Presenilins in the Developing, Adult, and Aging Cerebral Cortex

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Mutations in presenilins are the major cause of familial Alzheimer disease. The involvement of presenilins in the pathogenesis of Alzheimer disease, therefore, has been the subject of intense investigation during the past decade. Genetic analysis of phenotypes associated with presenilin mutations in invertebrate and vertebrate systems has greatly advanced our understanding of the in vivo functions of presenilins. In this review, the authors will summarize the current understanding of presenilin function, with an emphasis on the mammalian cerebral cortex. During development, presenilins play crucial roles in the maintenance of neural progenitor cell proliferation, the temporal control of neuronal differentiation, the survival of Cajal-Retzius neurons, and proper neuronal migration in the developing cerebral cortex. Analysis of presenilin function in the adult cerebral cortex has revealed essential roles for presenilins in synaptic plasticity, long-term memory, and neuronal survival. The authors will also discuss the molecular mechanisms through which presenilins may mediate these functions, including the Notch, CREB, and NMDA receptor–mediated signaling pathways. These diverse functions of presenilins in cortical development and function and neuronal survival have important implications for the pathogenesis of neurodegenerative dementia. NEUROSCIENTIST 11(5):441–451, 2005. DOI: 10.1177/1073858405278922

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Presenilins in Alzheimer Disease and Frontotemporal Dementia

Presenilins (PS1 and PS2) are the major causative genes of early-onset (<65 years of age) familial Alzheimer disease (FAD). Alzheimer disease is characterized clinically by progressive memory loss and deterioration of cognitive functions, and neuropathologically by extracellular amyloid plaques, intracellular neurofibrillary tangles, and synaptic and neuronal losses. PS1 was initially identified by human linkage analysis followed by sequencing of candidate loci to detect mutations that cosegregate with early-onset FAD (Sherrington and others 1995). Shortly after the cloning of PS1, PS2 was identified by sequence similarity to PS1 (67% sequence identity) and by its mutations associated with patients with FAD (Levy-Lahad and others 1995; Rogaev and others 1995).

Large numbers of FAD-associated mutations have been identified in PS1 (n > 140), whereas a smaller number of FAD-linked mutations have been found in PS2 (n = 8) and the amyloid precursor protein (APP) (n = 23) (St George-Hyslop 2000; Sorbi and others 2001). Presenilin mutations are the causative genetic lesions in approximately 50% of FAD cases, whereas APP mutations represent only 5% to 7% of early-onset FAD cases (Sorbi and others 2001). All FAD mutations identified to date are dominantly inherited, and most are missense mutations, with the exception of a few exonic deletion mutations in PS1.

In addition to AD, mutations in PS1 may also result in frontotemporal dementia (FTD), which shares some common features with AD and is sometimes associated with mutations in the microtubule-associated protein tau (Lee and others 2001). FTD is clinically characterized predominantly by behavioral changes including emotional blunting, frontal disinhibition, apathy, and loss of initiative, followed by language impairment, whereas memory is relatively preserved at early stages. Neuropathologically, the most striking feature of FTD is focal lobar atrophy affecting the frontal and temporal lobes. Histopathologically, there is regional loss of cortical neurons in the frontal and temporal lobes, accompanied by neurofibrillary tangles and in some cases Pick bodies. The distinguishing feature of FTD relative to AD is the absence of amyloid plaques (Lee and others 2001). Recent reports have identified three PS1 mutations in FTD and Pick disease (Amtul and others 2002; Dermaut and others 2004; Hutton 2004). Furthermore, one *PS1*

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mutation associated with FTD has been found to exhibit no γ-secretase activity (Amtul and others 2002).

Presenilins: Structure, Expression, and Subcellular Localization

PS1 is a transmembrane protein containing eight membrane-spanning domains and a hydrophilic loop region (Doan and others 1996; Li and Greenwald 1996; Li and Greenwald 1998). PS1 is localized primarily to the endoplasmic reticulum (ER)/Golgi subcellular compartment with the N-terminal, loop, and C-terminal domains oriented toward the cytoplasm (Doan and others 1996; Kovacs and others 1996; Walter and others 1996). Presenilins have also been localized to the plasma membrane (Dewji and Singer 1996; Dewji and Singer 1997a, 1997b; Ray and others 1999; Kaether and others 2002). The majority of endogenous PS1 undergoes regulated and rapid endoproteolytic processing into 27 kDa N-terminal and 18 kDa C-terminal fragments (Borchelt and others 1996; Doan and others 1996). Full-length PS1 is primarily localized in the ER where it undergoes endoproteolysis, whereas the resulting fragments are colocalized in the Golgi compartment, which remain closely associated with each other within the lipid bilayer (Xia and others 1998; Yu and others 1998).

Presenilins are broadly expressed in a variety of tissues including the brain (Levy-Lahad and others 1995; Rogaev and others 1995; Sherrington and others 1995). The level of *PS1* mRNA is significantly higher in the developing than in the adult mouse brain, and *PS1* transcripts are more abundant than the *PS2* mRNA (Lee and others 1996). The *PS* genes are predominantly expressed in neurons (Cook and others 1996; Kovacs and others 1996), although their expression in glia has also been reported (Lah and others 1997). The PS proteins are principally localized in the cell body and dendrites, but they have also been detected in neurite growth cones and axonal vesicles (Cook and others 1996).

