

Journal club. 2014.12.19 Miao

Neuron. 2014 Oct 1; 84(1):63-77.

Deficiency in LRP6-mediated Wnt signaling contributes to synaptic abnormalities and amyloid pathology in Alzheimer's disease.

Liu CC, Tsai CW, Deak F, Rogers J, Penuliar M, Sung YM, Maher JN, Fu Y, Li X, Xu H, Estus S, Hoe HS, Fryer JD, Kanekiyo T, Bu G.

The low-density lipoprotein receptor-related protein 6 (LRP6) is an essential coreceptor for Wnt signaling. Genetic evidence has suggested a role of LRP6-mediated Wnt signaling in AD pathogenesis; however, biological and pathological evidences are lacking. In this article, authors report that conditional deletion of *Lrp6* gene in mouse forebrain neurons leads to cognitive impairment, synaptic Deficits, and neuroinflammation in aged mice. Neuronal LRP6 deficiency in an amyloid mouse model also leads to exacerbated amyloid pathology due to increased APP processing to amyloid- β . In humans, LRP6 and Wnt signaling are significantly downregulated in AD brains. A β Downregulates LRP6-Mediated Wnt Signaling. So their results define that LRP6-mediated Wnt signaling is a critical pathway to AD pathogenesis and suggest that restoring LRP6-mediated Wnt signaling can be explored as a viable strategy for AD therapy.