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SPECIAL ISSUE

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The function of presenilin-1 in amyloid β-peptide generation and brain development

Abstract Several mutations in genes that cause the familial form of Alzheimer's Disease (FAD) have been identified. All mutations in the three FAD genes, i.e., amyloid precursor protein (APP), presenilin 1 (PS-1), and presenilin 2 (PS-2) cause an increased production of a longer, more amyloidogenic form of the amyloid peptide corroborating strongly the idea that abnormal processing of APP is central to the pathogenesis. In PS-1 deficient mice, 80% less amyloid peptide was produced. Instead, membrane associated carboxyterminal fragments generated by α- and β-secretase accumulated suggesting that PS-1 is involved in the gamma-secretase activity cleaving the transmembrane domain of APP after α- and β-secretase cleavage has occured. The clinical mutations in PS-1 which increase the production of $\beta A4_{1\text{-}42}$ therefore seem to cause a "selective" gain of its normal function.

During cortical plate development in PS-1-deficient mice, neurons do not terminate their movement at the outer margin of the cortical plate, but enter the marginal zone and subarachnoid space. These focal heterotopias closely resemble those occuring, e.g., in human lissencephaly type II. The extracellular matrix of the cortical plate and marginal zone was altered as a consequence of a loss of Cajal-Retzius (CR) neurons from the marginal zone. The pathogenesis of this neuronal migration disorder is associated with a reduction and redistribution of notch-1 immunoreactivity in CR- and cortical plate neurons, a cell surface receptor operative in cell fate selection, which similar to APP is cleaved in its transmembrane domain during activation by a γ-secretase like protease.

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Introduction

The complex biochemical processes that lead to Alzheimer's disease (AD) pathology is not yet fully understood. A distinguishing feature of AD is the deposition of amyloid plaques in the brain, which arise by abnormal accumulation of βA4 peptide (Selkoe 1991). The 39-43-residue βA4-amyloid peptide, the main component of the amyloid plaque in the brain of Alzheimer's disease patients is generated from amyloid precursor protein (APP) by proteolytical processing (Haas and Selkoe 1993).

Familial, early onset AD is caused by point mutations in the amyloid precursor protein gene on chromosome 21 (Goate et al. 1991), in the presenilin 2 (PS-2) gene on chromosome 1 (Rogaev et al. 1995; Levy-Lahad et al. 1995), or, most frequently, in the presenilin-1 (PS-1) gene on chromosome 14 (Sherrington et al. 1995; Alzheimer's Disease Collaborative Group, 1995; Van Broeckhoven 1995). Point mutations in the presenilins are responsible for most of the familial forms of the disease (Cruts and Van Broeckhoven 1998), although still a considerable number of families exist for which the responsible gene remains to be identified. Dominant inherited familial AD constitutes only a small fraction of all forms of AD. The neuropathological lesions observed in the brains of these patients are, however, very similar – if not identical – to those of the not inheritated, sporadic cases (10-15% of the cases of AD). It is our working hypothesis that a common pathogenic pathway underlies AD that is related to an initial deposition of βA4.

Since the identification of PS-1 and PS-2, considerable progress has been made in defining their structure and intracellular localization. Immunocytochemical studies revealed that they are situated mainly in the endoplasmic reticulum and, to a lesser extent, in the Golgi compartment (Kovacs et al. 1996; Walter et al. 1996; De Strooper et al. 1997; Annaert et al. 1999). PS-1 (Fig. 1) is a transmem-

