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Function and Dysfunction of the Presenilins

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Alzheimer disease (AD), a progressive neurodegenerative disorder, is the most common type of dementia, occurring in mid to late life. The neuropathological hallmarks of this disease include the presence of extracellular deposits of highly fibrillogenic A β 42 peptides in senile plaques and intraneuronal accumulations of hyperphosphorylated τ in neurofibrillary tangles (see Giulian 1999 [in this issue]). Although most cases of AD occur as age-associated disorders, autosomal dominant inheritance of mutant genes encoding the β -amyloid precursor protein (APP), presenilin 1 (PS1), or presenilin 2 (PS2) cause early-onset AD in several families (i.e., familial AD [FAD]; for review, see Price and Sisodia 1998). In large part, the clinical and neuropathological features of PS1-linked AD are much more severe than those of sporadic AD: the age at onset of disease can be as early as the mid 20s, in some pedigrees, with more-rapid progression than is typically seen in late-onset AD. Brains from individuals with PS1-linked FAD show severe A β deposition and neurofibrillary tangles (for review, see Price and Sisodia 1998). Here we summarize genetic and developmental findings on the normal biology of presenilin, as well as data from cell-culture and transgenic animal experiments that probe the dysfunction of disease-related presenilin variants.

Genetics of Presenilin-Linked Early-Onset AD

The families examined for identification of the locus harboring PS1 were selected on the basis of the presence of a family mean age at onset \leq 52 years and clear autosomal dominant inheritance of AD. The locus, called "AD3," was linked to a marker on 14q24.3 (Schellenberg et al. 1992; reviewed by Tanzi 1996). AD3 does not appear to be subject to epistasis from other loci.

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Positional cloning defined a minimal cosegregating region in 21 pedigrees with autosomal dominant AD, and Sherrington et al. (1995) isolated a novel cDNA that corresponded to a sequence from this interval. The AD3-linked disease gene, now called "*presenilin-1*" (PS1), encodes a protein of 467 amino acids, and Sherrington and colleagues identified missense mutations in this gene that cosegregate with FAD in five of these families. Subsequent database searches revealed a close homologue of PS1, called "*presenilin 2*" (PS2), which maps to 1q31-42, a region implicated in a large, well-characterized FAD pedigree, the Volga Germans (VG). Missense mutations in PS2 cosegregate with FAD in an unrelated Italian FAD pedigree as well as in the VG group (Levy-Lahad et al. 1995a, 1995b; Rogaev et al. 1995).

To date, >60 different mutations in PS1 or PS2 have been described in >100 families, of various ethnic origin, with early-onset FAD (for review, see Tanzi et al. 1996). More than 75% of the reported FAD mutations in PS1 occur in single kindreds, thus the characterization of them as "private" mutations. With two notable exceptions, all presenilin mutations are missense substitutions. However, in several unrelated pedigrees, intronic mutations in PS1 lead to transcripts that lack exon 9 (Δ Ex9), which encodes PS1 with an in-frame deletion of 29 amino acids and an amino acid substitution. Furthermore, a single-nucleotide deletion at the consensus splice-donor sequence in intron 4 has been observed in two related individuals with autopsy-confirmed early-onset AD. The mutant transcripts that result are predicted to encode prematurely truncated PS1 polypeptides (reviewed by Price and Sisodia 1998).

Presenilin Structure and Metabolism

The topology of PS1 (and of its *Caenorhabditis elegans* homologues, SEL-12 and HOP-1) has been determined with use of a variety of biochemical and cell-biological approaches. These studies reveal that presenilins span the membrane eight times, with exposure of N- and C-termini and of a "loop" region between transmembrane helices 6 and 7 to the cytosol (Doan et al. 1996; Li and Greenwald 1996). PS1 and PS2 are not substrates for sulfation, glycosylation, or acylation (reviewed by Selkoe 1998), but serine residues in the N-

terminus and loop domains of PS1 and PS2 are phosphorylated *in vivo*. Although PS1 is synthesized as a polypeptide with an apparent molecular weight of ~42–43 kD, the preponderant PS1-related species that accumulate in cultured mammalian cells, brain, and systemic tissues are ~30 kD N-terminal fragments (NTF) and ~20 kD C-terminal fragments (CTF) (reviewed by Selkoe 1998). PS1 endoproteolysis occurs at amino acids 292 and 299 (Podlisny et al. 1997), and the FAD-associated PS1 variant, Δ Ex9, which lacks amino acids 290–319, is not cleaved (Thinakaran et al. 1996).

