Presenilin-interacting proteins

Qi Chen and David Schubert

Familial Alzheimer's disease (FAD) accounts for 5–10% of deaths from Alzheimer's disease (AD), and approximately 50% of these cases have been definitely linked to missense mutations in three genes, encoding the amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2). Of these, the vast majority of FAD-linked mutations are within PS1. There has been an extensive effort to identify proteins that functionally interact with PS1 and PS2 because of their clear roles in FAD. The goal of this review is to describe these proteins and to discuss in more detail the probable biological functions of a subset of the better-studied interacting proteins. In particular, the review examines APP, Notch, nicastrin, modifier of cellular adhesion (MOCA), β-catenin, and the group of proteins involved in cell death, calcium metabolism and cell adhesion. We argue that, although a few of the interacting proteins are unambiguously involved in well-studied cellular pathways, their exact roles within these pathways have not been clearly defined, and indeed might vary between cell types. We also question the physiological relevance of some of the work linking PS to cell death pathways. Finally, we point out the value of using flies and worms to sort out the often contradictory work in the PS field, and we mention how knowledge of PS-interacting pathways will contribute to the development of new therapeutic strategies in AD.

Alzheimer's disease (AD) is the most common form of dementia among older individuals and has become a prolific field of research. However, despite first being discovered almost a century ago by Alois Alzheimer (Ref. 1), there is no clear consensus on precisely how it is caused or how it might be cured. A recent article in *Expert Reviews in Molecular Medicine* (Ref. 2) reviewed the many theories for the underlying pathogenesis of this disease, and these are not discussed further here.

All forms of AD are characterised by the presence of neuritic senile plaques (SPs) and neurofibrillary tangles (NFTs); SPs are composed of β-amyloid (Aβ) and NFTs are composed of hyperphosphorylated and aggregated microtubule-associated Tau proteins. Following

Qi Chen
Research Fellow, Cellular Neurobiology Laboratory, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA. Tel: +1 858 453 4100 (x1392); Fax: +1 858 535 9062; E-mail: qchen@salk.edu

David Schubert (corresponding author)
Professor, Cellular Neurobiology Laboratory, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA. Tel: +1 858 453 4100 (x1528); Fax: +1 858 535 9062; E-mail: schubert@salk.edu

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

the determination of the Aβ protein sequence by Glenner and Wong in 1984 (Ref. 3), research in AD has been driven primarily by the discovery of rare mutations in three genes that cause some of the inherited forms of the disease [familial Alzheimer's disease (FAD)]. These mutations are in the amyloid precursor protein (APP) in or around the domain encoding the toxic Aβ peptide (reviewed in Ref. 4), and in the genes encoding presenilin (PS) 1 and 2 (reviewed in Ref. 5). This article focuses on the PSs and the biological functions of the proteins that interact with them – APP, Notch, nicastrin, β-catenin, MOCA (for 'modifier of cellular adhesion') and others – before summarising how knowledge of these interacting pathways is a prerequisite to designing therapeutics based on regulation of Aβ production.

APP structure and function: an introduction

APP is a ubiquitously expressed type I integral membrane protein of approximately 700 amino acids, with at least six different alternatively spliced isoforms (Ref. 6). Of the two most commonly expressed isoforms, APP_{695} and APP_{751}, APP_{695} lacks the Kunitz-type serine protease inhibitor domain (Fig. 1) but is otherwise identical. APP is a proteoglycan-like molecule that contains both N- and O-linked carbohydrate, including O-linked glycosaminoglycans (Refs 6, 7, 8), and also sulphated tyrosines (Ref. 9). The protein is proteolytically processed by secretases in several different pathways, some of which might lead to the pathogenesis of AD. The most common and benign pathway is the cleavage of APP near the extracellular side of the plasma membrane (the α cleavage site, cleaved by α-secretase) to release the N-terminal ectodomain (Ref. 7) by cleavage within the Aβ sequence (Ref. 10; Fig. 1). The alternative processing pathway results in the cleavage of APP at the β and γ sites, which define the Aβ peptide, generating Aβ sequences of 40 or 42/43 residues (Refs 11, 12) (Fig. 1). The enzymes responsible for the α and β cleavages have been identified, but the γ activity has not yet been associated with a unique protease. The $Aβ_{1–42/43}$ form aggregates more rapidly than $Aβ_{1–40}$ and is associated with the most aggressive forms of AD. Dominant mutations in the gene encoding

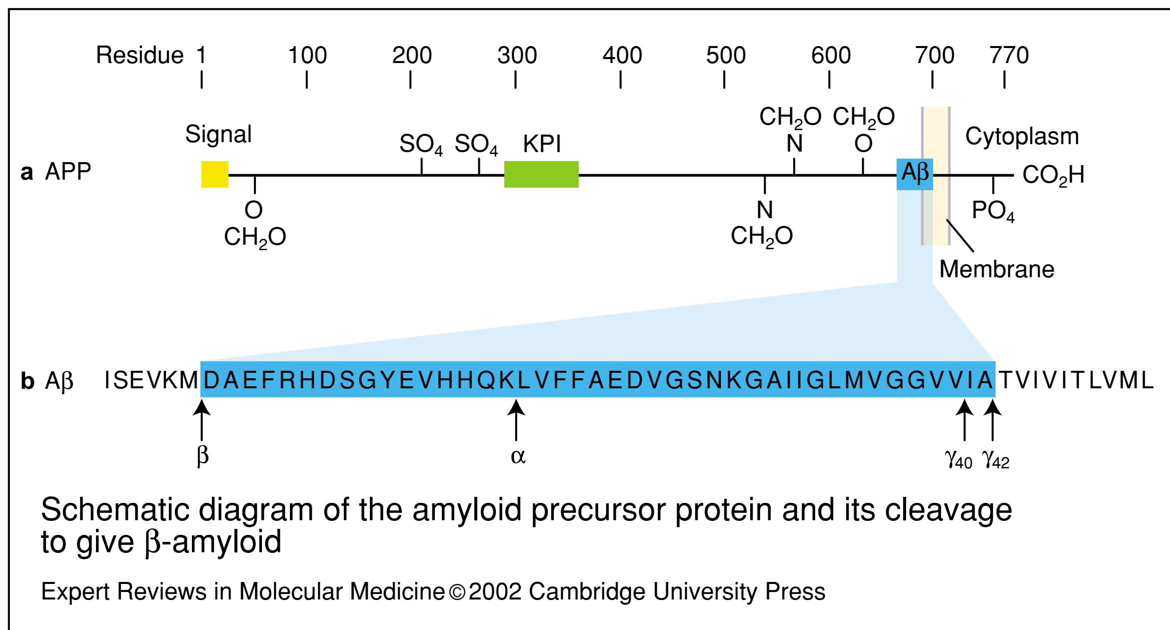

Figure 1. Schematic diagram of the amyloid precursor protein and its cleavage to give β-amyloid. (a) Amyloid precursor protein (APP) is an integral membrane, proteoglycan-like molecule of approximately 700 amino acids; sulphation (SO_4), phosphorylation (PO_4) and carbohydrate attachment (CH_2O) sites, the Kunitz-type protease inhibitor domain (KPI) and the secretory signal sequence ('Signal') are shown. (b) The protein is proteolytically processed by secretases in several different pathways. Cleavage of APP at the β and γ sites, which define the β-amyloid (Aβ) peptide, generates Aβ sequences of 40 or 42/43 residues (amino acids in single-letter code). The most common cleavage by α-secretase precludes Aβ formation **(fig001dss)**.

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

APP that cause AD are clustered around the Aβ sequence and usually result either in the accumulation of more Aβ or a shift to the longer $Aβ_{1–42/43}$ isoform.

The major biological function of APP is probably cell adhesion (Ref. 13), although other roles have recently been proposed (Ref. 14). The normal biological function of extracellular Aβ is not known. The processing of APP to generate Aβ is intimately associated with the only other group of proteins that have been genetically linked to the cause of AD – the PSs.

PS structure and function: an introduction

PS1 and PS2 proteins are composed of 467 and 448 amino acids, respectively, and are 67% identical (Ref. 5). They are both membrane proteins with eight predicted transmembrane (TM) domains and a hydrophilic loop of approximately 120 amino acids between the sixth and seventh TM domains (Fig. 2). The vast majority of the early-onset FAD-linked mutations occur as autosomal dominant mutations within PS1. Over 70 missense mutations, two in-frame deletions, and two splicing mutations have been found in PS1, whereas only six missense mutations have been demonstrated in PS2. The PS1 mutations are distributed throughout the protein (Ref. 5). PS1 and PS2 appear to be ubiquitously expressed throughout the body, with PS1 usually being the more abundant of the two (Refs 15, 16). Within the brain, PSs are expressed in both nerve and glial cells, in NFTs and in SPs. Within cells, the PSs were initially thought to be predominantly localised to the endoplasmic reticulum (ER) and Golgi but, as discussed later, there are more-recent reports of cell-surface expression.

