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Pathogenic Role of FcγRIIb in Amyloid and Tau Pathogenesis in Alzheimer's Disease

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Amyloid-beta (Aβ) induces neuronal loss and cognitive deficits and is believed as a prominent cause of Alzheimer's disease (AD). However, cellular mechanism of the pathogenesis is not fully understood. Here we show that Fcgamma-receptor IIb (FcγRIIb) mediates Aβ neurotoxicity and neurodegeneration. We found that FcγRIIb is a receptor of $A\beta_{1-42}$ oligomers and genetic depletion of FcγRIIb rescues the memory impairments in AD model mice. In addition, the FcγRIIb-SHIP2 axis is critical in $A\beta_{1-42}$-induced tau pathology. *Fcgr2b* knockout or antagonistic FcγRIIb antibody inhibited $A\beta_{1-42}$-induced tau hyperphosphorylation and rescued memory impairments in AD mouse models. As a action model, SHIP2 is recruited into phosphorylated FcγRIIb to affect PtdIns(3,4)P_2 metabolism for tau phosphorylation. Further, targeting SHIP2 expression by lentiviral siRNA in 3xTg-AD mice or pharmacological inhibition of SHIP2 potently rescued tau hyperphosphorylation and memory impairments. Thus, we conclude that the FcγRIIb-SHIP2 axis links Aβ neurotoxicity to tau pathology by dysregulating PtdIns(3,4)P_2 metabolism, providing insight into therapeutic potential against AD. More, emerging evidences suggest that intraneuronal Aβ correlates with the onset of Alzheimer's disease (AD) and highly contributes to neurodegeneration. Our findings illustrate that FcγRIIb2 is essential for neuropathogenic function of Aβ in AD.

Biography:

Yong-Keun Jung obtained his Ph.D from the Albert Einstein College of Medicine, NY, USA at 1993. From 1993-1996, he was a post-doctoral fellow in the department of cell biology, Harvard Medical School, USA. He then returned to Korea and is now a professor at Department of Biological Science, Seoul National University (SNU), Korea. He contributed to elucidation of the cell death machinery and our understanding of its association with human disease. In particular, the role of cell death and autophagy in the pathogenesis of human disease, including Alzheimer's disease, ischemia and cancer etc, is being investigated.