Analysis of PS1 expression in transgenic mouse brain and in cultured cells of neuronal and nonneuronal origin indicates that the accumulation of PS1 fragments is tightly regulated by associations with limiting cellular components (Thinakaran et al. 1996). Thus, overexpression of PS1 or of PS2 leads to very minimal elevations in the levels of fragments, whereas the bulk of the excess full-length PS1 and PS2 is rapidly degraded by the proteasome (Kim et al. 1997; Podlisny et al. 1997). Although the identity of the protease and the physiological significance of PS1 proteolysis are not known, the paucity of full-length PS1 and the tight regulation of the stoichiometry and expression level of presenilin fragments strongly suggest that the cleaved NTF and CTF are the biologically active forms of the protein. Like PS1, PS2, *C. elegans*, SEL-12, and *Drosophila melanogaster* presenilins are also subject to endoproteolytic cleavage, which indicates that presenilin endoproteolysis is a highly conserved process.

The observation that PS1 or PS2 fragments accumulate in 1:1 stoichiometry suggests that the NTF and CTF may coassociate, perhaps in higher-order assemblies. Two lines of evidence support this notion. First, fragments derived from PS1 or PS2 can be specifically coimmunoprecipitated from lysates of cultured cells or mammalian brain (Thinakaran et al. 1998). PS1- and PS2-derived fragments do not form mixed assemblies and, although fragments derived from a chimeric PS1/PS2 polypeptide can self-assemble, they do not interact with fragments derived from wild-type PS1 or PS2 (Saura et al. 1999). Thus, presenilin assembly appears to be tightly coupled with biosynthesis. Second, gel-filtration chromatography and velocity gradient-fractionation studies reveal that PS1, NTF, and CTF remain associated in large detergent-sensitive complexes (reviewed by Selkoe 1998; Yu et al. 1998). The components of the high-molecular-weight complexes are not known, although several proteins that interact with various domains of PS1 or PS2 have been identified by use of yeast two-hybrid assays. Among these putative presenilin-interacting proteins are five armadillo-related proteins: α -, β -, and γ -catenin; p0071; and neural-specific plakophilin (Zhou et al. 1997; Yu et al. 1998; Stahl 1999). Notably, FAD-linked PS1 missense variants are

reported to destabilize and cause defective intracellular trafficking of β -catenin (Zhang et al. 1998; Nishimura et al. 1999). None of the identified interactors appears to influence presenilin processing or accumulation of its derivatives.

Function of Presenilins

The first major insight regarding presenilin function emerged with the discovery of a homologous gene in *C. elegans*, *sel-12*. *sel-12* interacts with genes in the Notch-signaling pathway, which has been widely studied for clues to epithelial-cell determination and nervous system-tissue development. Gain-of-function alleles of *lin-12* and *glp-1*, two *C. elegans* homologues of *Notch* (Levitan and Greenwald 1995), cause a multivulval phenotype, but this effect can be suppressed by mutations in *sel-12*. In a wild-type background, mutant *sel-12* alleles cause a defect in egg laying. Because this phenotype is rescued efficiently by transgenic expression of human PS1 and PS2, it appears that the homologous proteins can function interchangeably (Levitan et al. 1996; Baumeister et al. 1997). Human FAD-linked PS1 variants, on the other hand, only partially rescue the egg-laying defect (Levitan et al. 1996; Baumeister et al. 1997). A second *C. elegans* protein, Hop-1, also rescues the egg-laying defect of a *sel-12* mutant (Li and Greenwald 1997), and reduction of *hop-1* activity in a *sel-12*-deficient strain reveals developmental phenotypes that are similar to those of single and double mutants of *lin-12* and *glp-1*. Because these phenotypes are not observed in worms with single homozygous deletions of *sel-12* or of *hop-1*, it appears that the products of these genes are functionally redundant (Li and Greenwald 1997; Westlund et al. 1999). Two models have been proposed to account for the genetic interactions between the worm presenilins (*Sel-1* and *Hop-1*) and the *Notch* homologues, particularly *Lin-12*. First, the presenilins could regulate LIN-12 trafficking and cell-surface expression. Alternatively, SEL-12 could act in a signaling capacity, to modulate pathways activated after LIN-12 binding to cognate ligands.