PSs are cleaved within the large hydrophilic loop by an unknown protease (Refs 17, 18) and also at different sites by caspases (Refs 19, 20) (Fig. 2). Cleavage by the unknown protease within this loop generates an N-terminal 28 kDa fragment and a C-terminal fragment of about 17 kDa, and these two fragments remain tightly associated with each other in a 1:1 ratio (Ref. 21). Microsequencing indicates that the cleavage probably occurs between Thr291 and Met292 in PS1 and between Ala297 and Met298 in PS2, with exoprotease removal of a few amino acids of the C-terminal fragment (Ref. 22). One group has claimed that the elimination of PS1 cleavage reduces the production of $Aβ_{1–42}$ (Ref. 23), whereas another has found that the prevention of PS1 cleavage does not alter $Aβ_{1–42}$ production (Ref. 24), presenting a common conundrum when reviewing this field. The study of multipass membrane proteins of unknown function is technically very difficult. However, opposing results such as these are probably a consequence of the use of a variety of different cell lines, including neuroblastoma cells, fibroblasts and other cells not from the central nervous system (CNS). In the studies on PS1 cleavage, the latter experiments were done in fibroblasts and the former in neuroblastoma cells, making them particularly difficult to interpret in the context of a CNS disease like AD. There is no reason to assume that the expression of the complex proteolytic, transport and sorting machinery required to produce Aβ is the same in fibroblasts and differentiated CNS neurons. Indeed, there are numerous publications showing that the subcellular distribution of transfected membrane proteins is completely dependent upon the cell type in which they are expressed (Ref. 25). It would therefore be advisable in future studies to use CNS cell lines to study CNS protein function.

Whereas the genetics of the PSs is well defined and a relatively clear picture has emerged of their metabolism, their physiological role in normal nerve cells is very far from being understood. A key to this knowledge would be provided by defining the molecules that interact with PSs, in order that these can be used to identify the signalling pathways leading to relevant cellular responses and phenotypes. As discussed later, experiments supporting a few biological activities of PSs have emerged. These data argue that PS1 is involved in APP metabolism, and even that it might be one of the secretases required for the liberation of Aβ from APP. Other data suggest that PSs regulate cell adhesion, apoptosis and several cell-signalling processes. Much of this information is based upon interactions of PSs with various other proteins, and it is the goal of this review to outline some of these claims, discussing in detail a few of the interactions that lead to clear biological consequences. The word 'interacting' is used rather than 'binding', for the latter implies a direct physical contact between two molecules; although this has been claimed in many cases, the data frequently do not justify this conclusion. Because of such ambiguities, we first discuss the assays used to identify PS-interacting proteins,

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

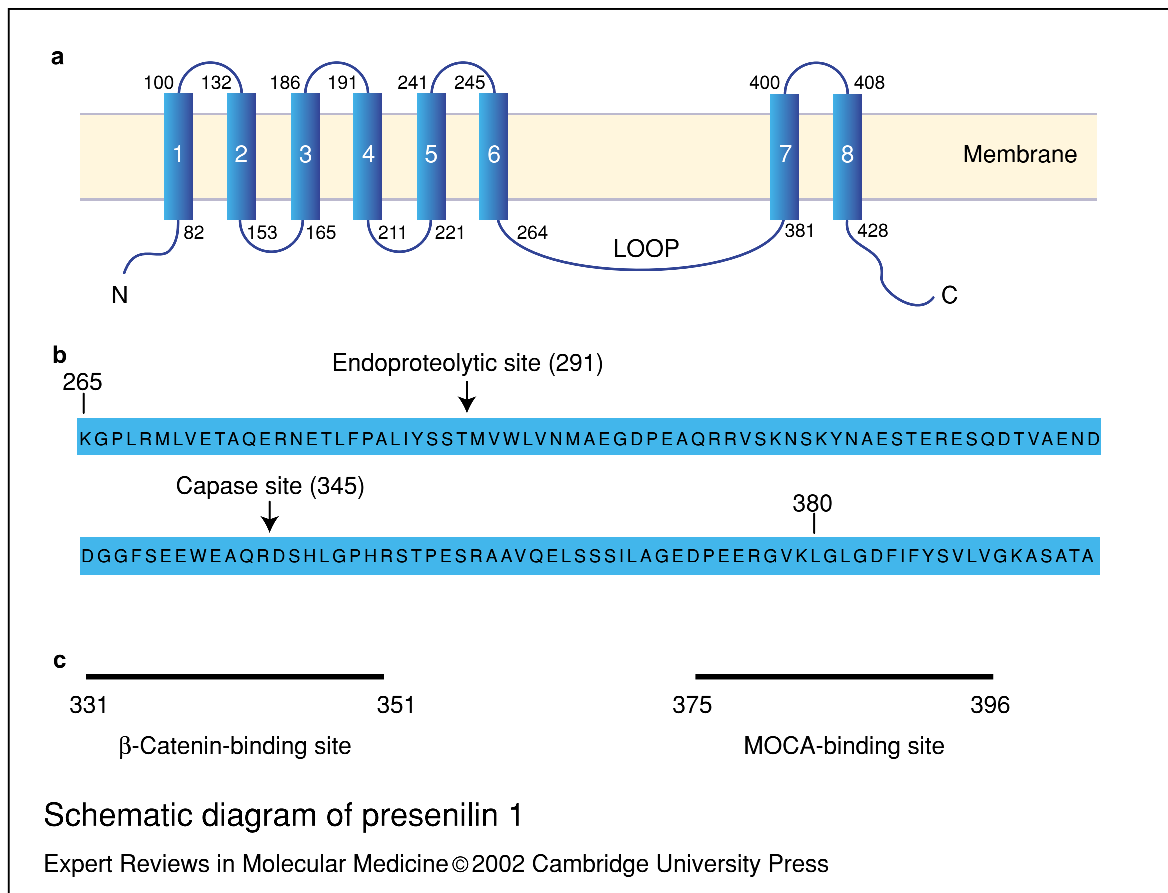

Figure 2. Schematic diagram of presenilin 1. (a) Preseniliin 1 (PS1), which contains 467 amino acids, has eight transmembrane domains, with a large cytoplasmic loop between the sixth and seventh transmembrane domains. PS2 has a similar structure, but contains 448 amino acids. (b) The large cytoplasmic loop of PS1 comprises residues 265–381 (residues given in single-letter code). The endoproteolytic cleavage site (which generates the two stable fragments) and a putative caspase cleavage site are shown. (c) The binding site for β-catenin has been mapped to residues 331–351, within the large cytoplasmic loop, whereas the MOCA-binding site spans the junctional region between the loop and transmembrane domain 7 (residues 375–396). MOCA, 'modifier of cellular adhesion' **(fig002dss)**.

and then provide a more detailed discussion of a few of the best-studied molecules.

Assays used to identify PS-interacting proteins: complicating factors

Many proteins have been found to interact with PSs (Table 1), although the relevance of some of these interactions is not yet known. The PSs and some PS-interacting proteins are multipass membrane proteins whose native conformations must be dictated by their local membrane environment. Since very few of the procedures employed to detect protein–protein interactions allow the proteins to adopt their native state, it is difficult to believe the interactions detected are significant if only one interaction assay is used and no biological function is demonstrated. The same argument is true for protein fragments, whose folding and binding properties are frequently distinct from those of the complete protein.