PS1 transcripts are expressed from the beginning of neurogenesis (E8.5) at low levels throughout the neural tube. By E12.5 in mice and E13.5 in rats, *PS1* expression becomes noticeably enriched within the ventricular zone, where neural progenitor cells reside (Moreno-Flores and others 1999; Handler and others 2000). By E18.5, PS1 expression is also visible in the dorsal root and trigeminal ganglia (Moreno-Flores and others 1999). Although relative *PS2* mRNA levels remain lower than those of *PS1* throughout embryogenesis, there are two transient peaks of *PS2* expression at E12.5 and E15.5 (M.W.S. and J.S., unpublished results). During early postnatal development in rats, a peak in *PS1* expression was observed at postnatal day 10 (P10) during the period of synaptogenesis in the developing cerebellum and hippocampus (Moreno-Flores and others 1999). In contrast to the diminishing expression of *PS1* in the postnatal brain, *PS2* expression increases by postnatal day 21 (P21), and its expression level becomes similar to that of PS1 in the adult cerebral cortex (M.W.S., S.G., and J.S., unpublished results).

Animal Models of Presenilins

Caenorhabditis elegans

In *C. elegans*, identification of the *PS1* homolog *sel-12,* which facilitates signaling mediated by LIN-12, provided the first evidence that PS1 interacts with the LIN-12/Notch signaling pathway (Levitan and Greenwald 1995). LIN-12 is a member of the LIN-12/Notch family of receptors, which mediate cell-cell interactions that specify cell fate during development. SEL-12 affects LIN-12 activity by regulating its processing and/or trafficking (Levitan and Greenwald 1998; Okochi and others 2000). PS1 shares functional homology with SEL-12, based on the finding that wild-type human *PS1* cDNA complements the *sel-12* mutant phenotype (Levitan and others 1996; Baumeister and others 1997). However, six different PS1 cDNAs containing FAD-linked mutations A246E, M146L, H163R, L286V, C410Y, or PS1DE9 exhibited reduced ability to rescue *sel-12* mutations, suggesting that mutant PS1 has reduced biological activity (Levitan and others 1996; Baumeister and others 1997). Double presenilin mutants, *sel-12* and *hop-1* (the worm homolog of mammalian *PS2*), have been reported to exhibit altered temperature memory and abnormal neurite morphology (Wittenburg and others 2000). Subsequent studies were unable to corroborate these data (Altun-Gultekin and others 2001), making it less clear whether presenilins contribute to complex neurological functions such as learning and memory in *C. elegans*.

Drosophila

Studies of the single *Drosophila* presenilin homolog have further emphasized the functional connection between presenilin and Notch, and the essential role of presenilin in the central nervous system. *Drosophila* mutants lacking both maternal and zygotic presenilins exhibit a neurogenic phenotype and are virtually indistinguishable from *Notch* loss-of-function mutant (Struhl and Greenwald 1999; Ye and others 1999). Similar to *Notch* loss-of-function mutants, flies deficient in maternal and zygotic PS display neural hyperplasia and disorganization of the central nervous system at embryonic stages, indicating that presenilin normally regulates progenitor proliferation and/or differentiation (Ye and others 1999). More specifically, flies lacking zygotic PS have a loss of dorsal-ventral organization and marker expression in the wing discs, concomitant with expanded sensory organ precursor pools and proneural gene expression (Ye and others 1999). Furthermore, in *Drosophila,* it was demonstrated that presenilin is required for the ability of *Notch* overexpression to induce the neurogenic phenotype; however, the requirement of PS function is bypassed when the extracellular domain of Notch is absent (Struhl and Greenwald 1999). Thus, PS may be required to activate Notch via release of its intracellular domain and initiation of downstream signaling.

Mouse

In addition to genetic studies in flies and worms, mice are a valuable genetic system to evaluate the role of presenilins in brain development and in higher cognitive functions within the adult brain. Mice carrying a germline deletion of *PS1* die immediately after birth, which may result from impaired respiratory mechanics due to marked deformities of the ribcage (Shen and others 1997). In addition to perinatal lethality, *PS1–/–* mice display severe cerebral hemorrhage and widespread skeletal abnormalities: shortened vertebral column with truncated tail, abnormal ribcage, and curved spine (Shen and others 1997; Wong and others 1997). The segmentation and somitogenesis defects of *PS1–/–* embryos resemble those of *Notch1–/–* mice (Swiatek and others 1994; Conlon and others 1995). Detailed analysis of the brain of *PS1*-null embryos revealed enlarged lateral ventricles and reduced neural progenitor and neuronal populations caused by premature differentiation of neural progenitor cells (Shen and others 1997; Handler and others 2000). Combined, these abnormalities illustrate the key role presenilins serve in morphogenesis of the developing cortex.

Although *PS2–/–* mice lack any detectable phenotype, mice deficient in both PS1 and PS2 exhibit a more severe phenotype than *PS1–/–* and *Notch1–/–* mice, with earlier embryonic lethality (before E9.5) and more severe morphological abnormalities (Donoviel and others 1999; Herreman and others 1999). Specifically, *PS1–/–* and *PS2–/–* embryos have abnormal somite segmentation, disorganized ventral neural tube, delayed neuropore closure, and other patterning deficits involving the heart and second branchial arch. Similar to *Notch1* mutants, *PS1–/–* and *PS2–/–* embryos have mesenchymal cell loss in the midbrain, disorganized neuroepithelium, and heart malformation (Donoviel and others 1999).

