.

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ABSTRACT

Familial British and Danish dementia (FBD and FDD) are two neurodegenerative disorders sharing common features with Alzheimer disease (AD), such as neuroinflammation, amyloid deposits, neurofibrillary tangles. While AD is either caused by pathological familial mutation in APP, PSEN1 and PSEN2 or is associated with high-risk gene variants, such as TREM2, APOE4 and ABCA7, both FBD and FDD, as well as recently characterized Familial Chinese dementia (FCD), are caused by mutations in the Integral membrane protein 2B (ITM2B), which encodes a protein known as BRI2. Two not mutually exclusive pathogenic mechanisms for FDD and FBD have been proposed, either loss of BRI2 function or accumulation of amyloidogenic mutant BRI2-derived peptides. However, the precise site and physiological function of BRI2 in CNS are remain unclear. In this thesis, to investigate Bri2 physiological function in neuronal synapses, we genetically inactivated Itm2b expression in either presynaptic (CA3), postsynaptic (CA1) or both (CA3+CA1) neurons of the hippocampal Schaeffer-collateral pathway and found that Bri2 regulates excitatory synaptic transmission at both presynaptic termini and postsynaptic termini. In addition, by using FBD and FDD knock in mice and newly generated FDD knock in rats, we show a similar impairment in glutamatergic synaptic transmission in these disease models. The evidence that Bri2 deletion and pathogenic mutations cause similar synaptic transmission deficits suggest a loss of Bri2 function pathogenetic mechanism at synapses in FDD and FBD. The observation that FDD and FBD pathogenetic Bri2 mutations target mutant Bri2 to the ER-Lysosomal associated degradation mechanism undelines a mechanism by which FDD and FBD pathogenic mutation cause loss on BRI2 function. However, neither loss of Bri2 nor FBD and FDD knock in model organisms showed brain histological changes linked to neuropathology. To determine whether Bri2 may regulate physiological processes in other CNS cell types, we analyzed the cell specific Bri2 expression in the CNS. We found that Bri2 is widely expressed in all CNS cells, with expression being the highest is in microglia, the main cell type linked to neuroinflammation responses, and that Bri2 interacted with the microglia specific protein Trem2. Via this interaction, Bri2 modulates α-secretase mediated proteolytic processing of Trem2. Given that several Trem2 variants increase sporadic AD risk and Amyloid-β precursor Protein (APP), whose mutations cause familial AD, also interacts with Bri2, the functional alterations of these Bri2 interactions may be critical to dementias' pathogenesis. Further studies will be needed to determine whether loss of Bri2 function in the CNS leads to dementia and neurodegeneration in FBD, FDD, FCD and as well as AD.