The yeast two-hybrid (Y2H) system (see Table 1 for references) is a screening technique that is commonly used to identify genes encoding interacting proteins, and has been used as a starting point for most of the studies on PS-interacting proteins. Although this assay suffers from the problems described above, it has still been surprisingly successful as a first step in identifying relevant PS-interacting proteins. This is probably owing to the frequent use of the large hydrophilic loop between TM domains 6 and 7

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

Table 1. Current state of knowledge on proteins that interact with presenilin 1 (PS1) and PS2[a] (tab001dss)

Name	Binding region[b]	Interaction assay[c]	Tissue express.	IC colocal.	AD pathol.[d]	Function[e]	Ref.
APP	PS1-FL, PS2-FL	Co-IP in PS+ and normal cells	(All)	–	(+)	(Adhesion)	27
APP	PS1-FL, PS2-FL	None	(All)	–	(+)	(Adhesion)	21
δ-Catenin	PS1-Loop	Y2H system; direct binding	Brain	–	–	(Signalling)	50
β-Catenin	PS1-Loop	Y2H system; co-IP in normal cells	(All)	–	(+)	(Signalling)	50
NRAP	PS1-Loop	Y2H system; co-IP in PS+ and brain cells; direct binding	Many	+	–	None	107
GSK-3β	PS1-Loop	Co-IP in PS+ and brain cells	(All)	–	–	(Signalling)	108
Tau	PS1-Loop	Co-IP in PS+ and brain cells	(All)	–	(+)	(Actin binding)	108
MOCA/PBP	PS1-Loop, PS2-Loop	Y2H system; co-IP in PS+, brain and normal cells	Brain	+	+	(APP processing)	56
Bcl-2	PS1-FL	Y2H system; co-IP in PS+ and normal cells; crosslinking	(All)	–	–	Cell death	67
Bcl-X_L	PS1-CT, PS2-CT	Y2H system; co-IP in PS+ cells; crosslinking	(All)	+	–	Cell death	68
Calsenilin	PS2-CT	Y2H system; co-IP in PS+ cells	All	+	–	PS2 cleavage	86
Filamin, Fh1	PS1-Loop, PS2-Loop	Y2H system; direct binding	All	+	+	(Cytoskeleton)	109
Rab11	PS1-Loop, PS2-Loop	Y2H system; co-IP in PS+ cells	UK	–	–	(Vesicular transport)	110
RABDGI	PS1-NT	Y2H system; co-IP in PS+ and brain cells; direct binding	(Brain)	+	–	(Vesicular transport)	111
Jif-1	PS1-FL	Y2H system	All	+	–	Signalling, apoptosis	112

(continued on next page)

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

Table 1. Current state of knowledge on proteins that interact with presenilin 1 (PS1) and PS2[a] (tab001dss) *(continued)*

Name	Binding region[b]	Interaction assay[c]	Tissue express.	IC colocal.	AD pathol.[d]	Function[e]	Ref.
CLIP170/ Restin	PS1-Loop	Y2H system; co-IP in PS+ cells; direct binding	(All)	+	–	(Cytoskeleton)	113
TPIP	PS1-NT	Y2H system; co-IP in brain cells	All	+	–	(Adaptor)	114
Notch	PS1-FL	co-IP in PS+ and normal cells	(Most)	–	–	(Signalling)	115
G_0	PS1-CT	co-IP in PS+ cells; direct binding	(All)	+	–	(Signalling)	116
Calmyrin	PS2-Loop	Y2H system; co-IP in PS+ cells; direct binding	Most	+	–	Cell death	117
HC5/ZETA	PS1-Loop	Y2H system; co-IP in PS+ and normal cells; direct binding	All	–	–	Protein breakdown	118
PSAP	PS1-CT	Y2H system; co-IP in PS+ cells	All	–	–	(Adaptor)	119
Nicastrin	PS1-FL, PS2-FL	co-IP in PS+, brain and normal cells; direct binding	UK	–	–	Secretase complex	44
Syntaxin 1A	PS1-Loop	Y2H system; direct binding	(Brain)	–	–	(Ca^{2+} signalling)	120
Sorcin	PS2-Loop	co-IP in PS+ and brain cells	(All)	+	–	(Ca^{2+} signalling)	121
Telencephalin	PS1-CT, PS2-CT	Y2H system; co-IP in brain cells; direct binding	Brain	–	–	(Adhesion)	122
Cadherin	PS1-FL	co-IP in brain and normal cells	(All)	+	–	Adhesion	99
DRAL	PS2-Loop	Y2H system; co-IP in PS+ and normal cells; direct binding	All	–	–	(Adaptor)	123
Metl	PS1-Loop, PS2-Loop	Y2H system; direct binding	All	+	–	Methyl-transferase	124
Ubiquilin	PS1-CT, PS2-CT	Y2H system; co-IP in PS+ cells; direct binding	All	+	+	PS1 levels	125

(for footnotes and abbreviations see next page)

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

Footnotes and abbreviations for Table 1

[a] With the exception of AD pathology and function, all of the information reflects data in the original publications.
[b] Binding regions are as follows: FL, full length; loop, large cytoplasmic loop; CT, C-terminus, NT, N-terminus.
[c] Normal cells in the context of co-IP indicate that the interaction was observed in non-transfected tissue culture cells; PS+ cells indicate cells overexpressing PS.
[d] AD pathology (pathol.) refers to whether or not the protein is found in plaques or tangles, or is otherwise changed in AD brain.
[e] Function without parentheses indicates that this was demonstrated in the original publication in the context of PS; function with parentheses indicates a previously known or more recently discovered function of the interacting protein. Parentheses are used in the same way for tissue expression and AD pathology.

Abbreviations:
AD, Alzheimer's disease; APP, amyloid precursor protein; CLIP170/Restin, 170 kDa cytoplasmic linker protein/Reed-Sternberg cells of Hodgkin's disease – expressed intermediate filament associated protein; co-IP, co-immunoprecipitation; DRAL, a member of the four and a half LIM protein family; express., expression; Fh1, filamin homologue 1; GSK-3b, glycogen synthase kinase 3b; HC5/ZETA, subunits of 20S catalytic particle of the 26S proteasome; IC colocal., intracellular colocalisation; Jif-1, QM/Jun-interacting factor; Metl, methyltransferase; MOCA/PBP, modifier of cellular adhesion/PS-binding protein; NPRAP, neural plakophilin-related armadillo protein; pathol., pathology; PSAP, PS-1-associated protein; RABGDI, rab GDP-dissociation inhibitor; TRIP, tetra tricopeptide repeat interacting protein; Y2H, yeast two-hybrid.

of PS as the bait sequence in the Y2H system. This amino acid sequence might have fewer conformational restrictions than the TM and small loop regions.

The other major criterion for interaction is co-immunoprecipitation (co-IP). In a co-IP assay, PS is immunoprecipitated, the immune complex run on SDS-acrylamide gels, and the proteins that co-precipitate with PS determined by western blotting or microsequencing. This procedure is also problematic for analysing interactions of membrane proteins, because they require detergent solubilisation before assay and it is clear that the choice of detergent and salts can influence the results. In addition, pure proteins are usually not used, and third-party bridge interactions cannot be ruled out. Furthermore, many co-IP studies use transfected non-neuronal cells that overexpress PSs, which can lead to precipitation of the proteins in the ER, self-aggregation of PS and the detection of artificial interactions that would not normally occur (Ref. 21). It is critical that such studies test normal tissue lysates, ideally brain, but in fact co-IP from CNS tissue or untransfected cell lines has rarely been used as a criterion for interaction (Table 1). Finally, if overexpression (transfection) and intracellular colocalisation by immunological methods are used to study CNS proteins it is important to use nerve cell lines or primary cultures for these purposes because, as stated above, there is no reason to assume that protein compartmentalisation in fibroblasts is the same as that in neurons.

In summary, conventional assays of protein–protein interaction have yielded many possibilities for PS-interacting proteins that require further physiological validation. Probably the best indication of an actual physical interaction between two proteins comes from either the use of chemical crosslinkers followed by immunoprecipitation or direct binding assays with fusion proteins. Unfortunately, these techniques have been rarely employed in the study of PS binding (Table 1). Ultimately, the only relevant observation relating to PS interactions is whether or not a presumed PS-interacting protein alters a PS-dependent function in animals. Historically, proteins involved in development and behaviour have been identified in flies or worms and then studied in mammals. This is no longer always the case. Indeed, the physiological role of proteins first identified in mammalian systems is frequently being understood in flies and worms. A good example of this is the transmembrane, PS-interacting protein nicastrin, which is discussed later in the context of Notch signalling.

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

PS-interacting proteins and pathways

APP

As outlined above, there is a very strong correlation between the expression of mutant forms of PS and the production and accumulation of $A\beta_{1-42/43}$ in cultured cells, mouse models of AD and diseased human brain. Accordingly, there has been intense interest in the functional and physical relationship between PSs and the precursor protein from which Aβ is derived. Aspects of this relationship have been controversial. First, do APP and PS directly interact under normal conditions? Second, does PS1 cleave APP at the γ-secretase site to release the toxic peptide? There have been many published attempts to demonstrate a physical interaction between the two proteins, but all fall short of showing that this interaction occurs in the intact nerve cell. However, if it can be demonstrated unambiguously that APP is a substrate for PS1 enzymatic activity, then the co-IP and Y2H data become irrelevant, and it is quite clear that there is a de facto interaction between the two proteins. The following paragraphs briefly outline the data further; details can be found in reviews (Refs 11, 12).

