

AMYLOID PRECURSOR PROTEIN AND PRESENILIN1 INTERACT WITH THE ADAPTOR GRB2 AND MODULATE ERK1,2 SIGNALING

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The amyloid precursor protein (APP) and the presenilins 1 and 2 are genetically linked to the development of familial Alzheimer's disease. APP is a single-pass transmembrane protein, precursor of A β peptides, which are considered the main responsible for AD neurodegeneration. Presenilins are multipass membrane proteins, involved in the enzymatic cleavage of APP and other signaling receptors and transducers. The role of APP and Presenilins in AD development seems related to the formation of A β peptides; although their physiological function, their reciprocal interaction and the molecular mechanisms leading to the neurodegeneration are unclear. APP and Presenilins are also involved in multiple interactions with intracellular proteins, the significance of which is under investigation. Among different APP-interacting proteins we focused our interest on Grb2 adapter protein, which connects cell surface receptors to intracellular signaling pathways. In this work we provide evidence by co-immunoprecipitation experiments, confocal and electron microscopy, and by fluorescence resonance energy transfer experiments, that both APP and Presenilin1 interact with Grb2 in vesicular structures at the centrosome of the cell. The final target for these interactions is ERK1,2, which is activated in mitotic centrosomes in a PS1 and APP-dependent manner. These data suggest that both APP and Presenilin1 can be part of a common signaling pathway that regulates ERK1,2 and the cell cycle.