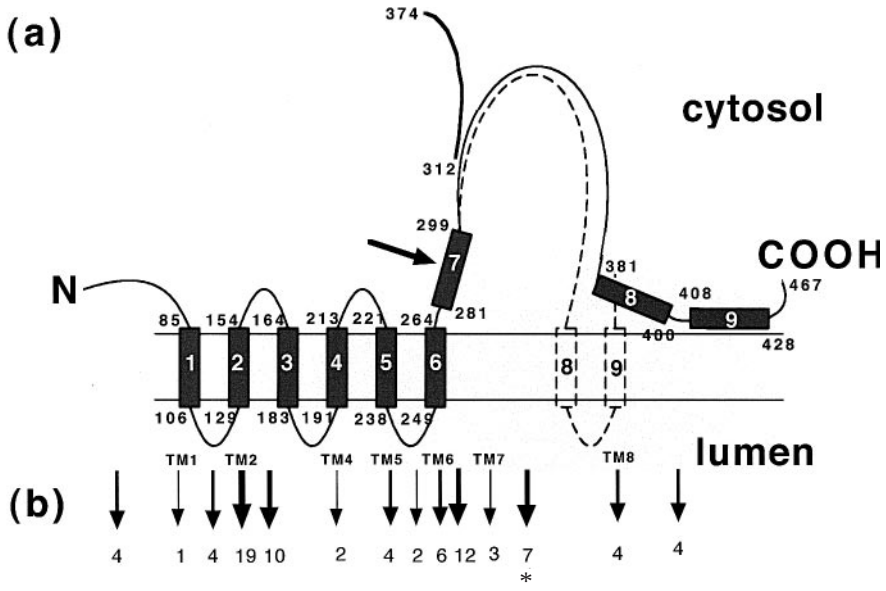

Fig. 1 a Schematic representation of presenilin-1. The exact topology of presenilins is still not established although the evidence for an eight transmembrane domain model is preponderating. The numbers indicate the hydrophobic domains. The arrow represent the approximate site of endoproteolytic cleavage of PS-1. Small numbers indicate the number of the respective amino acid residues where transmembrane domains begin and end, respectively. The fragment from amino acid 312 to 374 represents the missing peptide in the splice site-mutant of PS-1, which causes the in-frame skipping of exon 9 (Δ9; asterix in (b)). (**b**) Distribution and frequency of known FAD mutations in the presenilin-1 gene. The number of affected families is indicated. The arrows represent the respective protein domains with each mutation as shown in (a). The thickness of the arrows represent the frequency of the mutations. TM = transmembrane domain

brane protein containing between seven and nine candidate transmembrane domains and a hydrophilic loop region (Sherrington et al. 1995). The N-terminal domain, loop, and C-terminal domains of PS-1 are orientated towards the cytoplasm (Doan et al. 1996; De Strooper et al. 1997; Lehmann et al. 1997; Li and Greenwald 1996). PS-1 is proteolytically cleaved to generate two fragments of 17 and 27 kDa (Thinakaran et al. 1996; Podlinski et al. 1997). PS-1 is expressed in a variety of tissues, including the embryonic and adult brain (Sherrington et al.1995; Lee et al. 1996; Berezovka et al. 1997). In brain it appears to be primarly expressed in neurons, with highest concentrations in the cerebellum and hippocampus (Kovacs et al. 1996; Lee et al. 1996; Suzuki et al. 1996).

PS-1 and mutations

To date, 43 different AD-related PS-1 mutations have been identified (Fig. 1b), while only 3 mutations were detected in PS-2. All AD mutations are missense mutations, except for one splice site-mutation in PS-1 resulting in the in-frame skipping of exon 9 (Δ9). The Δ9 patients have additional clinical features of spastic paraplegia (Kwok et al. 1997). The pathological activity of PS1Δ9 is independent of its lack to undergo proteolytic processing (Steiner et al. 1999). The majority of mutations involve the second transmembrane domain and the sixth hydrophilic loop. The other mutations are spread over the rest of PS-1 (Fig. 1b).

Studies in primary cultures of fibroblasts derived from patients with inherited presenilin mutations, backed up by experiments in cell culture and in transgenic mice (Borchelt et al. 1996; Duff et al. 1996; Citron et al. 1997), demonstrated that the mutations in the presenilins affect APP metabolism. All PS-1 and PS-2 mutations analyzed so far affect the cleavage of βAPP at the C terminus of the Aβ domain, resulting in an approximately twofold increase of Aβ42 generation (Borchelt et al. 1996; Borchelt et al. 1997; Citron et al. 1996; Citron et al. 1997; Duff et al. 1996; Holcomb et al. 1998; Scheuner et al. 1996; Tomita et al. 1997; Xia et al. 1997). This form of the peptide is highly amyloidogenic compared to the more abundant 40 amino acid residues containing βA4(1-40)-peptide and precipitates in the plaques of brains from sporadic and familial AD alike. There is no evidence that the APP expression level and cleavage by α- and β-secretases is affected by PS mutations. However, Naruse and collegues also observed an increased amount of soluble APP ($APP^{s\alpha}$) derivatives in medium of presenilin-1 deficient cells (Naruse et al. 1998).

