A TAG1-APP SIGNALING PATHWAY THROUGH FE65 NEGATIVELY MODULATES NEUROGENESIS

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The release of amyloid precursor protein (APP) intracellular domain (AICD) may be triggered by extracellular cues through ã-secretase-dependent cleavage. AICD binds to Fe65, which may play a role in AICD-dependent signaling. However, the functional ligand was not characterized. We have identified TAG1 as a functional ligand of APP. Through extracellular interaction with APP, TAG1 both increases AICD release and triggers Fe65-dependent activity in a ã-secretase-dependent manner. TAG1, APP and Fe65 co-localize in the neural stem cell niche of the fetal ventricular zone. Neural precursor cells from TAG1-/-, APP-/- and TAG1-/-&APP-/- mice show aberrantly enhanced neurogenesis, significantly reversed in TAG1-/- mice by TAG1 or AICD but not AICD mutated at the Fe65 binding site. Notably, TAG1 reduces normal neurogenesis in Fe65+/+ mice. Abnormally enhanced neurogenesis also occurs in Fe65-/- mice but cannot be reversed by TAG1. These results describe a TAG1-APP signaling pathway that negatively modulates neurogenesis through Fe65.