To circumvent the perinatal lethality associated with *PS1–/–* mice and to restrict spatial and temporal inactivation of PS1 alone or both PS1 and PS2, a panel of single and double conditional mutants have been generated and characterized (Feng and others 2001; Yu and others 2001; Dewachter and others 2002; Feng and others 2004; Saura and others 2004; Wines-Samuelson and others 2005) using the Cre/loxP recombination system. Three lines of Cre transgenic mice have been used to inactivate *PS1* in a cell type–specific manner. First, *Nestin-Cre* mice, in which Cre is expressed under the control of the *Nestin* promoter in neural progenitor cells (NPCs) beginning at E9.5 and NPC-derived neurons and glia, were used to generate NPC-*PS1* cKO mice (Wines-Samuelson and others 2005). Second, *CaMKII-Cre* mice, in which Cre is expressed under the control of the α isoform of the *calcium/calmodulin-dependent kinase II* promoter in excitatory neurons of the forebrain (FB) beginning at postnatal day 18 (P18), were used to generate FB-*PS1* cKO and FB-*PS* cDKO mice (Feng and others 2001; Yu and others 2001; Feng and others 2004; Saura and others 2004). Thy1-*Cre* mice, in which Cre is expressed under the control of the *Thy1* promoter in postmitotic neurons beginning at the perinatal stage (Moechars and others 1996; Spittaels and others 2000), were used to generate neuron-specific *PS1* cKO mice (Dewachter and others 2002).

Presenilins in the Developing Cerebral Cortex

Neuronal Differentiation and Cell Fate Decision

The first evidence that presenilins play a critical role in normal development of the brain was derived from the analysis of *PS1–/–* mice (Shen and others 1997). This analysis of the in vivo function of presenilin demonstrated that PS1 is required for the normal maintenance of neural progenitor population. Beginning at E12.5, before the widespread development of cerebral hemorrhage, *PS1*-null mice exhibit marked reductions in the ventricular zone, where neural progenitor cells reside, followed by subsequent loss of neurons, leading to severe cerebral cavitation. These observations raised the possibility that PS1 may be required for neuronal survival, in addition to its role in the maintenance of neural progenitor cells.

Further studies elucidated the precise nature of the neural progenitor depletion as premature differentiation of the progenitors into neurons. In Handler and others (2000), it was documented that excessive numbers of postmitotic neurons populated the diencephalon and telencephalon of *PS1–/–* embryos from E10.5 through E12.5. Concomitant with the increase in postmitotic neurons, the number of progenitors decreased, indicating a premature depletion of neural progenitor population in the absence of PS1. Thus, PS1 is involved in the cell fate decision between postmitotic neurons and dividing neural progenitor cells. Furthermore, expression of the Notch target gene, *Hes5*, was reduced while expression of the Notch ligand gene, *Dll1*, was increased in *PS1–/–* brains, consistent with reduced Notch signaling in the absence of PS1 (Handler and others 2000). Thus, PS1 may regulate the cell fate decision between postmitotic neurons and neural progenitor cells via the Notch signaling pathway, which is known to regulate cell fate decisions during neural development (Artavanis-Tsakonas and others 1999; Justice and Jan 2002).

Evidence from both invertebrates and mammals suggests that Notch activation suppresses the neuronal lineage cell fate (Schweisguth 2004). In *Drosophila*, Notch-mediated lateral inhibition determines the epidermal-neural cell fate, with Notch activation favoring the suppression of the neural lineage (Simpson 1997). In mammalian development, Notch activation is known to be involved in the maintenance of neural progenitor identity and the suppression of neuronal differentiation (Schuurmans and Guillemot 2002). Targeted disruption in mice of *Notch1* or *RBP-Jκ*, through which the activated Notch intracellular domain exerts its transcriptional activation, results in up-regulation of proneuronal transcription factors and depletion of neural progenitor cells (Swiatek and others 1994; Conlon and oth-

ers 1995; Oka and others 1995; de la Pompa and others 1997; Hitoshi and others 2002). The role of Notch signaling in the maintenance of neural progenitor cells is further supported by gain-of-function studies showing that Notch activation prevents neuronal differentiation (Nye and others 1994; Dorsky and others 1995; Henrique and others 1997; Chambers and others 2001; Scheer and others 2001; Hitoshi and others 2002). Mice deficient for PS1 alone or both presenilins and mice lacking RBP-Jκ display premature neuronal differentiation and/or up-regulation of neuronal markers (Oka and others 1995; de la Pompa and others 1997; Donoviel and others 1999), indicating that the role of Notch activation in suppression of neural or neuronal fate at the level of differentiation is conserved from flies to mice.