The problems to be addressed here are how presenilin mutations can affect APP processing and whether the increased production of amyloidogenic $\beta A4_{1\text{-}42}$ reflects a gain or a loss of function (Levitan et al. 1996; Baumeister et al. 1997). The egg-laying deficiency in *C. elegans* caused by the null mutation of *sel12*, the worm's homologue of mammalian presenilin, can be rescued by wild type, but not mutated, human presenilin (Baumeister et al. 1997; Levitan et al. 1996). This suggested that the clinical PS-1 mutations cause a loss of function with respect to its actions in nematodes. However, since familial AD is inherited as a dominant trait, the gain of function hypothesis appears to be the more likely one regarding its involvement in APP processing.

PS-1 and APP

To tackle this question and the presumed role of PS-1 in APP processing directly, we generated PS-1 deficient mice and first concentrated on the analysis of the metabolism of APP in neuronal cultures derived from E14 embryos (De Strooper et al. 1998; Saftig et al. 1998).

Genotyping of embryos taken between day 14 and 16 p.c. from heterozygote crosses revealed a frequency of 27 % for homozyous mutants. No mutants were found in litters after natural delivery. In agreement with the two independently generated PS-1 knockout models (Wong et al. 1997; Shen et al. 1997), we confirm that PS-1 -/- mice die late in embryogenesis.

To circumvene embryonic lethality of PS-1 -/- mice and to allow the biochemical analysis of APP processing, mixed brain cultures from embryos at day 14pc were prepared according to protocols previously used for hippocampal neurons (De Strooper et al. 1995; Tienari et al. 1996; Simons et al. 1996). PS-1-deficient and control cultures were metabolically labeled (Saftig et al. 1996) and amyloid peptide and carboxyterminal fragments from endogenously expressed mouse APP were immunoprecipitated and analyzed in SDS-PAGE. Apart from a strong inhibition of β-amyloid peptide and the p3-fragment secretion in the culture medium, an accumulation of carboxyterminal fragments of APP in the PS-1 -/- cultures was observed (De Strooper et al. 1998). An increasing amount of carboxyterminal APP fragments in presenilin-1 deficient mice could also be demonstrated in Western blot experiments using entire mouse brain extracts. These findings already indicated a direct role of PS-1 in the amyloidogenic processing of APP. To further quantitatively analyze this effect, neuronal cultures were infected with recombinant Semliki Forest Virus that drives the expression of human wild-type APP or APP containing the clinical mutations causing AD. Two striking effects were observed: amyloid peptide secretion (both $\beta A4_{1\text{-}40}$ and $\beta A4_{1\text{-}40}$) was markedly decreased. The fivefold decrease in amyloid peptide secretion was accompanied by a concomitant twofold increase in β-secretase and a fivefold increase in α-secretase cleaved carboxyterminal fragments in the cell extracts (De Strooper et al. 1998).

No differences between genotypes were found concerning the secretion of APP ectodomain (APPs), indicating normal α- and/or β-secretase processing of APP. Pulse chase experiments confirmed that PS-1 deficiency specifically decreased the turnover of the membrane associated fragments of APP (De Strooper et al. 1998).