APP and PS2 co-immunoprecipitate in studies using overexpressing transfected cells (Refs 26, 27). However, the principal forms of APP precipitated were the less mature forms of the molecule lacking extensive glycosylations, and the interaction could not be demonstrated in CNS tissue. Further co-IP studies have shown that only the N-terminus of PS2 containing the secretory signal sequence, not the cytosolic form, interacts with APP (Ref. 28). The observation that PS only interacts with APP containing this sequence suggests either that the interaction is transient or that it is not relevant to the physiology of the cell. Furthermore, another group was unable to demonstrate any interaction between PS1 and APP using co-IP experiments with similar cell lysis and immunoprecipitation conditions, as well as crosslinking experiments (Ref. 21). Although the reason for these discrepancies is unclear, it might be caused by the extensive use of transfected cells overexpressing membrane proteins. Similarly contradictory results have come from two Y2H studies, both of which used fragments of APP and/or PS1 (Refs 29, 30). Therefore, an interaction between PS1 and APP, if it exists at all, is not very robust. These data also reinforce the fact that an unambiguous demonstration of a direct interaction between pairs of membrane proteins in the absence of a clearly defined function is very difficult.

Despite the inability to reproducibly show a direct interaction between APP and PS1, there is evidence to support the view that PS is required for γ-secretase activity but that it is not likely to be the γ-secretase enzyme. First, neural cells derived from $PS1^{-/-}$ (knockout) mouse embryos show impaired Aβ production and γ-secretase activity (Ref. 31). More-recent studies showed that PS2 makes a small contribution to γ-secretase activity since there is about an 80% reduction in γ-secretase activity in cells derived from $PS1^{-/-}$ mice, whereas $PS1^{-/-}PS2^{-/-}$ (double knockout) mice show a complete elimination of this activity (Ref. 32). This result does not, however, answer the technically more challenging question of whether PS1 is sufficient to execute the γ-site cleavage.

Second, from the use of protease inhibitors, it was suggested that the γ-secretase is an aspartyl protease that cleaves APP within the lipid bilayer, and it was argued that an aspartic acid to alanine mutation of either of the two intramembranous aspartic acids in domains TM6 or TM7 of PS1 is sufficient to generate a cell unable to produce Aβ (Ref. 23). It was subsequently shown in one laboratory that only one of the two aspartic acids is required for γ-secretase activity (Ref. 33), and by another research group that the simultaneous elimination of the two TM PS1 aspartates had no effect on Aβ production in mouse N2a neuroblastoma cells (Ref. 34). It is therefore unlikely that the intramembrane aspartic acids are necessary for Aβ production, thereby eliminating the argument that PS is an aspartyl protease.

Third, using structurally unrelated transition-state analogue γ-secretase inhibitors, which should bind to and affinity label the active site of the enzyme, two laboratories showed that PS1 is the major labelled protein (Refs 35, 36). These results suggest that the active site for γ-secretase is at least closely associated with PS1. However, until it is demonstrated that PS1 cleaves APP, or any other substrate as a component of a chemically defined complex, the question of whether PS1 is the γ-secretase will not be formally answered, nor will it be known if APP and PS1 bind to each other in neurons.

Notch and nicastrin

Elucidation of the role of PS1 in the *Caenorhabditis elegans* Notch pathway was crucial in focusing the

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

study of PS mutations in FAD (for reviews see Refs 37, 38). Conversely, the discovery of nicastrin as a PS-binding protein in mammalian cells was immediately followed by studies linking it to the Notch pathway in flies and worms.

Notch proteins are a group of large [molecular weight (MW) approximately 300 000] cell-surface membrane receptors that mediate complex cell fate decisions during development. For example, during neurogenesis in flies, the Delta protein signals from prospective neuroblasts through the Notch receptor on adjacent cells to prevent the latter from becoming neuroblasts and neurons. When this type of lateral inhibition is blocked by loss-of-function mutations in the ligand, Notch receptor or other necessary components of the Notch signalling pathway, there is an overproduction of neurons in the embryo. In vertebrates, Notch is synthesised as a 300 000 MW precursor that is cleaved initially by a protease at site S1 near the N-terminus to generate two extracellular proteins that remain together to form a receptor. Upon ligand binding, there is another proteolytic cleavage (S2) near the membrane to remove the entire extracellular domain of Notch from the cell surface. Finally, a third cleavage (S3), which occurs within the membrane lipid bilayer, releases the intracellular domain of Notch. This Notch fragment is translocated to the nucleus where it interacts with DNA-binding proteins, and together they act as transcriptional activators. In nematodes, the SEL-12 protein is required for the S3 cleavage of Notch (Ref. 39). Human PS1 is both structurally and functionally homologous to SEL-12, and wild-type human PS1 complements SEL-12 in nematodes (Ref. 40). Furthermore, several FAD-linked mutant human PSs were less effective at rescuing the SEL-12 mutation, demonstrating that that these mutations have biological consequences.

Drosophila lacking PS have phenotypes that are indistinguishable from Notch$^{-/-}$ mutants, again arguing for a role of PS1 in Notch signalling (Refs 41, 42). In PS1$^{-/-}$ mice there are also defects in the Notch signalling pathway, and specifically there is a reduction in the CNS nerve cell population caused by the premature differentiation of neural progenitors (Ref. 43). Note that the Notch signalling pathway is different in flies and mice: in flies, Notch promotes epidermal production over neuronal production from a common precursor, whereas in mice Notch promotes precursor cell division at the expense of differentiation to neurons. PS1$^{-/-}$ mice also have a defect in neural migration during cortical neurogenesis (Ref. 43), an observation that is compatible with the fact that a number of PS-interacting proteins, such as MOCA and the cadherins (see later), are involved in cell adhesion and motility. Since several inhibitors of γ-secretase also inhibit Notch proteolysis at the S3 site, and Notch and APP are cleaved in a PS-dependent manner at similar positions in their TM domains, it has been argued that PS is the enzyme responsible for both. In addition, PS1$^{-/-}$ mice have similar phenotypes to Notch$^{-/-}$ mice. However, it is more likely that two or more different enzymes, both of which require PS1 as a cofactor for enzymatic activity or intracellular trafficking, affect Notch and PS1 cleavage. Some mutations in PS1 TM domains have differential effects on Notch and APP cleavage, arguing for different mechanisms (Refs 33, 38).

This scenario has been complicated by the discovery of a new player in the Notch pathway: nicastrin (named after the Italian town of Nicastro, which was the home of one of the first-studied FAD families). Nicastrin was identified as a component of a high-MW PS1 fraction in HEK293 cells overexpressing PS1. Nicastrin is a protein of 709 amino acids with a large hydrophilic N-terminal domain, a single TM domain, and small intracellular C-terminus of 20 amino acids (Ref. 44). Because of the association of PS1 with both Aβ production and the Notch signalling pathway, it was immediately asked how nicastrin affects these processes. When the gene encoding nicastrin is deleted in *C. elegans* or *Drosophila*, phenotypes similar to those caused by the loss of PS1 or Notch are induced. The cleavage of APP and Notch at the PS1-dependent site is also lost, along with the ability to produce Aβ (Refs 44, 45, 46, 47). In addition, PS1 cleavage in the large loop region and subsequent PS1 maturation is eliminated in the absence of nicastrin (Ref. 47). These data strongly suggest that nicastrin and PS1 are necessary components of the machinery that carries out Aβ production and signal transduction within the Notch pathway, but their exact roles in these processes remain to be determined.

β-Catenin

β-Catenin is a member of the armadillo-repeat family of proteins (containing a 42 amino acid repeat originally described in the *Drosophila* armadillo protein encoding β-catenin), and

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

plays a major role in cell adhesion through the Wnt signalling pathway. *Wnt* genes encode a family of secreted signalling proteins with a conserved pattern of 23/24 cysteines and overall sequence homology. They activate cell-surface receptors, leading to a complex signalling cascade involving the serine threonine kinase GSK-3β (glycogen synthase kinase 3β) and β-catenin (Ref. 48). β-catenin is distributed between two cellular pools, with a large fraction associated with the plasma membrane and the remainder in the cytoplasm. Plasma-membrane-associated β-catenin binds to cadherins, the major class of cell–cell adhesion molecules, as well as to the actin cytoskeleton via α-catenin to form the adherens junction complex (anchoring points where the cytoskeleton of neighbouring cells are connected to each other: for a review of the molecular interactions see Ref. 49).

In the absence of appropriate signals from the Wnt pathway, cytoplasmic β-catenin is rapidly degraded by proteasomes. β-catenin degradation requires the phosphorylation of β-catenin by GSK-3β, a process that is dependent upon the APC (adenomatous polyposis coli) protein and axin. Activation of the Wnt pathway inactivates GSK-3β, which results in stabilisation of free β-catenin and its subsequent transport to the nucleus where it binds transcription factors of the Tcf/Lef family and promotes gene expression involved in cell fate determination.