Although it was initially thought that PS1 might regulate Notch signaling at the transcriptional level, two subsequent independent studies demonstrated that presenilin regulates Notch signaling at the level of proteolytic cleavage (Wong and others 1997; De Strooper and others 1999; Song and others 1999). Notch is a type I transmembrane protein, with 29 to 36 extracellular EGF-like repeats, 3 Notch repeats, a transmembrane domain, 6 intracellular cdc10/ankyrin-like repeats, and a PEST degradation domain at the carboxyl terminus (Weinmaster 2000; Fortini 2001). There are four mammalian Notch orthologs, with Notch 4 being the smallest of the four, containing fewer EGF-like repeats and a shorter intracellular tail. Notch proteins are processed with three sequential proteolytic steps during protein maturation and ligand-induced activation. During maturation in the *trans*-Golgi compartment, Notch is cleaved by the serine protease furin, resulting in a heterodimer of noncovalently associated extracellular and transmembrane/intracellular fragments (Weinmaster 2000; Fortini 2001). Following ligand binding at the cell surface, the ectodomain is removed by the second proteolytic cleavage of Notch mediated by the ADAM metalloprotease TACE. The final proteolytic cleavage, which releases the intracellular domain of Notch, NICD, is mediated by presenilin-dependent γ-secretase activity. In cultured cells, it has been demonstrated that γ-secretase inhibitors impair Notch proteolysis and signaling (Nakajima and others 2000; Jack and others 2001).

Neuronal Migration and Cortical Lamination

In addition to its central role in the cell fate decision between neural progenitor cells and postmitotic neurons, PS1 is also required for neuronal migration and cortical lamination. The developing *PS1–/–* brain exhibits significant cortical disorganization, including a disrupted demarcation between the intermediate and ventricular zones, along with a thinner cortical plate (Handler and others 2000). Further analysis of NPC-*PS1* cKO mice showed a specific neuronal migration defect of late-born neurons (Wines-Samuelson and others 2005). In contrast to the largely normal positioning of neurons born during early corticogenesis at E12, many of the neurons born later at E16 fail to arrive at their appropriate positions in the superficial layer II/III and are scattered throughout the cortical layers, including layers V and VI (Wines-Samuelson and others 2005). Consistent with these data, gross histological analysis of NPC-*PS1* cKO brains also showed less clear demarcations of the cortical layers. Thus, in the absence of PS1, the late-born neurons exhibit a more pronounced migration defect and fail to migrate past the early-born neurons to arrive at their appropriate destination in the superficial cortical layers.

Radial migration, or the movement of neurons toward the pial surface from the ventricular zone, is guided by the long processes of radial glial cells, which span the cortical wall from the lateral ventricle to the pial membrane (Goldman 2003; Rakic 2003). Interestingly, radial glial generation is impaired in NPC-*PS1* cKO mice, as indicated by the gradual reduction in radial glia in the developing cerebral cortex from E13.5 to E17.5 (Wines-Samuelson and others 2005). Thus, in NPC-*PS1* cKO mice, the inability of late-born cortical neurons to migrate to their appropriate destinations may be explained by the gradual loss of radial glia. The reduction in radial glial generation in NPC-*PS1* cKO mice is consistent with reduced neural progenitor cells in these mice, as radial glia have recently been shown to give rise to neurons and glia (Malatesta and others 2000; Hartfuss and others 2001; Miyata and others 2001; Noctor and others 2001). Furthermore, Notch signaling has been shown to be involved in radial glial development (Gaiano and others 2000; Patten and others 2003; Schmid and others 2003). Thus, reduced Notch signaling in the absence of PS1 may underlie the radial glial and neuronal migration phenotypes observed in NPC-*PS1* cKO mice.

Another mechanism that presenilins may employ to control the proper development of the cerebral cortex is tangential migration of interneurons, which is one of the neuronal migration modes in the mammalian brain (Kriegstein and Noctor 2004). Cortical interneurons born in the ganglionic eminences relocate to the cortex via tangential migration, or horizontal movement roughly parallel to the cortical surface. Once the interneurons enter the cortex, they contact radial glial fibers and begin their second mode of migration, radial migration, to achieve more superficial positions within the cortical wall (Marin and Rubenstein 2001, 2003). Recent work by Louvi and co-workers (2004) reported tangential migration deficits in another *PS1–/–* mouse. The authors found abnormal expression patterns for two markers of GABAergic interneurons, *Gad67* and *Dlx2* in *PS1–/–* mice at E17.5, which they interpreted as failure of the interneurons to migrate tangentially. *Gad67*-positive interneurons aggregate superficially in the *PS1–/–* E17.5 cortex, in contrast to controls, which display migration of *Gad67*-positive interneurons through the deep cortical layers (Louvi and others 2004). The level of *Dlx2* expression in the cortex is increased in *PS1–/–* mutants,

concomitant with decreased expression in the ganglionic eminence, indicating increased tangential migration of *Dlx2* interneurons into the cortex. These data reflect altered regulation of interneuron migration within the embryonic cortex of PS1 mutants, although the mechanism was not addressed. Combined with the radial migration data above, these two studies reveal the multiple neuronal populations dependent on presenilin function for migration.