Two major conclusions were drawn from these findings: (i) PS-1 plays a crucial role in the γ-secretase cleavage event and (ii) mutations in PS-1 that manifest clinically cause a gain of function by selectively enhancing γ-secretase cleavage after residue 42 of Aβ. However, it is still not clear why the FAD-causing mutations in PS-1, in contrast to the deletion mutation of PS-1, selectively affect the production of the amyloid 42 peptide. Taken together, the direct or indirect effect of wild-type PS-1 on γ-secretase cleavage

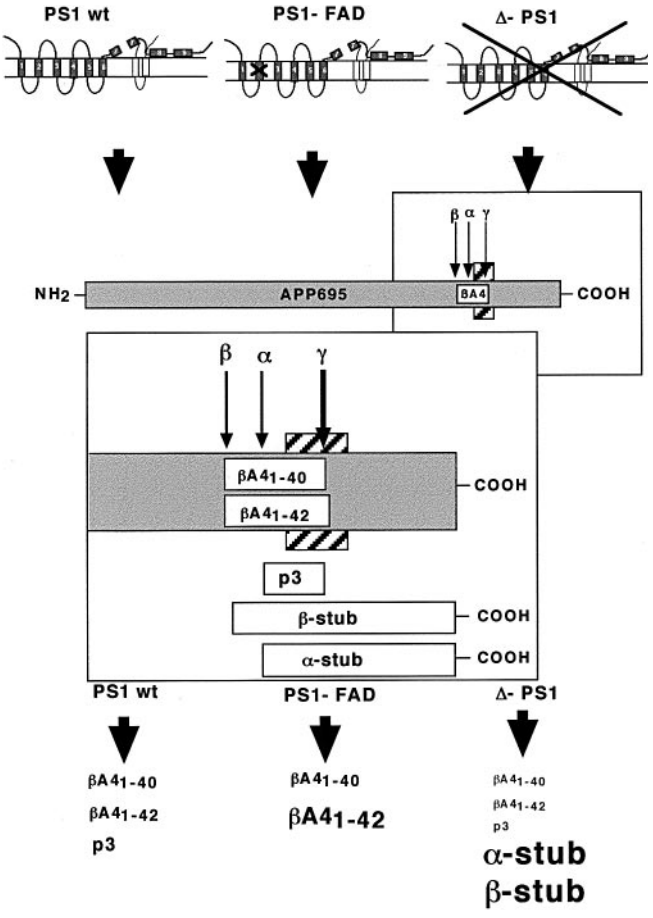

Fig. 2 Schematic representation of presenilin-1 interaction with the amyloid precursor protein (APP695). Top: wild-type presenilin-1 (PS-1 wt), presenilin-1 with a known FAD mutation (PS-1-FAD) and disrupted presenilin-1 in PS-1-knockout mice (Δ-PS-1) are indicated. Middle: Processing of APP695 at the β-, α-, and γ-secretase cleavage sites, respectively. APP processing leads to the generation of β-$A_{41\text{-}40}$, β-$A4_{1\text{-}42}$, p3 fragment (β- and γ- secretase cleavage) and in the case of PS-1-deficient neurons to an accumulation of carboxyterminal β-stubs (only cleavage at the β-secretase site) and α-stubs (only cleavage at the α-secretase site). The hatched box represent the transmembrane domain of APP. Bottom: The consequences of the different mutations of PS-1 on APP processing are indicated. The size and the thickness of the letters reflect roughly the quantitative effects of PS-1 clinical FAD mutations and absence of PS-1 on the APP fragment. PS-1-FAD mutations cause increased levels of β-$A4_{1\text{-}42}$, whereas PS-1 deficiency leads to a decrease in both β-$A4_{1\text{-}40}$ and β-$A4_{1\text{-}42}$

may be needed for producing physiological concentrations of Aβ and p3 fragments, although the exact cellular functions of these fragments are still not known. Mutant PS-1 molecules increase $A\beta_{1\text{-}42}$ production, whereas the lack of PS-1 causes severely decreased β-amyloid production and accumulation of carboxyterminal fragments (Fig. 2).

PS-1 and γ-secretase

The altered metabolism of APP in PS-1 deficient neurons conclusively demonstrates that PS-1 is involved in the

normal proteolytic cleavage of the carboxyterminal fragments of APP. One is tempted to speculate that PS-1 is actually the γ-secretase. However so far PS-1 sequence homology to any protease domain known is missing. The observation of coimmunoprecipitation of APP and PS-1 (Weidemann et al. 1997; Xia et al. 1997a) and the fact that APP and PS-1 are at least temporally colocalized in the endoplasmic reticulum and early Golgi apparatus (Kovacz et al. 1996; Walter et al. 1996; De Strooper et al. 1997) could support the idea of a direct involvement of PS-1 in γ-secretase cleavage. Since a deletion of the carboxyterminal domain of APP did not preclude coimmunoprecipitation (Xia et al. 1997b), it is conceivable that the association of APP and PS-1 is confined to the transmembrane domains of these molecules. In such an environment PS-1 could mediate the cleavage of APP (Selkoe 1998; Wolfe et al. 1999). It should be noted that the association of APP and PS-1 has been questioned (Thinakaran et al. 1998).