β-Catenin has been found in high-MW PS complexes (Refs 50, 51, 52). The interaction between PS1 and β-catenin was also demonstrated by co-IP in various cell types including primary brain cells; by contrast, β-catenin and PS2 do not co-immunoprecipitate (Ref. 53). The β-catenin-binding region within PS1 was initially localised to residues 322–450 in the large hydrophilic loop (Ref. 54), and then more finely localised to residues 331–351 (Ref. 55), which lies within the C-terminal fragment of endogenously cleaved PS1 and is near the MOCA-binding site (Refs 53, 56, 57) (Fig. 2). Although PS1 and β-catenin co-immunoprecipitate, a direct interaction between the two has not been demonstrated in the Y2H system. Therefore, a third protein, which may be δ-catenin, is assumed to be required for their interaction (Ref. 58). The association of PS1 and β-catenin is altered by the phosphorylation of β-catenin by at least two kinases – p35/CDK5 and GSK-3β (Ref. 59) – and both the pathogenic mutant forms and wild-type PS1 bind β-catenin with about the same affinity (Refs 54, 57, 60). The physiological consequences of the association between β-catenin and PS1 have been difficult to identify, but PS1 might regulate β-catenin turnover and trafficking to the nucleus.

The translocation of β-catenin to the nucleus is reduced in human fibroblasts carrying PS mutations associated with FAD but not in cells expressing a nonpathogenic mutant (Glu318Gly) or in $PS1^{-/-}$ fibroblasts (Ref. 60). This study suggests a direct effect of mutant PS1 on nuclear translocation, since cytoplasmic accumulation of β-catenin was not observed. The defective translocation of β-catenin appears to be a dominant 'gain of an aberrant function' effect. Since the interaction between β-catenin and mutant PS1 was not affected as defined by co-IP studies, perturbations in the interactions of the other components in the PS–β-catenin complexes are likely.

Although there are conflicting results on the roles of PS1 in β-catenin turnover, most evidence suggests that the expression of PS1 facilitates β-catenin turnover and inhibits β-catenin–Tcf/Lef-regulated transcription by a mechanism independent of GSK-3β (Refs 54, 57, 61, 62). Conversely, PS1 deficiency in mice results in the accumulation of cytosolic β-catenin, an increase in Tcf/LEF-dependent transcription, and accelerated entry into the S-phase of the cell cycle (Ref. 61). The PS1-deficient animals developed epithelial hyperplasia and skin tumours, as well as elevated β-catenin levels and upregulated Tcf/LEF-dependent cyclin D transcription in the skin, suggesting an augmentation of Wnt signalling (Ref. 63). In *Drosophila* $PS1^{-/-}$ embryos, β-catenin is lost from the membrane and accumulates as large ubiquitin-immunoreactive cytoplasmic inclusions (Ref. 58). This study argues that, in addition to Notch signalling, PS regulates the trafficking of β-catenin between the adherens junction and the proteasome.

Studies of the effects of PS1 mutations associated with FAD on β-catenin turnover have produced inconsistent results probably because of the use of different PS1 mutants and cell types by each investigator. For example, the rate of β-catenin degradation and the levels of β-catenin are lower in cells expressing PS1 FAD mutants relative to wild-type PS1 in some studies (Refs 64, 65), and higher in others (Ref. 57). Additional studies have found no correlation between the PS1–β-catenin interaction and β-catenin signalling

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

(Ref. 66), although this result is complicated by the fact that the cells used in this study (HEK293) express considerable amounts of endogenous PS1; the use of cells from PS1-deficient mice would generate less-ambiguous results. These results are, however, in agreement with the other data, which show that PS1 action can be independent of GSK-3β (Ref. 62).

In summary, since PS1 binds not only β-catenin but also other components of the complex β-catenin signalling pathway (GSK-3β, cadherins and δ-catenin; Table 1), which regulate many cell functions, cross-talk among these pathways might be mediated by PS1; thus, PS1 might integrate the multiple signals that lead to cell fate decisions. It is unlikely, however, that the PS–β-catenin interaction alters Aβ production.

Cell death pathways

Since the discovery of the PSs in 1995, there have been many reports that the forced expression of PSs or, more frequently, PS mutations associated with FAD, cause cell death or an increased sensitivity to inducers of cell death in transfected cells or cells from PS1-transgenic animals. However, some studies show that PS or its mutants have no effect on cell survival (see below). Others report a direct interaction between PSs and two anti-apoptotic proteins: Bcl-2 and Bcl-X_L (Refs 67, 68). Although reports linking the PSs and cell death are far too numerous to be dismissed, they should be viewed with a degree of caution for several reasons. First, given that individuals who ultimately die of PS-linked FAD develop normally and live for half a century before any manifestation of the disease, it is unreasonable to expect a strong phenotype as a direct consequence of expressing the mutation. It is likely that there are more-subtle cumulative effects that are exacerbated by age-associated stress and probably other molecular changes in CNS neurons. Second, the majority of the published work has used transient overexpression of PS in non-neuronal cells, systems that, as mentioned above, are prone to problems of interpretation. For example, the overexpression of PS in non-neuronal cells, where it cannot be properly processed or utilised, might lead to cell death. Third, if subtle differences in the sensitivities to toxic agents of cells expressing different forms of PS are to be detected, it is mandatory that careful dose–response (DR) curves be conducted rather than picking one concentration of toxin. If there are differences, they will most likely be detected as shifts in the DR curve that might not be detected if a concentration is used that is on the high (top) end of both curves (for example, see Ref. 69). In addition, very high concentrations of toxin might ‘swamp out’ the normal response, and indeed could lead to cell death by a very different mechanism. With these caveats in mind, the following paragraphs discuss some of the extensive literature in this field. This discussion uses the term cell death or programmed cell death (PCD) as opposed to apoptosis, for there is a continuum between these modes of cell death, and most of the papers in the AD field do not make the distinction. For example, TUNEL labelling of DNA, a frequently used marker for apoptosis, occurs in both forms of cell death (for review, see Ref. 70).

The ER is responsible for the synthesis, export and, under some conditions, breakdown of membrane and secreted proteins. Under some conditions, the ER becomes overloaded with improperly folded or insoluble proteins, resulting in a stress response that can lead to either a clearance of the proteins or, if the stress is sustained or sufficiently potent, to cell death (for reviews, see Refs 71, 72). Since AD is associated with the deposition of insoluble proteins in the form of plaques and tangles as well as oxidative stress, which also induces the ER stress response, there has been a great deal of interest in ER stress and its relationship to the potential role of PS in promoting cell death.

The expression of PS mutations associated with FAD has been shown to lead to nerve cell death in AD brain, resulting in a large number of groups studying the effects of overexpression of PS and mutated PS in the context of cell death. Many reports have shown that the expression of PS1 or PS2 causes cell death and that cell death is enhanced by FAD mutations (see for example Refs 64, 73, 74). There are several possible explanations for these results, but the most widely accepted seems to be that the expression of PS mutations associated with FAD initiates and overrides the ER stress response, resulting in a breakdown of the ER-protective responses, followed by cell death. These types of results have been reported with overexpressing cell lines and also with primary nerve cell cultures from mice bearing AD-linked mutated PS1 (Ref. 75). In the context of overexpressing transfected cell

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

lines, the ER stress scenario is a likely outcome of the additional burden of synthesising a surplus of a very hydrophobic membrane protein such as PS, whose utilisation and disposal might be complicated by mutations that cause misfolding and expression in the inappropriate cell type. It should be noted that in few of the cell culture studies were other proteins of a similar size and hydrophobicity used as controls.

Is the ER stress pathway relevant to the nerve cell death that occurs well after mid-life in AD? This is certainly plausible, for the disease is characterised by the accumulation of Aβ, which has the potential to cause cell death. This issue is best addressed in transgenic animals as opposed to transfected cell lines. There have been two reports that claim to demonstrate an increase in ER-stress-induced nerve cell death associated with the expression of PS mutations linked with FAD (Refs 75, 76). However, several other reports show that there is no association between AD-linked PS1 mutations and ER-stress-induced nerve cell death, either in primary cultures or in transfected fibroblasts (Refs 77, 78), nor is there an increase in nerve cell death per se in mice expressing pathogenic PS mutations (Refs 78, 79). In addition, there is no apparent increased sensitivity of neurons or fibroblasts derived from these animals to reagents that induce ER stress artificially, such as thapsigargin or staurosporin (Refs 77, 78). However, differences in the sensitivities (i.e. death threshold) of cells expressing PS or mutated PS could have been missed in the latter (negative) studies because DR curves versus the toxin were not conducted.