Despite the insights derived from the *C. elegans* experiments, the biological functions of PS1 and PS2 in mammals during development and aging are not fully understood. The general spatial and temporal expression patterns of *presenilin* mRNA during embryonic development do not coincide directly with the expression patterns of any specific member of the known mammalian *Notch* homologues, suggesting either that PS1 functions promiscuously or that its role is not limited to Notch signaling (Lee et al. 1996). Mice with homozygous disruptions of *PS1* die in late embryogenesis (Shen et al. 1997; Wong et al. 1997) and exhibit severe defects in somite development and, subsequently, in the develop-

ment of the axial skeleton and ribs. The early somite defect in *PS1*^{-/-} embryos is highly reminiscent of the phenotype in mice lacking Notch1 or its ligand, Dll1, although the latter animals die too early in development for a skeletal phenotype to be manifest. Remarkably, *Notch1* and *Dll1* mRNA expression is considerably reduced in the presomitic mesoderm of *PS1*^{-/-} mice (Wong et al. 1997). In addition, all the observed *PS1*^{-/-} embryos exhibited intraparenchymal hemorrhages after day 11 of gestation, a phenotype shared with embryos lacking Dll1. A series of transgenic rescue experiments have shown that either wild-type or FAD-linked PS1 variants can rescue *Notch1* mRNA expression in the presomitic mesoderm in early embryos and in the entire spectrum of developmental deficits in *PS1*^{-/-} mice (reviewed by Price and Sisodia 1998). Because the FAD-linked PS1 variants retain their normal function during mammalian embryonic development, we argue that PS1-linked FAD is not a haploinsufficiency condition but, rather, is due to the mutant protein's gain of function (see The Role of Presenilin in Metabolism of APP and Notch). There are no reports of mice lacking *PS2*, either alone or in combination with *PS1*.

The Role of Presenilin in Metabolism of APP and Notch

In both naive and stably transfected cells, PS1 is restricted to the endoplasmic reticulum (reviewed by Selkoe 1998; S. H. Kim, G. Thinakaran, J. Lah, A. Levey, S. S. Sisodia, unpublished data). Analyses done with cell fractionation, light microscopy, and electron microscopy show that the presenilins and their endoproteolytic derivatives are associated predominantly with rough and smooth endoplasmic reticulum (ER) elements and are excluded from the Golgi apparatus and the ER-Golgi intermediate compartment (Lah et al. 1997; Zhang et al. 1998; S. H. Kim, G. Thinakaran, J. Lah, A. Levey, S. S. Sisodia, unpublished data).

The most provocative insight pertaining to the mechanisms by which mutant PS1 predisposes carriers to FAD emerged initially from studies of the biosynthesis and maturation of APP. As depicted in figure 1, APP is subject to cleavage at several sites. A β peptides are liberated from APP by the concerted action of two enzymatic activities, β - and γ -secretases. The β -secretase acts first, by clipping the protein at a single site, releasing an extracellular N-terminal domain and leaving a C-terminal "stub" that encompasses 28 amino acids of the ectodomain, as well as the transmembrane (TM) and the cytoplasmic domains. Two γ -secretase sites are found 12 and 14 amino acids into the TM, and cleavage at these sites releases A β 42 and A β 40, respectively. Both of these products accumulate in the extracellular space, but A β 42 is particularly susceptible to fibril formation in vitro. As

