Metabolism and Function of Presenilin 1


Summary

Neither the normal functions of presenilins nor the mechanism(s) by which familial Alzheimer’s disease (FAD)-linked mutations cause AD have been defined. Presenilin 1 (PS1) is a polytopic membrane protein that is subject to endoproteolytic processing in vivo; PS1 derivatives accumulate to saturable levels and to \( \sim 1:1 \) stoichiometry by mechanism(s) that are not fully defined. We show here that the two fragments coassemble. Moreover, we have detected neither interactions between PS1/PS2 and amyloid precursor protein (APP) nor influences of presenilin expression on APP maturation/secretion. To examine the in vivo function(s) of PS1, we developed mice with functionally inactivated PS1 alleles. These animals die before birth and exhibit several developmental defects, including a poorly differentiated vertebral column, a phenotype traced to abnormal segmentation of somites. Whole mount in situ hybridization analyses reveal that specification of somitic cell lineages is apparently unaffected, despite the clear disruption in somite segmentation. However, notable differences in expression of Notch1 and Dll1 mRNAs were observed in PS1\(^{-/-}\) embryos; in contrast to wild-type embryos in which abundant expression of Notch1 and Dll1 mRNAs are observed in the presomitic mesoderm, the expression of these genes is nearly abolished in the PS1\(^{-/-}\) embryos. Hence, PS1 serves to regulate the spatiotemporal expression of Notch1 and Dll1 in the paraxial mesoderm. Finally, we failed to detect any differences in the levels of A\(\beta\)42 and A\(\beta\)40 in brains of mice heterozygous for PS1 relative to wild-type littermates. Thus, mutations in PS1 probably cause AD not by the loss but rather by the gain of deleterious function of mutant polypeptides.

*From the Departments of Pathology (SSS, GT, PCW, DRB, MKL, DLP), Neurology (DLP), Neuroscience (SSS, JR, DLP), and the Neuropathology Laboratory (SSS, GT, PCW, DRB, MKL, AD, HC, HHS, TR, FD, CH, DLP), The Johns Hopkins University School of Medicine, Baltimore, Maryland; Merck Research Labs (HZ, LHTV), Rahway, New Jersey; Mayo Clinic (CE, SGY), Jacksonville, Florida; Mammalian Genetics Laboratory, ABL-Basic Research Program, NCI-Frederick Cancer Center Research & Development (NAJ, NGC), Frederick, Maryland
Introduction

Alzheimer’s disease (AD), the most common cause of dementia in the elderly, is associated with several risk factors, including age and inheritance. The majority of early-onset cases of AD (onset <60 years) are inherited as autosomal dominant disorders. To date, mutations have been identified in three genes that cosegregate with affected members of FAD pedigrees: the \textit{APP} gene on chromosome 21 (Goate et al. 1991; Chartier-Harlin et al. 1991; Naruse et al. 1991; Mullan et al. 1992; Hendricks et al. 1992), the \textit{PS1} gene on chromosome 14 (Schwab 1977; Sherrington et al. 1995), and the \textit{PS2} gene on chromosome 1 (Levy-Lahad et al. 1995; Rogaev et al. 1995). Although mutations in \textit{APP} cosegregate with \(\sim 19\) pedigrees with FAD, mutations in \textit{PS1} are causative in \(\sim 25-30\%\) of pedigrees with early-onset FAD (Schellenberg 1995). Over 35 missense mutations (Cam­pion et al. 1995; Chapman et al. 1995; Clark et al. 1995; Cruts et al. 1995; Sherrington et al. 1995; Wasco et al. 1995; Boteva et al. 1996) and a point mutation upstream of a splice acceptor site that results in an inframe deletion of exon 9 (\textit{PS1}\_E9; Perez-Tur et al. 1995) have been identified in the \textit{PS1} gene in families with early onset FAD.

The normal function(s) of presenilins in vertebrates has not been defined. In this regard, a homologous gene in \textit{C. elegans}, termed \textit{sel-12}, has been identified that facilitates signalling mediated by the Lin-12/Notch family of receptors involved in developmental cell fate specification and lateral inhibition (Levitan and Greenwald 1995). Moreover, the mechanism(s) by which FAD-linked mutations cause AD is unresolved. The absence of nonsense or frameshift mutations leading to truncated PS1/PS2 supports the notion that AD is caused not by the loss but rather by the gain of deleterious function of mutant polypeptides. In support of this view, studies of A\(\beta_{40}\) and A\(\beta_{42} (43)\) production in the conditioned medium from fibroblasts or plasma of affected members of pedigrees with \textit{PS1}/\textit{PS2} linked mutations (Scheuner et al. 1996) transfected mammalian cells, and the brains of transgenic mice (Borchelt et al. 1996; Duff et al. 1996; Citron et al. 1997; Tomita et al. 1997) reveal that one mechanism by which mutant PS1 cause AD is by the acquisition (or enhancement) of property(ies) that influence APP processing in a manner that leads to increased extracellular concentrations of A\(\beta_{42} (43)\). In addition, ICC studies have demonstrated massive A\(\beta_{42} (43)\) deposition in the cerebral cortex and severe cerebellar pathology, including A\(\beta_{42}\)-reactive plaques, many bearing dystrophic neurites and reactive glia in individuals with a PS1-linked E280A mutation (Lemere et al. 1996). These data suggest that the FAD-linked PS1/PS2 variants influence processing at the “\(\gamma\)-secretase” site and cause AD by increasing the extracellular concentration of highly amyloidogenic A\(\beta_{42} (43)\) species, thus fostering A\(\beta\) amyloid deposition in the brain.