Nerve cells do, however, die in PS-linked and APP-linked FAD (Ref. 11). The only common feature identified to date is the accumulation of Aβ, which is a neurotoxin. Thus, it could be concluded that, while the overexpression of PS or its FAD-associated mutants in cell culture systems might lead to increased cell death, this explanation for the in vivo situation is too simplistic since AD patients appear normal until well into mid-life. It is more likely that there is an accumulation of many problems, including a gradual deterioration of the protective ER stress response with age, leading to an accumulation of proteins such as Aβ. Over time, nerve cells might also become particularly sensitive to Aβ toxicity, and death could clearly be potentiated by an accumulation of overproduced Aβ within cells or reuptake and lysosomal accumulation (Refs 80, 81). This could be tested in older AD mice with careful DR curves to ER stress inducers.

Finally, there appears to be a correlation between Notch activity and cell death in both flies and mice. There is an increase in cell death in Notch-deficient flies (Ref. 82), as there is in the neural tissue of mice lacking Notch (Ref. 83). In addition, flies lacking or overexpressing PS have increased cell death, and this phenotype is suppressed by constitutively active Notch (Refs 37, 41).

Calcium metabolism pathways

Dysregulation of intracellular calcium (Ca^{2+}) metabolism occurs at, or near, the ultimate stage of essentially all forms of cell death (for reviews see Refs 84, 85). Therefore, the mechanisms that regulate intracellular Ca^{2+} metabolism are critical for the maintenance of cell survival. There are several putative Ca^{2+}-binding proteins that interact with PS, including calsenilin, calmyrin, syntaxin 1A and sorcin (see Table 1 for references). In addition, other proteins that interact with PS, such as Bcl-2, Bcl-X_L, cadherin and β-catenin are involved in Ca^{2+}-dependent signalling pathways. Aside from Bcl-2 and Bcl-X_L, perhaps the best-studied of these proteins is calsenilin. Calsenilin was identified in the Y2H system using a C-terminal fragment of PS2 as 'bait' (Ref. 86), and binds PS1 and PS2, as well as Ca^{2+}. It has sequence homology with neuronal Ca^{2+} sensor 1 and is identical to a novel Ca^{2+}-binding transcription factor whose activity is inhibited by Ca^{2+} (Ref. 87). Its overexpression alters the proteolytic cleavage of PS2 by an undefined mechanism.

Many laboratories have shown that the overexpression of PS1 or PS2 alters intracellular Ca^{2+} levels, an effect that is claimed by some groups to be augmented by PS mutations associated with FAD (Ref. 88). The effect on intracellular Ca^{2+} might be mediated by inositol trisphosphate (IP_3) since FAD-linked PS1 mutations potentiate IP_3-mediated Ca^{2+} release from the ER (Ref. 88). More recently, it was shown in oocytes that PS mutations associated with FAD potentiated Ca^{2+} release by IP_3 and that this effect is reversed by the co-expression of calsenilin (Ref. 89). Since calsenilin alone did not alter the kinetics of Ca^{2+} mobilisation, it was argued that calsenilin is acting in response to FAD-linked PS mutations in a manner independent of its potential Ca^{2+}-buffering capacity. Another Ca^{2+}-binding protein, socrin, also binds to PS1, and

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

modulates intracellular Ca^{2+} levels through both ryanodine receptors and voltage-gated Ca^{2+} channels (Ref. 90). These observations, along with those that show abnormalities in Ca^{2+} metabolism in cells expressing FAD-linked PS mutations (see for example Ref. 91) and the claim that changes in IP_3-mediated Ca^{2+} signals can be used to distinguish patients with FAD-linked mutations from unaffected family members (Ref. 92), suggest that a perturbation in Ca^{2+} signalling might play a central role in PS-associated disease. These data also provide a link to claims that cell death is augmented by PS mutations, since Ca^{2+} clearly plays a central role in PCD, and in particular in the ER stress response that has been linked by some to PS-mediated FAD.

MOCA and cell-adhesion pathways

MOCA (also known as MOCA/PBP, where PBP stands for PS-binding protein) was originally isolated using the Y2H system, and the interaction of MOCA with PS1 and PS2 was confirmed by co-IP studies, co-localisation and cellular fractionation (Ref. 56). The region of PS that is responsible for this interaction is localised to a conserved region of PS1 and PS2 (amino acids 375–396 of PS1), within the junctional region between the large loop and TM domain 7 of PS (Fig. 2). This region is near the β-catenin-binding site. MOCA is composed of 2027 amino acids with a predicted molecular mass of 233 kDa, and contains a Src-homology 3 (SH3) domain at the N-terminus and several Crk-binding motifs near the C-terminus. MOCA belongs to the DOCK family and has 40% homology with DOCK180, a Crk-binding protein that is involved in the regulation of cell movement and morphology (Ref. 93). The amino acid sequence of MOCA is highly conserved, with 98% identity between humans and mice. The gene contains at least 51 exons and is localised to human chromosome 3q14.3-21.3. The primary cellular location of MOCA is the cytoplasm; however, overexpression of PS1 re-localises MOCA to the membrane (Ref. 56).

Unlike most other PS-binding proteins, MOCA is expressed only in the brain and is highly localised to the cerebral cortex and hippocampus, which are areas prone to cell death in AD (Ref. 56). One of the most striking findings for MOCA localisation is its distribution in AD brain. There is a dramatic reduction of MOCA levels in the soluble fraction of AD brain relative to age-matched controls, with a corresponding increase in the particulate fractions. This change of subcellular localisation of MOCA in AD brain was not observed for PS1, synaptophysin or three neurofilament subunits. Immunostaining data show that, in the cortex and hippocampus of AD brains, MOCA accumulates in NFTs, which are enriched with hyperphosphorylated Tau proteins (Ref. 94). Tau and MOCA co-localise in NFTs and the MOCA antibody does not stain Lewy bodies. Additional studies have shown that the phosphorylation of specific sites in Tau are increased in MOCA-expressing cells relative to control cells. GSK-3β is one of the major kinases that phosphorylates Tau, and preliminary evidence suggests that MOCA associates with GSK-3β (Q. Chen, unpublished). Surprisingly, the kinase activity of GSK-3β in MOCA-expressing cells is decreased rather than increased (Ref. 94). Since brains from cases of sporadic AD have been used in all of the studies with MOCA, it is possible that MOCA has a broad functional significance in the pathogenesis of the disease.

The effect of MOCA on APP metabolism has been recently evaluated. The expression of MOCA in CNS nerve cells and fibroblasts at levels significantly below those found in rodent hippocampus specifically decreases both APP and Aβ accumulation (Ref. 95). These effects of MOCA are due to an acceleration in the rate of intracellular APP degradation, as shown by pulse–chase analysis and by the fact that the inhibitory effect of MOCA on APP secretion can be rescued by specific proteasome inhibitors. Since the effect of MOCA on APP secretion is the same when the γ-secretase activity of PS1 is inhibited, the function of MOCA in APP processing can be separated from the PS-related γ-secretase activity. This is a novel mechanism by which APP secretion might be regulated. In this model, nascent APP might pass through an early ER-secretory environment in which complexes required for protein degradation coexist with those required for protein assembly and modification. In the absence of MOCA, the precursor protein follows the secretory pathway; in the presence of MOCA, a significant fraction of APP is directed to proteasomes where it is degraded. The fact that Aβ secretion is reduced by MOCA suggests that the impaired function of MOCA could lead to AD.

MOCA is also involved in the regulation of cell adhesion. Using CNS nerve cell lines that