Cell Death

Consistent with a role for PS1 in cortical lamination, PS1 is also required for the survival of Cajal-Retzius (CR) neurons (Hartmann and others 1999; Wines-Samuelson and others 2005). CR neurons are transient pioneer neurons residing in layer I of the developing cerebral cortex. They secrete the extracellular glycoprotein Reelin, which provides a guidance signal for cortical neurons migrating toward the pial surface (Rice and Curran 2001; Tissir and Goffinet 2003). In the absence of Reelin, later born cortical neurons fail to migrate past the earlier born neurons, resulting in inverted cortical layers (Ogawa and others 1995). Quantitative analysis of reelin-positive cells identified premature loss of CR neurons in the marginal zone of *PS1–/–* brains at E17.5; more specifically, approximately 25% fewer CR neurons remained in mutants relative to control littermates (Wines-Samuelson and others 2005). Intriguingly, the premature degeneration of CR neurons was not observed in NPC-*PS1* cKO mutant embryos, indicating a non–cell-autonomous requirement of PS1 in survival of these neurons (Wines-Samuelson and others 2005). As meningeal fibroblasts have been shown to be important for CR neuron survival (Super, Martinez, and Soriano 1997; Super, Perez Sust, and Soriano 1997), and meningeal cells overproliferate in *PS1–/–* mice but not in NPC-*PS1* cKO mice, overproliferation of meningeal cells caused by loss of PS1 function may compromise the production or secretion of trophic factors normally provided by meningeal cells to support the survival of CR neurons.

A role for PS1 in survival of newly generated postmitotic neurons during cortical development was suggested by analysis of *PS1–/–* mice. By E16.5, prominent cerebral cavitation caused by massive neuronal depletion in the ventrolateral region of the ventricular zone, intermediate zone, and deep portions of the cortical plate becomes evident in *PS1–/–* brains (Shen and others 1997). Although the morphological features suggested that the cavitation was caused by neuronal loss, reduced neuronal generation as a secondary consequence of the reduction in the neural progenitor population could not be excluded as a possibility. To bypass the requirement of PS function in neural progenitor cells, conditional KO mice with restricted PS inactivation in postmitotic neurons are necessary to address whether presenilins are required for neuronal survival in a cell-autonomous manner.

Presenilins in the Adult and Aging Cerebral Cortex

Learning and Memory

In addition to regulating neuronal differentiation and migration during embryonic development, presenilins also play essential roles in the mature cerebral cortex. To study PS1 function in the adult cerebral cortex, Yu and others employed α*CaMKII-Cre* transgenic mice to generate the first *PS1* cKO mouse, in which the spatial and temporal pattern of PS1 inactivation was restricted to excitatory neurons of the forebrain beginning at postnatal day 18 (Yu and others 2001). In contrast to striking developmental defects in *PS1–/–* and NPC– *PS1* cKO mice, this postnatal forebrain-specific *PS1* cKO mouse (FB-*PS1* cKO) was viable and displayed only a mild deficit in hippocampal spatial reference memory, as indicated by increased latency to reach the target quadrant during training and reduced numbers of platform crossings in the posttraining probe trial in the hidden platform version of the Morris water maze task (Yu and others 2001). This was the first evidence supporting a role for PS1 in long-term memory. This mild memory deficit could be overcome if the mutant mice were given intensive training (Saura and others 2004). Furthermore, FB-*PS1* cKO mice performed normally in contextual fear conditioning, another commonly used memory task (Saura and others 2004). Feng and others also similarly generated a postnatal forebrain-restricted *PS1* cKO mouse and reported no significant deficit in performance in the Morris water maze using a more intensive training protocol, which may have contributed to the failure to detect the subtle memory defect in FB-*PS1* cKO mice (Feng and others 2001). Using Thy1-*Cre* mice, in which Cre is expressed under the control of the *Thy1* promoter in postmitotic neurons beginning at the perinatal stage (Moechars and others 1996; Spittaels and others 2000), Dewachter and others (2002) generated neuron-specific *PS1* cKO mice, which exhibited normal performance in the object-recognition task.

Studies of these *PS1* cKO mice indicated that in contrast to the crucial functions of PS1 during development, PS2 could largely compensate for the loss of PS1 function in the adult cerebral cortex. This is consistent with the higher PS2 expression level in the adult brain, relative to PS1 expression. To uncover the roles of presenilins in the adult cerebral cortex, Saura and colleagues (2004) generated a *PS1* and *PS2* double conditional knockout mouse (FB-*PS* cDKO), in which both presenilins are inactivated in the postnatal forebrain. Compared to *PS1* cKO mice, young *PS* cDKO mice exhibited more marked spatial memory deficits in the water maze. Under intensive training, whereas *PS1* cKO and *PS2–/–* mice performed normally in the water maze, *PS* cDKO mice showed significantly longer latencies to reach the target quadrant during training and reduced numbers of platform crossings in the posttraining probe

trial. In the contextual fear conditioning, *PS* cDKO mice also showed reduced contextual memory. These studies of *PS* cDKO mice corroborated with earlier findings, showing a mild memory deficit in *PS1* cKO mice, and demonstrated an essential role of presenilins in long-term memory (Saura and others 2004). The memory impairment exhibited by *PS* cDKO mice at this age (two months) was rather specific, as these mice performed normally in open field and rotarod tasks and their cortical neuronal morphology was also unaltered (Saura and others 2004). As *PS* cDKO mice grew older (e.g., six months), however, their spatial and contextual memory deficits became much more pronounced. The failure of *PS* cDKO mice to learn either of the tasks was accompanied by gradual, progressive neurodegeneration in the cerebral cortex, as indicated by loss of synapses, dendrites, and neurons as well as astrogliosis (Saura and others 2004).

