DISC1

Wang et al., showed levels of Disrupted-in-schizophrenia-1 (DISC1), which is genetically associated with psychiatric disorders and AD, decrease in the brains of AD patients and transgenic model mice and in Aβ-treated cultured cells. Disrupted-in-schizophrenia-1 contains a canonical LC3-interacting region (LIR) motif (210 FSFI213), through which DISC1 directly binds to LC3-I/II. Overexpression of DISC1 enhances mitophagy through its binding to LC3, whereas knocking-down of DISC1 blocks Aβ-induced mitophagy. We further observe overexpression of DISC1, but not its mutant (muFSFI) which abolishes the interaction of DISC1 with LC3, rescues Aβ-induced mitochondrial dysfunction, loss of spines, suppressed long-term potentiation (LTP). Overexpression of DISC1 via adeno-associated virus (serotype 8, AAV8) in the hippocampus of 8-month-old APP/PS1 transgenic mice for 4 months rescues cognitive deficits, synaptic loss, and Aβ plaque accumulation, in a way dependent on the interaction of DISC1 with LC3. These results indicate that DISC1 is a novel mitophagy receptor, which protects synaptic plasticity from Aβ accumulation-induced toxicity through promoting mitophagy [1].

1)
Wang ZT, Lu MH, Zhang Y, Ji WL, Lei L, Wang W, Fang LP, Wang LW, Yu F, Wang J, Li ZY, Wang JR, Wang TH, Dou F, Wang QW, Wang XL, Li S, Ma QH, Xu RX. Disrupted-in-schizophrenia-1 protects synaptic plasticity in a transgenic mouse model of Alzheimer's disease as a mitophagy receptor. Aging Cell. 2018 Nov 28:e12860. doi: 10.1111/acel.12860. [Epub ahead of print] PubMed PMID: 30488644.