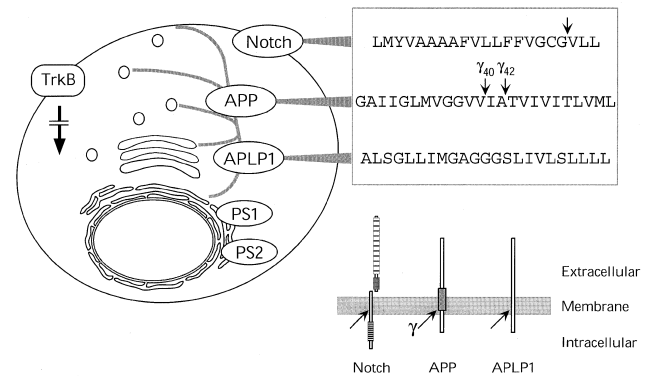


Figure 1 Effects of PS1 deficiency on membrane protein trafficking and cleavage. PS1-deficient neurons fail to cleave the amyloid-precursor protein APP and to secrete the APP extracellular fragment, A β . This defect has been ascribed to the absence of so called γ -secretase activity, which perhaps is mediated directly by PS1. However, PS1-deficient cells also secrete soluble APP derivatives at a faster rate, suggesting that the trafficking of APP is altered. Recent studies indicate that, in addition to APP, APLP1 and Notch1 are also cleaved inefficiently in PS1-deficient cells. Interestingly, the transmembrane domains of APP, APLP1, and Notch1 (boxed) contain little sequence similarity. In neurons lacking PS1, the maturation and the ligand-dependent autophosphorylation activity of the receptor tyrosine kinase TrkB are also severely compromised. Thus, it is likely that PS1 may influence trafficking and metabolism of selected membrane proteins, including APP, APLP1, Notch 1, and TrkB.

discussed below, cleavage at both of these γ -secretase sites is strongly suppressed in animals that lack PS1 function, so the larger C-terminal APP stub accumulates in PS1-deficient cells. However, the dominantly acting presenilin mutations that are found in patients with FAD have a different effect on this pathway. As Scheuner et al. (1996) showed, affected individuals in kindreds with PS1 or PS2 exhibit an elevated A β 42:A β 40 ratio in their plasma, an effect that is also seen in conditioned medium from patients' fibroblasts or from mammalian cells transfected with mutant PS1 cDNA. The brains of transgenic mice expressing mutant PS1 show the same elevation of A β 42 relative to A β 40 (reviewed by Price and Sisodia 1998; Selkoe 1998).

Transgenic mice coexpressing FAD-linked PS1 variants and the Swedish APP FAD variant (APP^{Swe}) exhibit numerous amyloid deposits associated with dystrophic neurites and reactive astrocytes, and these lesions appear much earlier than those seen in mice expressing APP^{Swe} only (Borchelt et al. 1997; Holcomb et al. 1998). These data demonstrate that the PS1 mutations act in synergy with APP^{Swe}, to accelerate the rate of amyloid deposition. Similarly, immunocytochemical investigations of brains of patients with PS1-linked FAD show significant increases in A β 42 deposition, compared with brain tissue from patients with sporadic AD (Lemere et al. 1996). Collectively, these findings suggest that mutations in PS1

cause disease primarily by elevating extracellular concentrations of A β 42 to promote amyloid deposition.

The mechanisms by which mutant presenilin influences production of A β 42 peptides are not known. However, reports that full-length PS1 and PS2 form stable heteromeric assemblies with APP in cultured mammalian cells suggest that mutant PS1 facilitates cleavage by the activity of an ill-defined proteolytic enzyme, described as a γ -secretase (Weidemann et al. 1997; Xia et al. 1997). On the other hand, we and others have failed to detect any interaction between the presenilins and APP (Thinakaran et al. 1998; Ray et al. 1999). The latter findings, together with the nonoverlapping subcellular distributions of the presenilins in the ER and in the endosomal/plasma membrane sites where A β peptides are generated, argue against a direct role of PS1 or PS2 in the cleavage of APP.

In this regard, the recent observation that neurons from PS1 knockout mice fail to secrete A β peptides (DeStrooper et al. 1998; Naruse et al. 1998) might support the view that PS1 itself acts as a γ -secretase. Studies done by Selkoe and colleagues show substantial reductions in A β secretion and increased accumulation of cytoplasmic APP fragments in Chinese-hamster-ovary cells that express variants of PS1 harboring artificial mutations of aspartate residues in transmembrane domains 6 and 7 (Wolfe et al. 1999). Interestingly, these mutant PS1 molecules are not subject to endoproteolysis, and the suggestion that PS1 contains an intrinsic proteolytic activity may support the view that PS1 acts directly on APP, as a γ -secretase (Wolfe et al. 1999). It will be critical for investigators to test this model by reconstituting these proteolytic activities with purified components.