Although Notch is the key functional mediator of presenilins in development, it is less clear whether presenilins regulate long-term memory through the Notch signaling pathways, as little is known about the role of Notch receptors in learning and memory. Recently, it was reported that *Notch1*+/– and *RBP-J*κ+/– mice showed subtle memory deficits in the water maze, suggesting that Notch signaling may play a role in learning and memory (Costa and others 2003). The critical role of Notch signaling in neural development, however, makes it more difficult to interpret the results and to rule out the possibility that the behavioral phenotype may be secondary to developmental effects caused by Notch haploinsufficiency. To circumvent the development requirement of Notch receptors, it would be necessary to generate cell-type restricted conditional knockout mice, similar to the *PS1* cKO and *PS* cDKO mice, to determine whether Notch receptors are indeed required for learning and memory.

Synaptic Plasticity

Long-term potentiation (LTP) is the best understood model of the experience-dependent synaptic strengthening involved in learning and memory (Malenka and Nicoll 1999; Bailey and others 2000). Although *PS1* cKO mice exhibited a mild memory defect in the water maze, early and late phases of LTP in the Schaeffer collateral pathway were normal, suggesting that the electrophysiological phenotype may be too subtle to be detected in these mice (Yu and others 2001). In contrast, FB-*PS* cDKO mice exhibit a marked reduction in LTP in the Schaeffer collateral pathway, consistent with the more severe memory defects exhibited by these mice, compared to *PS1* cKO mice (Saura and others 2004). Furthermore, paired pulse facilitation (PPF), a measure of presynaptic plasticity, was also impaired in *PS* cDKO mice, indicating an increased probability of neurotransmitter release in the absence of both presenilins. The molecular player(s) mediating the presynaptic plasticity regulated by PS remains to be identified. Long-term depression (LTD), another form of synaptic plasticity, and basal synaptic transmission, however, were normal in *PS* cDKO hippocampal slices, indicating the reductions of LTP and PPF were specific synaptic plasticity defects.

Further intracellular and field recordings showed that the reduction in LTP was likely due to reduced N-methyl-D-aspartate (NMDA) receptor–mediated responses, suggesting a molecular connection between PS and NMDA receptors (Saura and others 2004). Consistent with this result, synaptic levels of NMDA receptor 1 (NR1) and 2A were reduced in the cerebral cortex of *PS* cDKO mice, suggesting that presenilins are required for the trafficking and synaptic delivery of NMDA receptors. Furthermore, a direct physical interaction between PS1 and NR1 subunit was identified, based on coimmunoprecipitation of endogenous PS1 and NR1 derived from cortical extracts (Saura and others 2004). As most of the PS1 and NMDAR proteins are colocalized in the ER/Golgi compartment, these proteins may interact with each other in this subcellular compartment. The detailed mechanism by which PS1 affects the synaptic delivery of NMDARs is not yet clear. A role for PS1 in the trafficking of membrane proteins is supported by the sequence homology between PS1 and the sperm integral membrane protein SPE-4 in *C. elegans*, which suggests that PS1 might be involved in intracellular trafficking as well as localization and recycling of synaptic proteins (Sherrington and others 1995). Previous studies have implicated PS1 in the trafficking of other synaptic transmembrane proteins, including APP and TrkB (Naruse and others 1998; Cai and others 2003), which provide further support for such a mechanism.

Because of the lack of the appropriate *Notch* conditional knockout mice, little is known about its function in synaptic transmission and plasticity. Recently, a report using transgenic mice, which expressed a Notch antisense construct and showed a 50% reduction of Notch proteins in hippocampal extracts, showed that reduction in Notch expression resulted in significant impairments in LTP and LTD, although basal synaptic transmission and PPF were normal (Wang and others 2004). It will be interesting to confirm these findings using *Notch* conditional knockout mice to determine whether conditional inactivation of one allele of Notch1 would result in similar synaptic plasticity impairments. To determine unequivocally the role of Notch receptors in synaptic transmission and plasticity, it would be necessary to generate and analyze cell type–specific conditional knockout mice lacking Notch1, Notch2, or both. This method circumvents the requirement of Notch receptors in development and allows the generation of genetic null mutants in a cell type–specific manner.

Neuronal Survival

The presence of cerebral cavitation and loss of neurons and neural progenitor cells in the developing brain of *PS1*–/– mice raised the possibility that PS1 may be required for neuronal survival (Shen and others 1997).

