the rate and extent of homopolymerization. We found that tau isoforms arising from alternative splicing or from autosomal dominant missense mutations associated with frontal temporal lobe dementia and parkinsonism linked to chromosome 17 (FTDP-17) differ markedly in their efficiency of assembly. In addition, mimicry of tau phosphorylation by mutation of select serine residues to glutamic acid residues greatly accelerated tau polymerization. Mutation of cysteine residues showed that oxidation may contribute to final paired helical morphology, but is not a necessary prerequisite for efficient nucleation or elongation of tau filaments. Together these data suggest that tau polymerization is modulated by multiple protein segments, some of which mediate and others which inhibit polymerization. It is proposed that phosphorylation, truncation, alternative splicing, and missense mutation of residues within these segments can greatly influence the ability of tau protein to form filaments.

599 LOSS OF PRESENILIN 1 LEADS TO EPIDERMAL HYPERPLASIA AND TUMORIGENESIS IN ADULT MICE

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Presenilin 1 (PS1) is a multi-pass transmembrane protein expressed in all tissues examined. PS1 is essential for mammalian development and is required for extracellular production of Aβ peptides. These activities are likely mediated by its absolute requirement in the proteolytic processing of two distinct molecules: Notch and amyloid precursor protein (APP). In addition, PS1 associates with β-catenin. Here we report that this interaction plays a critical role in regulating β-catenin signaling pathway *in vivo*. Using transgenic mice deficient in mouse PS1 but rescued with human PS1 whose pattern of expression is restricted to neuronal tissue, we show that lack of PS1 expression in skin results in increased stability of β-catenin and activation of its downstream target cyclin D1. Importantly, consistent with the established roles of β-catenin and cyclin D1 in turmorigenesis, these mice develop epidermal hyperplasia and neoplasia. Our results document that PS1 is a negative modulator of β-catenin stability and downstream signaling and loss of PS1 is linked to turmorigenic process.

600 FAD ALLELES OF PS1 AND PS2 HAVE DIVERGENT EFFECTS ON SKELETAL DEVELOPMENT, γ-40- AND γ-42-SECRETASE

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Presenilin 1 (PS1) knockout (k/o) mice exhibit skeletal and CNS abnormalities, accumulation of APP-terminal fragments (CTFs) and absence of Aβ1-40 and Aβ1-42 peptides: these defects are attributed to lack of secretase cleavage within the transmembrane domains of Notch and APP, respectively. We assessed biological activities of Familial Alzheimer Disease (FAD) alleles of PS1 and PS2 by genetic complementation. Both PS1 and PS2 transgenes expressed from the prion protein promoter rescued the skeletal abnormalities present in PS1 k/o mice. Unlike the M146L FAD allele of PS1, however, N141I and M239V PS2 transgenes reduced APP CTFs in the brain by only 20-30% and failed to restore Aβ1-40 synthesis. Thus, whereas mutant PS1 activates both γ-42-secretase and γ-40-secretase, mutant PS2 only activates the former endoprotease. These data make it unlikely that Notch is processed by γ-40-secretase. The ability to genetically dissociate γ-40- and γ-42-secretase activity, as established here, will be of use in assigning contributions of the two secretase pathways in developmental processes and in the pathogenesis of AD.

601 GENERATION OF AN ANIMAL MODEL OF AMYLOID DEPOSITION WITHOUT OVERPRODUCTION OF AMYLOID PRECURSOR PROTEIN

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To date, animal models of amyloid (Aβ) deposition have utilized the transgenic approach to overexpress amyloid precursor protein (APP) bearing familial Alzheimer's disease (FAD) mutations. These mutations increase Aβ to the point that amyloid deposition occurs, but the transgenes also increase APP production well beyond physiological levels. Recently Aβ deposition has been further enhanced by crossing these APP transgenic mice with transgenics overproducing FAD mutant presenilin-1 (PS-1). We have utilized a gene-targeting approach to generate AD models that do not involve protein overexpression. Our first model introduced the Swedish K670N/M671L FAD mutations and "humanized" the mouse Aβ sequence in the APP gene. This mouse ($APP^{NLh/NLh}$) produced normal levels of APP, overproduced human Aβ1-40 and 1-42, but did not deposit Aβ as late as 22 months of age. Next, the P264L mutation was introduced into the mouse PS-1 gene. The P264L mutation is a non-conservative amino acid substitution in the cluster of mutations in exon 8, leading to an onset of FAD in the middle forties to middle fifties. This mouse ($PS\text{-}1^{P264L/P264L}$) also did not deposit Aβ as late as 12 months of age. Crosses have produced $APP^{NLh/NLh}$ X $PS\text{-}1^{P264L/P264L}$ double gene-targeted mice. These mice have elevated levels of Aβ1-42, sufficient to cause Aβ deposition. Aβ deposits were not present at 3 months of age but were seen at 6 months. Deposition was most prominent in telencephalic structures, consistent with the distribution of Aβ deposition in AD. The double gene-targeted mouse is a model of Aβ deposition that faithfully expresses normal levels of both APP and PS-1 under the control of their endogenous promoters in a cell- and tissue-appropriate manner.

602 PRESENILIN 1 INTERACTS WITH A NEURONAL CELL ADHESION MOLECULE AND MEDIATES ITS INTRACELLULAR TRAFFICKING

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Presenilins are multitransmembrane proteins that play important physiological roles in the proteolytic cleavage of APP and Notch and are key players in amyloid formation and development. It is unclear whether presenilin 1 (PS1) is the elusive γ-secretase or a co-factor involved in efficient processing, targeting or sorting of APP, Notch and other candidate substrates. To explore further the exact function of PS1 we used two-hybrid screening with the carboxy-terminus of PS1 as a bait. We have identified a PS1-interacting protein (PIP-1) which, like APP and Notch, is a type I transmembrane protein. PIP-1 is a cell adhesion molecule that is exclusively expressed in specific areas of the brain including hippocampus and dentate gyrus where it localizes at the plasmamembrane of neurites. Both the topology and the neuronspecific expression make PIP-1 a highly interesting protein to analyze the functions of PS1 in brain. In brain extracts, endogenous PIP-1 interacts specifically with GST fused to the 39 carboxyterminal amino acids of PS1 and 2 in a salt-dependent way. Inversely, endogenous PS1-CTF could be precipitated using GST-PIP-1 recombinant proteins. By *in vitro* coupled transcription/translation we were able to demonstrate that the intracellular domain of PIP-1 is not required for the interaction with PS1 as is the case for APP. Instead, we narrowed the site of interaction with PS1 to a sequence close to or within the transmembrane region of PIP-1. Furthermore we found a vast accumulation of PIP-1 at the plasmamembrane and in an as yet unidentified membrane compartment within the cell body of PS1-/- hippocampal neurons, providing functional evidence for the interaction of PIP-1 with PS1. Identifying the exact nature of the compartment where PIP-1 accumulates is in progress, as well as studies aiming to elucidate the potential role of PS1 in the proteolytic processing of PIP-1.