Regardless of the outcome of such studies, PS1 deficiency clearly affects the proteolytic activation of Notch1. In PS1-deficient immortalized fibroblasts, a constitutively active Notch1 variant is clipped from its membrane domain only inefficiently and it fails to be released from the plasma membrane or to accumulate in the nucleus, where it would otherwise activate the transcription of target genes (DeStrooper et al. 1999). Since these conclusions were derived from analysis of a constitutively active form of Notch1, it will be of interest to evaluate the role of PS1 in the proteolysis and biological activity of wild-type Notch, in both the absence and presence of ligand. In this regard, Struhl and Greenwald (1999) demonstrated that null mutations in the *D. presenilin* gene lead to extensive neuronal hyperplasia and deformed wing phenotypes, similar to those observed in *Notch* flies; these authors found that, in the absence of *presenilin*, ligand-dependent Notch-signal transduction is abolished, and the cytosolic domain, derived from transmembrane forms of Notch, fails to enter the nucleus. Nuclear import of a constitutively active cytosolic form of Notch is normal in these flies, sug-

gesting that the loss of Notch proteolysis in *presenilin* flies accounts for their signaling failure and for the consequent developmental abnormalities. However, Ye et al. (1999) also studied *Drosophila* with loss-of-function alleles of *presenilin* and, although they confirm the neurogenesis defects in these strains, their work leads to different conclusions about the role of proteolysis. In contrast to the observations by Struhl and Greenwald (1999), Ye et al. (1999) observe that *presenilin* mutations block signals mediated by either the membrane-tethered or the cytosolic forms of Notch1, indicating that presenilin acts elsewhere in the Notch pathway to permit normal neuronal and wing-disk development. To date, there is no explanation for these divergent findings; but, in view of differences in the chimeric Notch reporters used in these studies, it is plausible that these molecules are differentially sensitive to loss of *presenilin* function.

Although there are obvious parallels between the proteolysis of APP and Notch1, we find it inconceivable that PS1 is the endoprotease involved in intramembrane cleavage of each substrate. There is little, if any, homology between the Notch1 and APP transmembrane domains, and the positions of the scissile bonds, with respect to the boundaries of each transmembrane helix, are quite different (see fig. 1). Furthermore, we recently demonstrated that a C-terminal portion of the APP homologue APLP1 also accumulates in *PS1*^{-/-} neurons (Naruse et al. 1998). Because the APP and APLP1 transmembrane domains also have very limited homology (fig. 1), we favor the alternative hypothesis—that ER-associated PS1 indirectly influences the endoproteolysis of APP, APLP1, and Notch1 by altering trafficking and compartmentalization of these proteins with specific proteases that act later in the secretory pathway. In this regard, the maturation of other integral membrane glycoproteins, such as the receptor tyrosine kinase TrkB, are also impaired in PS1-deficient neurons (Naruse et al. 1998). In *C. elegans*, as well, reduced Sel-12 activity appears to perturb development by altering the localization of critical signaling molecules. Thus, vulval precursor cells in mutant animals express abnormally low levels of Lin-12 protein on their apical membrane (Leviton and Greenwald 1998). Because Sel-12 is localized primarily to the ER or Golgi in nematode cells, it appears that one widely conserved function of the presenilins may be the control of intracellular transport of Notch homologues.

Conclusions and Future Directions

The discovery that mutations in genes encoding PS1 and PS2 are linked to FAD has ushered in a new and extremely exciting era of research, aimed at clarifying the cellular and molecular biology of the presenilin polypeptides and the relationships of the genetic variants to

the pathogenesis of AD. Neither the manner in which the presenilin derivatives assemble in the lipid bilayer nor the nature of the apparatus responsible for endoproteolysis and regulation of presenilin localization and stability is known. Equally intriguing are the mechanisms by which FAD-linked mutant PS1 causes selective increases in the production of highly fibrillogenic A β 42 peptides and accelerates A β deposition in brains of transgenic mice. The surprising discovery that loss of PS1 function abrogates A β production and causes the C-terminal stub of APP to accumulate in cells has led to the suggestion that PS1 acts as a γ -secretase. However, because multiple structurally unrelated membrane proteins are abnormally distributed and incorrectly processed in cells that lack PS1, we favor the view that presenilins act indirectly in the processing of APP, by promoting the colocalization of APP with some specific proteinase.

Although the importance of the role of PS1 in the regulation of somitogenesis is now established, the mechanisms by which PS1 facilitates Notch processing and signaling in mammalian cells, *Drosophila*, and *C. elegans* are just beginning to emerge. Despite widespread interest in the significance of presenilins to aging, no postembryonic functions of PS1 have been defined. Future efforts directed at generation of transgenic animals in which PS1 genes can be conditionally ablated in a temporal and/or tissue-specific manner will be necessary in order to address this important issue.

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