An interesting analogy exists with the role of SCAP and the proteolytic cleavage of SREBP (Brown and Goldstein 1997). SCAP, which stands for Sterol Regulatory Element Binding Protein (SREBP) Cleavage Activating Protein, is an endoplasmic reticulum protein with a similar serpentine structure as presenilin. SCAP and PS-1 could belong to a novel class of protein-chaperones that are responsible for the access to or exposure of protein domains for proteolytic processing. SREBP is also associated with the endoplasmic reticulum but becomes a soluble transcription factor after proteolytic cleavage. Interestingly, one of the two obligatory cleavages of SREBP at the so-called site 2 occurs in the transmembrane domain of SREBP. The recently identified multimembrane metallo-S2P protease is responsible for this cleavage (Rawson et al. 1998). However, the APP metabolism in S2P-deficient cell lines was shown to be unchanged (Ross et al. 1998), and SREBP cleavage is apparently not altered in PS-1 deficient cells (de Strooper et al. 1999). Therefore it is unlikely that S2P protease is the elusive γ-secretase.

Moreover, the fact that even in PS-1 -/- cells residual amyloid peptide secretion persists, suggests that PS-1 is only indirectly involved in γ-secretase cleavage, i.e., as a cofactor in this processing. The question whether PS-2 is responsible for the residual amyloid peptide secretion will be answered with the help of PS-2 and PS-1/PS-2 double knockout animals.

APP is first processed by the α- and β-secretases which are active in the Golgi apparatus, the cell surface, and endosomes, and only then by the γ-secretase controlled by PS-1. A recycling of APP carboxyterminal fragments to the endoplasmic reticulum is from a fundamental cell biological point of view not easily explained. However, presenilin-1 could be involved in the regulation of the transport of γ-secretase or carboxyterminal APP fragments from the endoplasmic reticulum to a not yet defined γ-secretase compartment, either defined as an organell or a specific microdomain in, e.g., the Golgi apperatus.

At present it is impossible to decide which model should be favored. Future work, to be mainly focused on the actual identification of the elusive γ-secretase(s), will resolve this issue.

PS-1 and notch-1

Inhibition of the γ-secretase itself and of PS-1 could decrease the amyloid peptide production in neurons and could possibly provide a target for anti-amyloidogenic therapy in sporadic Alzheimer's disease. However, the consequences of reducing the activity of γ-secretase and/or PS-1 for the adult brain have to be discussed in relationship with other known and presumed interactions of PS-1 (Fig. 3). In this respect, notch-1 function is one of the best studied examples. Notch is involved in cell fate determination during ontogenesis. Its activation depends on the proteolytic release of its intracellular domain, which is transported to the nucleus where it controls gene transcription (Struhl, G. and Adachi 1998; Schroeter et al. 1998, Lecourtois and Schweisguth 1998, Levitan and Greenwald 1995).

PS-1 knockout mice (de Strooper et al. 1998; Wong et al. 1997; Shen et al. 1997) exhibit a severe abnormal patterning of the axial skeleton which is associated with a generalized hypotrophy of the caudal body regions. This phenotype has been attributed to a reduction of *notch*-1 and dll-1 mRNA expression within the presomitic mesoderm (Wong et al. 1997). Very recently we came to the conclusion that notch expression is not directly affected by the absence of presenilin-1. In fact, folllowing an analogous approach as with the APP studies, we found that the proteolytic release of the notch intracellular domain is inhibited in the absence of PS-1 (de Strooper et al. 1999). Null mutations in the Drosophila Presenilin gene abolished Notch signal transduction and prevented its intracellular domain from entering the nucleus (Ye et al. 1999; Struhl and Greenwald 1999). Since this is a prerequisite for notch signaling (Schroeter et al. 1998), it was concluded that this deficit provides an molecular explanation for part of the notch-deficient-like phenotype of the PS-1