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

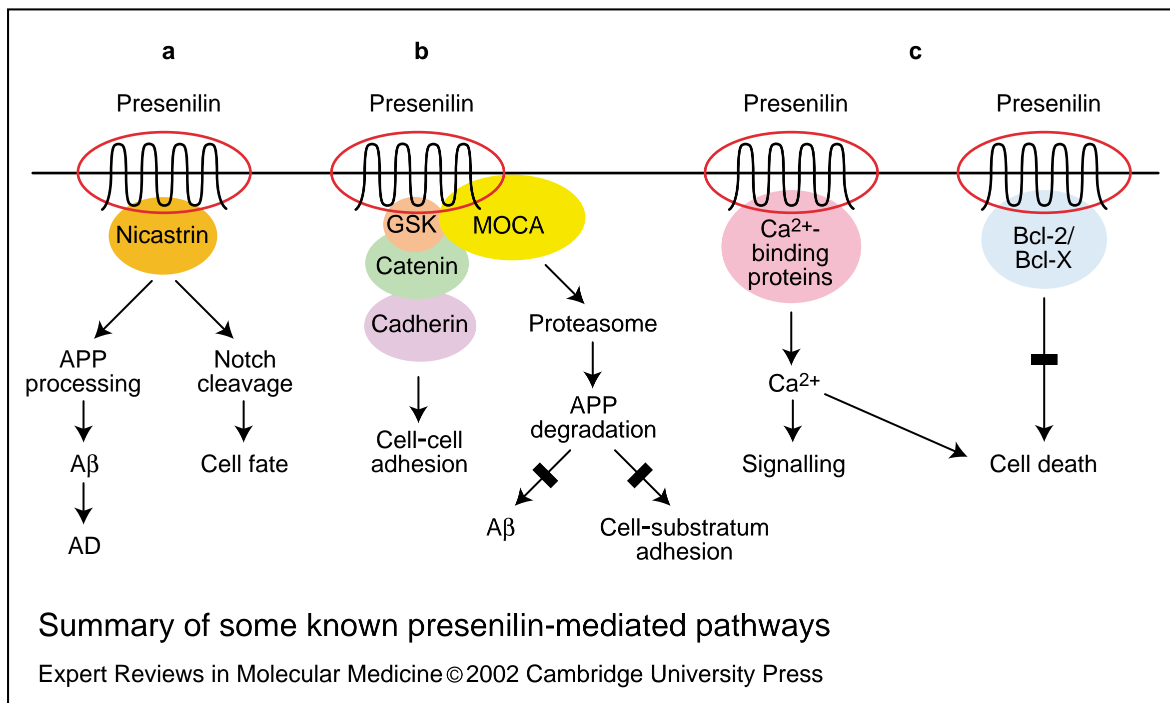

Figure 3. Summary of some known presenilin-mediated pathways. (a) Interaction of presenilin (PS) with nicastrin and Notch regulates amyloid precursor protein (APP) processing and cell fate decisions. (b) Interaction of PS with β-catenin, cadherin and MOCA ('modifier of cellular adhesion') mediates β-amyloid (Aβ) production and cellular adhesion. (c) Interaction of PS with calcium-binding proteins and with Bcl-2 and Bcl-X alters calcium signalling and cell death pathways. AD, Alzheimer's disease; GSK, glycogen synthase kinase **(fig003dss)**.

express no APP, or APP with or without MOCA, it was shown that MOCA reduces cell adhesion to extracellular matrix and that this effect is mediated by APP (Ref. 95). This is because there is very little accumulation of APP in cells that express MOCA. Therefore, the impaired function of MOCA could have pathological consequences in addition to its effect on Aβ production. In particular, since APP might be involved in synaptic function (Refs 96, 97, 98), abnormal metabolism of APP could lead to synaptic impairment and cognitive decline.

In addition to APP-mediated cell–substratum interactions, PS1 and some of its interacting proteins are involved in cell–cell adhesion mediated by the formation of adherens junctions (see section entitled 'β-Catenin', and Ref. 49 for review). PS binds to multiple components of the adherens junctional complex and the cytoskeleton, including cadherins, catenins, filamin and the Tau protein (Table 1). PS1 colocalises with E-cadherin at adherens junctions in confluent cultures of MDCK cells and in mouse CNS synaptic junctions (Ref. 99). Since components of adherens junctions are found in synaptic junctions along with PS1 (Ref. 100), mutated PS1 protein has the potential to disrupt the synapse. The overexpression of PS1 increases cadherin-based adhesion in cultured fibroblasts and epithelial cells (Refs 99, 101), a process that does not occur with at least one form of PS1 expressing a FAD-linked mutation (Refs 101, 102). Indeed, PS expression might have a direct impact on synaptic function, for memory performance is impaired in $PS1^{-/-}$ mice (Refs 103, 104). These results and others (see for example Refs 105, 106) clearly demonstrate that PSs are involved in important cell-surface-mediated biology and are not exclusively localised to the ER and Golgi as initially thought by some.

Conclusion

Figure 3 is a simplistic summary of several PS interactions that lead to characterised biological consequences. The most thoroughly studied of the interactions shown involves PS and the Notch signalling pathway, where both PS1 and nicastrin are required for Notch signalling and APP

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

cleavage at the γ-secretase site (Fig. 3a). However, it is not yet clear whether the γ-secretase activity resides within the PS1 molecule. This is an important issue, for the integrity of the Notch signalling pathway dictates both the short- and long-term survival of the individual. Notch signalling regulates cell fate decisions during development, and γ-secretase activity can determine whether or not an individual will die of AD because it regulates the production of the neurotoxic Aβ peptide.

The developmental significance of the interaction between PS and the β-catenin-mediated Wnt pathway is less clear, particularly in the CNS, but again this pathway regulates cell fate decisions and cell–cell adhesions (Fig. 3b). The more recently identified PS-interacting protein MOCA downregulates APP expression in nerve cells, leading to the production of less Aβ and a dramatic reduction of APP-mediated cell–substratum adhesion (Fig. 3b). Finally, PS and a large group of interacting proteins such as Bcl-2 and Ca^{2+}-binding proteins have been implicated in cell death pathways (Fig. 3c). These studies have been more problematic since most were carried out in overexpressing non-neuronal cell culture systems; it is unlikely that the expression of FAD-linked mutations have such a strong phenotype (i.e. death) in the nervous system since individuals with AD die late in life.

An understanding of the above pathways in CNS nerve cells is a prerequisite to designing therapeutics based upon both the regulation of Aβ production and the mechanisms that mediate its toxicity. For example, if PS1 is the γ-secretase for APP and if it also carries out the S3 cleavage in Notch processing, then it is very unlikely that γ-secretase inhibitors would be an effective therapy for a chronic disease such as AD because they would also block the Notch pathway, which is required for normal cell development and function. As additional substrates for PS1-dependent proteolysis are identified, the difficulty of using protease inhibitors as therapeutics will be increased. It is also unlikely that an inhibitor of APP cleavage at any of the Aβ-generating sites will be without serious side-effects because all type I cell-surface proteins are probably degraded in a manner similar to APP; it is unlikely that each has its own set of proteolytic enzymes. It is indeed surprising that additional toxic amphiphilic peptides like Aβ are not generated by the breakdown of these other membrane-spanning proteins. If, however, the cleavage of Notch and APP are shown to be carried out by different enzymes, or at least regulated by different mechanisms, then there is more hope of designing an effective therapy based upon γ-secretase inhibitors.

Since there is a wide-spread loss of nerve cells and the information they store in AD, it is clear that therapeutics based upon nerve cell replacement (through the use of stem cells or any similar technology) will not provide a viable possibility in the foreseeable future, for the information in the cells and their connections will not be replaced and the loss of nerve cells will continue. Furthermore, because most FAD-linked mutations lead to a gain-of-function, it is also unlikely that genetic engineering strategies that introduce a wild-type gene into at-risk cells will promote survival. Since early diagnosis of AD is now becoming possible, the best near-term therapy would be one that inhibits nerve cell death, which is the common denominator of the many causes of AD. Ideally, the most efficient method would be use of a reagent, ideally a small molecule, that blocks Aβ production, inhibits the formation of toxic Aβ fibrils, or stops the death of fragile nerve cells.

The complementary approaches of studying the pathology, genetics and biochemistry of AD in humans together with analysis of relevant proteins and pathways in simpler animal systems has led to the best understanding of the normal biological roles of the proteins directly linked to AD through their ability to interact with PS. With the continued contribution of such studies, it should be possible to understand the details of the pathways that lead to nerve cell death in this devastating disease and to design therapeutics based upon this information.

Acknowledgements and funding

This work was supported by the Bundy Foundation, the Anna Charlotte Hansen Fund for Alzheimer's Research, and the Alzheimer's Association of America. We thank Dr Pamela Maher and the members of the Salk Institute Cellular Neurobiology Lab for their critical reading and discussion of the manuscript, and Belle Wamsley for its preparation. We also thank Drs Gopal Thinakaran (University of Chicago, Chicago, IL, USA) and Edward Koo (University of California, San Diego, CA, USA) for their peer review of the article.