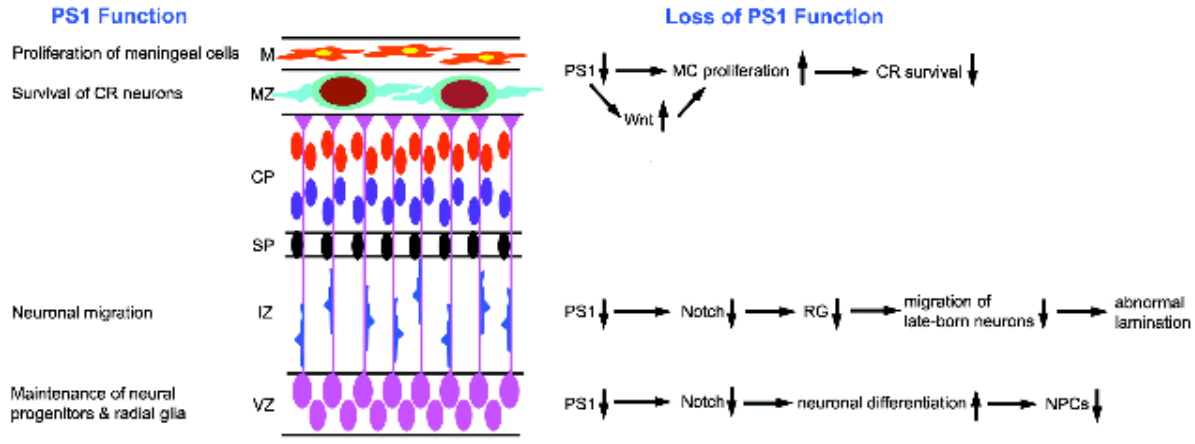

Fig. 1. The role of presenilins in cell cycle regulation during cortical development. The schematic diagram depicts the developing cerebral cortex. The uppermost layer is the meninges (M) containing meningeal cells (MC), where PS1 (presenilin 1) maintains proper cell proliferation. Loss of PS1 function leads to increased proliferation of MC. Up-regulation of Wnt signaling may underlie the increase in proliferation. In the marginal zone (MZ), PS1 promotes the survival of Cajal-Retzius (CR) neurons in a non–cell-autonomous manner through the maintenance of proper proliferation of MC. In the ventricular zone (VZ), PS1 is crucial for the proper maintenance of the neural progenitor cell (NPC) pool; loss of PS1 function results in premature differentiation and depletion of NPCs. This process is regulated through the Notch signaling pathway. Loss of PS1 function also causes reduced generation of radial glia (RG), a major population of NPCs, leading to failure of late-born neurons migrating to their appropriate positions in the superficial layers of the cortical plate (CP). IZ = intermediate zone; SP = subplate.

However, the defects in neuronal differentiation and migration make it difficult to rule out the possibility that the loss of neurons is secondary to the depletion of neural progenitor cells. The postnatal forebrain-restricted *PS* cDKO mice, in which presenilins are inactivated in mature pyramidal neurons, were the ideal model to determine whether presenilins are required for neuronal survival in a cell autonomous manner. Interestingly, at two months of age, approximately four weeks after PS inactivation, there was no loss of neurons, dendrites, or synapses in FB-*PS* cDKO mice. However, as the mice aged, they gradually developed neurodegeneration. For example, at the age of six months, synaptic and dendritic losses were evident in FB-*PS* cDKO mice. Quantification of cortical neurons showed a reduction of 18% in the neocortex of *PS* cDKO mice. By the age of nine months, cerebral atrophy, enlarged ventricles, loss of neurons (24%), dendrites, dendritic spines, and synapses were striking, indicating an age-dependent progression of neurodegeneration in neurons lacking both presenilins (Saura and others 2004). Neuronal degeneration was also accompanied by astrogliosis, up-regulation of inflammatory markers, and hyperphosphorylation of tau (Beglopoulos and others 2004; Saura and others 2004). Examination of the cerebral cortex of *PS* cDKO mice failed to identify apoptotic cells, which is consistent with the slow progression of the neuronal death in these mice. The presence of neurodegeneration was confirmed by a subsequent report in a similar *PS* cDKO mouse (Feng and others 2004); however, the authors indicated that increased apoptosis may underlie the neurodegeneration phenotype in these mutant mice.

Whether the mediation of neuronal survival by presenilins is through the Notch signaling pathway remains to be determined. One direct way to address this issue is to determine whether inactivation of Notch1 and Notch2, the only Notch family members that are expressed in neurons of the adult brain, is required for neuronal survival in the adult cerebral cortex through the generation of conditional double knockout mice. Interestingly, presenilins are required for normal expression of the CREB target genes, including *c-fos* and *BDNF*, which have been implicated in the promotion of neuronal survival (Saura and others 2004). Inactivation of CREB and its modulator CREM in conditional double knockout mice similarly causes striking neuronal degeneration in the adult forebrain as *PS* cDKO mice (Mantamadiotis and others 2002). However, expression and phosphorylation of CREB were unaffected in *PS* cDKO mice. Rather, transcription of CREB binding protein (CBP) was reduced in the absence of presenilins. The presence of the consensus recognition site for the transcription factor CBF1/RBP-Jκ, through which the active form of the Notch intracellular domain exerts its transcriptional activation effects, in the predicted *CBP* promoter suggests that CBP may be a downstream target of Notch (Saura and others 2004). Thus, presenilins may promote neuronal survival through the Notch signaling pathway, which in turn regulates the CREB pathway at the transcriptional level. Future studies will be necessary to confirm that Notch signaling is indeed required for neuronal survival in the adult cerebral cortex and that CBP is indeed a Notch downstream target gene.