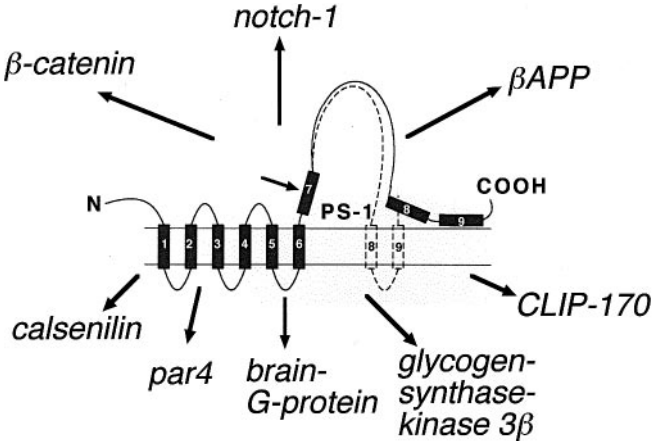

Fig. 3 Proteins interacting with presenilin-1. Proteins presumed to bind to presenilin-1 are indicated

deficient mice and the observed genetic interactions between *sel12* and glp1/Lin 12 in *C. elegans* (Levitan and Greenwald 1995), respectively. These results indicate also that a related enzymatic activity is involved in the proteolytic processing at the transmembrane domains of notch and amyloid precursor protein.

Another effect of PS-1 deficiency on embryonic development is the frequent occurence of defects of the cranial sagittal suture and the paraumbilical abdominal wall, leading to meningoencephalocele and umbilical hernia, respectively. Similar findings have been obtained in mice deficient for MARCKS, a key substrate for several protein kinase C isoforms (Stumpo et al. 1994). However, except for this similar pattern of defects, it has remained unclear as yet at what level PS-1 may interact with a protein kinase C-mediated signal transduction.

PS-1 and other interacting proteins

Other proteins interacting with PS-1 are β-catenin, which is a component of the Wnt/Wingless signaling pathway but also participates in the cytoskeletal anchoring of cadherins (Zhou et al. 1997; Yu et al. 1998); β-catenin has been shown to become destabilized in case of presenilin-1 mutations and presenilin-1 deficiency (Zhang et al. 1998). Other proteins believed to interact with PS-1 are calsenilin (Buxbaum et al. 1998), Par-4 (Guo et al. 1998), glycogen-synthase-kinase-3β (Takashima et al. 1998), brain-G-protein (Smine et al. 1998), actin-binding proteins (Zhang, W. et al. 1998), and CLIP-170 (Tezapsidis et al. 1998.) (Fig. 3). It appears that PS-1 is a key molecule in different cellular processes. One has to await however further experimentation to evaluate the significance of these findings.

PS-1 and brain development

Since PS-1 seems to be (i) in a central physiological position and (ii) is predominantly expressed within the CNS we have examined brain development in PS-1 deficient embryos in more detail. As yet, vascular lesions have been observed, causing severe hemorrhages in the parenchyma and the lateral ventricles (Shen et al. 1997). Additionally, a collapse of the ventricular proliferative zone during late pregnancy could either represent a secondary effect of these hemorrhages or be attributed to an interaction with signaling pathways depending on notch-1, which is expressed in the proliferative zones of the brain (Shen et al. 1997). More recently, it was found that PS-1 deficiency also causes a characteristical developmental aberration in the cortical anlage consisting of leptomeningeal fibrosis and a multifocal neuronal overmigration beyond the cortical plate, i.e., a pattern closely similar to human type 2 lissencephaly (Hartmann et al. 1999). In the region of cortical ectopia, the meninges and their underlying basement membrane either formed bulges ensheathing the overmigrated neural tissue or exhibited gaps, through which the neurons were directly exposed to the subarachnoid space (Fig. 4a,b). Similar alterations were seen within the diencephalon, brain stem, and spinal cord, but typically spared the medial hemispheral wall.