Conclusions

Multidisciplinary studies of various presenilin mutant mice during the past 10 years have elucidated the normal

physiological roles of presenilins in the cerebral cortex. In the developing cerebral cortex, presenilins play a pivotal role in maintaining the proliferating state of neural progenitor cells. Reduction of presenilin expression in neural progenitor cells results in premature cell cycle exit and neuronal differentiation, leading to depletion of progenitor populations (Fig. 1). Premature loss of neural progenitor cells, including radial glia, likely underlies the migration defect of late-born cortical neurons. Inactivation of PS1 expression in meningeal cells, however, causes overproliferation of these nonneural cells. Thus, presenilins regulate cell cycle in a context-dependent manner, likely through distinct signaling pathways. In neural progenitor cells, presenilins maintain the proliferative state of progenitor cells through the activation of the Notch signaling pathway, whereas in nonneural meningeal cells, presenilins prevent excessive cell division, likely through the Wnt signaling pathway, which was not discussed in this review because of space limitation (Fig. 1).

In the adult cerebral cortex, presenilins are essential for normal memory formation and synaptic plasticity. Loss of presenilin function in excitatory pyramidal neurons results in hippocampal-dependent spatial and contextual memory impairments and specific reductions in short- (PPF) and long-term (LTP) synaptic plasticity. The LTP deficit is likely caused by decreased NMDA receptor–mediated responses. At the molecular level, presenilin interacts directly with NMDA receptor subunits and controls the proper synaptic delivery of NMDA receptors. The functional defect in NMDA receptors further leads to decreased levels of synaptic and dendritic αCaMKII, which is a key mediator of NMDARs and plays a major role in synaptic plasticity and long-term memory (Fig. 2). Thus, αCaMKII serves as an additional molecular mediator of presenilin function in the adult cerebral cortex. Furthermore, presenilins are essential for the regulation of the CREB/CBP pathway, which is known to be important for synaptic plasticity and learning and memory. This is likely to be mediated through the Notch pathway, as the predicted CBP promoter contains the conserved consensus sequence for CBF1/RBP-jκ. Thus, in contrast to their functions in cell cycle regulation in dividing cells during development, presenilins play distinct but still important roles in nondividing mature neurons that are unique to the adult cerebral cortex. Specifically, presenilins impinge on several central pathways to exert their role in maintaining normal memory and synaptic plasticity (Fig. 2).

As the aging process begins, the defects at the molecular, cellular, and systems levels caused by loss of presenilin function develop into progressive and substantial neuronal degeneration, demonstrating that presenilins are required for neuronal survival in a cell-autonomous manner (Fig. 2). Unlike apoptosis, cell death caused by loss of presenilin function is slow and progressive, exhibiting all key features of neurodegeneration, such as gradual loss of synapses, dendrites, dendritic spines, and

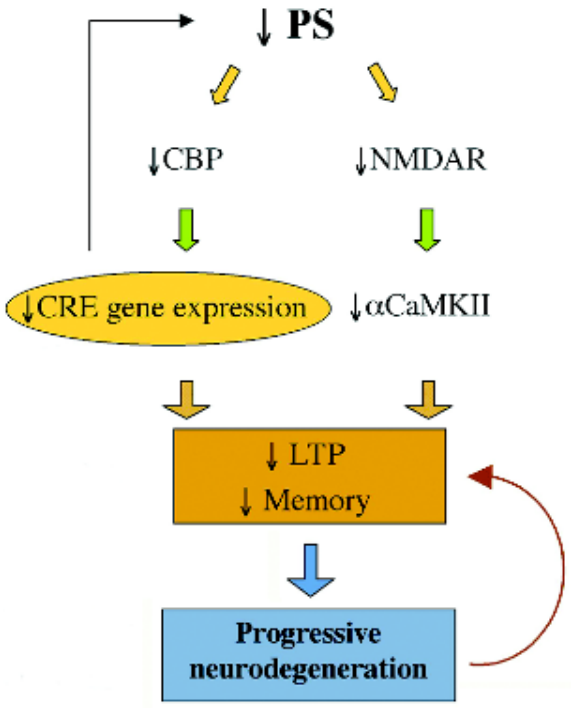

Fig. 2. Molecular pathways regulated by presenilins (PSs) in the control of synaptic plasticity and memory in the adult cerebral cortex. The model diagram depicts the molecular pathways through which PSs control neuronal function in the adult brain. Loss of PS function results in decreased expression of CREB binding protein (CBP), which in turn reduces expression of CRE-dependent (camp response element) genes regulated by CREB/CBP. Interestingly, expression of PS1 is regulated by CREB. In parallel, loss of PS function also causes reduced synaptic levels and responses of NMDARs, which leads to decreased synaptic and dendritic levels of αCaMKII. Attenuation of both molecular pathways downstream of PS culminates in functional deficits including LTP and memory impairment and eventually causes progressive neurodegeneration, which further worsens the synaptic and memory deficits.

neurons as well as astrogliosis and up-regulation of inflammatory markers. Neuronal degeneration is also accompanied by hyperphosphorylation of tau, which is the major constituent of neurofibrillary tangles, neuropathological hallmarks of Alzheimer disease. Elucidation of the normal physiological roles of presenilins in various cell types of the cerebral cortex will no doubt contribute to our understanding of the pathogenic mechanism of Alzheimer disease, which may in turn permit the development of effective, novel therapeutic strategies.

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