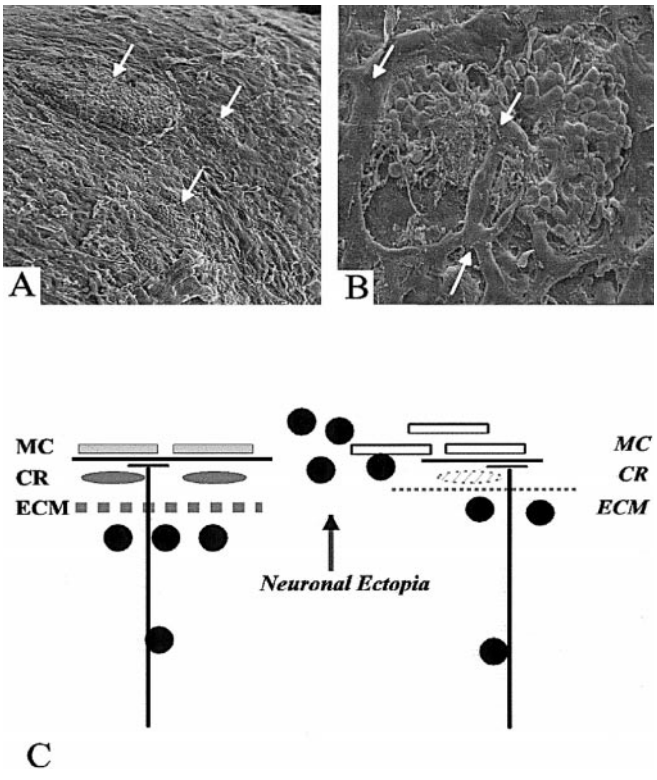

Fig. 4 Scanning electron micrographs of the dorsolateral hemispheral surface of PS-1 deficient embryos at E 14 (A) and E 18 (B). Note the numerous islands of ectopic neurons exposed to the subarachnoid space indicated by arrows in (A). At E 18, these large islands are mostly replaced by smaller groups of neurons separated by thick strands of fibrotic meninges (arrows in B). Fig. 4 C summarizes our present knowledge on the genesis of cortical ectopia in PS1 deficient mice. PS1 is early expressed in meninges (MC), which are known to have a mandatory trophic influence on Cajal-Retzius (CR) cell survival. These cells in turn produce the extracellular matrix (ECM) of the marginal zone, which terminates cortical neuron migration. PS1 deficient meninges *(MC)* are apparently unable to maintain the *CR* cell population; thus, the ECM is either reduced, leading to a partial shift of cortical plate position (right), or completely lacking, so that the neurons can migrate up to the brain surface and into the subarachnoid space (center)

Human type 2 lissencephaly has been found in a variety of inherited disorders such as Walker-Warburg, Aicardi, Neu-Laxova or Fukuyama syndromes (Williams et al. 1984; Ellison and Love 1998; Lazjuk et al. 1979). The primary involvement of the leptomeninges featuring fibrotic thickenings and defects of the basal lamina common to all these syndromes has led to the original concept of a 'meningoglial barrier' at the brain surface (Choi and Matthias 1987; Choi 1988; Lyon et al. 1993), consisting of pial fibroblasts, basal lamina, and radial glia endfeet, which demarcate the outer limit for neuronal movement. However, more recent experimental data obtained from neurologic mouse mutants (Goffinet 1984; d'Arcangelo et al. 1995, Ogawa et al. 1995; Frotscher et al. 1997) convincingly demonstrate the decisive role of marginal zone pioneer

neurons, the Cajal-Retzius (CR) – cells for both chemotactic attraction (Behar et al. 1996) and termination of cortical plate neuron migration (Frotscher et al. 1997). A major aspect of CR cell function is the secretion of a specific extracellular matrix. Especially chondroitin sulfate proteoglycans (CSPG) and reelin synthesized and secreted by CR neurons have been discussed to provide the 'stop signal' for neuronal migration (Perris and Johansson 1990; Ogawa et al. 1995; Meyer-Puttlitz et al. 1996; Frotscher 1997).

Most notably, CR cells have been shown to depend on trophic stimuli from meningeal cells for their survival (Super et al. 1997). Also, meningeal cells by themselves have been shown to secrete a chemotactic factor acting upon migrating neurons (Hartmann et al. 1998 a, b) and to participate in the control of radial glia differentiation (Hartmann et al. 1998 a).

The subsequent analysis of the cortical anlage of PS-1 deficient embryos (Hartmann et al. 1999) revealed the progressive loss of CR cells from the marginal zone between E 12 and E 18, corresponding to the period of cortical plate construction. As an immediate consequence, profound changes of the extracellular matrix within the marginal zone could be observed, most notably a considerable reduction of CSPG immuno-reactivity which may contribute to the observed overmigration in PS-1 knockouts.

Remarkably, the first cells in the developing brain to exhibit PS-1 immunoreactivity were found to be leptomeningeal fibroblasts, which are intensely immunoreactive from E 13 onward. Further experiments with neonate and juvenile wild-type mice revealed a continuous decrease of the meningeal immunoreactivity beyond E 18 resulting in a discontinuous staining pattern beyond P 5. Within the cortical anlage, PS-1 expression in neuronal cell bodies was first seen between E 16 and P 0 and became prominent at P 5 (Hartmann et al. 1999). Similar to the situation *in vivo*, cultured meningeal cells from control mice were found to be strongly immunopositive for PS-1. This indicates that the absence of PS-1 in those cells may be the primary cause of the observed neuronal migration disorder. This hypothesis finds further support in the observation that PS-1 is strongly expressed in the meninges that cover the basal and lateral hemispheres, which exhibit the most extensive migration disorder, while PS-1 is virtually absent from the meninges overlying the hippocampal anlage, which is apparently not affected by the migration disorder. It is thus tempting to speculate that PS-1 deficiency may interfere with protein processing and/or secretion of growth factors by these cells which in turn could impair their trophic action on CR cells. Candidate mechanisms for such an interaction could include the notch pathway, which has already been discussed to depend on PS-1 for its activation (see above). Evidence for this hypothesis comes from the observation that the loss of CR cells is preceded by a rearrangement and reduction of notch-1 receptor immunoreactivity on their cell membranes. Interestingly, these cells were found to be the major cell type which express notch-1 during early cortical development.

The redistribution and reduction of notch-1 immunoreactivity on CR cell membranes followed by their degeneration could be interpreted as a consequence of the lack of trophic action of meningeal cells on CR neurons. CR cells are known to establish focal contacts to meningeal fibroblasts, which may be a site for the interaction of notch with its ligands. Alternatively, these ligands could be presented by brain stem neurons which are discussed to be the source of the early innervation of the marginal zone. However, since the developmental biology of notch ligands in this part of the brain anlage have not been analyzed in detail as yet, current data do not exclude the possibility that the crucial event may take place in CR cells themselves, i.e., a defective notch activation rendering them incapable of responding to decisive stimuli.

The recently demonstrated role of PS-1 in APP (de Strooper et al. 1998) and notch-1 (de Strooper et al. 1999; Ye et al. 1999; Struhl and Greenwald 1999) processing fits in this concept. Interestingly, a recently described integrin knockout (Georges-Labouesse et al. 1998) and a MARCKS deficient mouse (Stumpo et al. 1995; Blackshear et al. 1997) display similar morphological alterations. It has therefore to be determined whether PS-1 also influences, via protein kinase C signal transduction pathways, and/or by adhesion events the development of type 2 lissencephaly in PS-1 deficient embryos.

Fig. 4c summarizes the central components of the marginal plate as they are altered in PS-1 deficient brains eventually leading to overmigration of cortical neurons beyond their normal destination. It is of great interest to correlate the findings in PS-1 deficient mice (Hartmann et al. 1999a) with the almost unknown pathological situation in human type 2 lissencephaly, which is underway.

Taken together, the generation and characterization of the PS-1 deficient mice have provided considerable insights in the multiple functions of this protein. PS-1 deficiency causes severe alterations in brain development illustrating the important role of PS-1 in many important physiological processes. Cell lines derived from PS-1 deficient tissues furthermore have been invaluable tools to study the molecular basis of the described pathology.

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