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

References

1 Alzheimer, A. (1911) Uber eigenartige Krankheitsfalle des spateren. Zeitschr. fdg. Neurol. u. Psychiatr. 4, 356-385

2 Gouras, G.K. (2001) Current theories for the molecular and cellular pathogenesis of Alzheimer's disease. Exp. Rev. Mol. Med. 31 May, http://www-ermm.cbcu.cam.ac.uk/01003167h.htm

3 Glenner, G.G. and Wong, C.W. (1984) Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. Biochem Biophys Res Commun 122, 1131-1135, PubMed ID: 84307522

4 Hardy, J. (1997) Amyloid, the presenilins and Alzheimer's disease. Trends Neurosci 20, 154-159, PubMed ID: 97260260

5 Fraser, P.E. et al. (2000) Presenilin structure, function and role in Alzheimer disease. Biochim Biophys Acta 1502, 1-15, PubMed ID: 20436999

6 Oltersdorf, T. et al. (1990) The Alzheimer amyloid precursor protein. Identification of a stable intermediate in the biosynthetic/degradative pathway. J Biol Chem 265, 4492-4497, PubMed ID: 90170956

7 Schubert, D. et al. (1988) Amyloid beta protein precursor is possibly a heparan sulfate proteoglycan core protein. Science 241, 223-226, PubMed ID: 88264430

8 Tsuchida, K. et al. (2001) Appican, the proteoglycan form of the amyloid precursor protein, contains chondroitin sulfate E in the repeating disaccharide region and 4-O-sulfated galactose in the linkage region. J Biol Chem 276, 37155-37160, PubMed ID: 21463085

9 Schubert, D. et al. (1989) Characterization of an amyloid beta precursor protein that binds heparin and contains tyrosine sulfate. Proc Natl Acad Sci USA 86, 2066-2069, PubMed ID: 89184568

10 Esch, F.S. et al. (1990) Cleavage of amyloid beta peptide during constitutive processing of its precursor. Science 248, 1122-1124, PubMed ID: 90260662

11 Esler, W.P. and Wolfe, M.S. (2001) A portrait of Alzheimer secretases—new features and familiar faces. Science 293, 1449-1454, PubMed ID: 21412361

12 Walter, J. et al. (2001) The cell biology of Alzheimer's disease: uncovering the secrets of secretases. Curr Opin Neurobiol 11, 585-590, PubMed ID: 21479317

13 Schubert, D. et al. (1989) The regulation of amyloid beta protein precursor secretion and its modulatory role in cell adhesion. Neuron 3, 689-694, PubMed ID: 90380410

14 Kamal, A. et al. (2001) Kinesin-mediated axonal transport of a membrane compartment containing beta-secretase and presenilin-1 requires APP. Nature 414, 643-648, PubMed ID: 21603016

15 Rogaev, E.I. et al. (1995) Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature 376, 775-778, PubMed ID: 95379971

16 Sherrington, R. et al. (1995) Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 375, 754-760, PubMed ID: 95319502

17 Mercken, M. et al. (1996) Characterization of human presenilin 1 using N-terminal specific monoclonal antibodies: Evidence that Alzheimer mutations affect proteolytic processing. FEBS Lett 389, 297-303, PubMed ID: 96335614

18 Thinakaran, G. et al. (1997) Evidence that levels of presenilins (PS1 and PS2) are coordinately regulated by competition for limiting cellular factors. J Biol Chem 272, 28415-28422, PubMed ID: 98019211

19 Kim, T.W. et al. (1997) Endoproteolytic cleavage and proteasomal degradation of presenilin 2 in transfected cells. J Biol Chem 272, 11006-11010, PubMed ID: 97268991

20 van de Craen, M. et al. (1999) Identification of caspases that cleave presenilin-1 and presenilin-2. Five presenilin-1 (PS1) mutations do not alter the sensitivity of PS1 to caspases. FEBS Lett 445, 149-154, PubMed ID: 99166920

21 Thinakaran, G. et al. (1998) Stable association of presenilin derivatives and absence of presenilin interactions with APP. Neurobiol Dis 4, 438-453, PubMed ID: 98330911

22 Jacobsen, H. et al. (1999) The influence of endoproteolytic processing of familial Alzheimer's disease presenilin 2 on abeta42 amyloid peptide formation. J Biol Chem 274, 35233-35239, PubMed ID: 20044792

23 Wolfe, M.S. et al. (1999) Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity. Nature 398, 513-517, PubMed ID: 99221485

24 Steiner, H. et al. (1999) Amyloidogenic function

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

of the Alzheimer's disease-associated presenilin 1 in the absence of endoproteolysis. Biochemistry 38, 14600-14605, PubMed ID: 20014554

25 Menotti, L. et al. (1999) Trafficking to the plasma membrane of the seven-transmembrane protein encoded by human herpesvirus 6 U51 gene involves a cell-specific function present in T lymphocytes. J Virol 73, 325-333, PubMed ID: 99102589

26 Weidemann, A. et al. (1997) Formation of stable complexes between two Alzheimer's disease gene products: presenilin-2 and beta-amyloid precursor protein. Nat Med 3, 328-332, PubMed ID: 97208920

27 Xia, W. et al. (1997) Interaction between amyloid precursor protein and presenilins in mammalian cells: implications for the pathogenesis of Alzheimer disease. Proc Natl Acad Sci USA 94, 8208-8213, PubMed ID: 97368345

28 Pradier, L. et al. (1999) Mapping the APP/presenilin (PS) binding domains: the hydrophilic N-terminus of PS2 is sufficient for interaction with APP and can displace APP/PS1 interaction. Neurobiol Dis 6, 43-55, PubMed ID: 99176858

29 Waragai, M. et al. (1997) Presenilin 1 binds to amyloid precursor protein directly. Biochem Biophys Res Commun 239, 480-482, PubMed ID: 98008864

30 Kim, S.S., Choi, Y.M. and Suh, Y.H. (1997) Lack of interactions between amyloid precursor protein and hydrophilic domains of presenilin 1 and 2 using the yeast two hybrid system. J Mol Neurosci 9, 49-54, PubMed ID: 98019774

31 De Strooper, B. et al. (1999) A presenilin-1-dependent gamma-secretase-like protease mediates release of Notch intracellular domain. Nature 398, 518-522, PubMed ID: 99221486

32 Zhang, Z. et al. (2000) Presenilins are required for gamma-secretase cleavage of beta-APP and transmembrane cleavage of Notch-1. Nat Cell Biol 2, 463-465, PubMed ID: 20342803

33 Capell, A. et al. (2000) Presenilin-1 differentially facilitates endoproteolysis of the beta-amyloid precursor protein and Notch. Nat Cell Biol 2, 205-211, PubMed ID: 20245869

34 Kim, S.H. et al. (2001) Multiple effects of aspartate mutant presenilin 1 on the processing and trafficking of amyloid precursor protein. J Biol Chem 276, 43343-43350, PubMed ID: 21561006

35 Li, Y.M. et al. (2000) Photoactivated gamma-secretase inhibitors directed to the active site covalently label presenilin 1. Nature 405, 689-694, PubMed ID: 20320322

36 Esler, W.P. et al. (2000) Transition-state analogue inhibitors of gamma-secretase bind directly to presenilin-1. Nat Cell Biol 2, 428-434, PubMed ID: 20342797

37 Fortini, M.E. (2001) Notch and presenilin: a proteolytic mechanism emerges. Curr Opin Cell Biol 13, 627-634, PubMed ID: 21428916

38 Strooper, B.D. and Annaert, W. (2001) Presenilins and the intramembrane proteolysis of proteins: facts and fiction. Nat Cell Biol 3, E221-225, PubMed ID: 21468421

39 Levitan, D. and Greenwald, I. (1998) Effects of SEL-12 presenilin on LIN-12 localization and function in Caenorhabditis elegans. Development 125, 3599-3606, PubMed ID: 98384316

40 Levitan, D. et al. (1996) Assessment of normal and mutant human presenilin function in Caenorhabditis elegans. Proc Natl Acad Sci USA 93, 14940-14944, PubMed ID: 97121494

41 Ye, Y. and Fortini, M.E. (1999) Apoptotic activities of wild-type and Alzheimer's disease-related mutant presenilins in Drosophila melanogaster. J Cell Biol 146, 1351-1364, PubMed ID: 99423674

42 Struhl, G. and Greenwald, I. (1999) Presenilin is required for activity and nuclear access of Notch in Drosophila. Nature 398, 522-525, PubMed ID: 99221487

43 Handler, M., Yang, X. and Shen, J. (2000) Presenilin-1 regulates neuronal differentiation during neurogenesis. Development 127, 2593-2606, PubMed ID: 20283523

44 Yu, G. et al. (2000) Nicastrin modulates presenilin-mediated notch/glp-1 signal transduction and betaAPP processing. Nature 407, 48-54, PubMed ID: 20445163

45 Chung, H.M. and Struhl, G. (2001) Nicastrin is required for Presenilin-mediated transmembrane cleavage in Drosophila. Nat Cell Biol 3, 1129-1132, PubMed ID: 21640648

46 Lopez-Schier, H. and St Johnston, D. (2002) Drosophila nicastrin is essential for the intramembranous cleavage of notch. Dev Cell 2, 79-89, PubMed ID: 21642114

47 Hu, Y., Ye, Y. and Fortini, M.E. (2002) Nicastrin is required for gamma-secretase cleavage of the Drosophila Notch receptor. Dev Cell 2, 69-78, PubMed ID: 21642113

48 Miller, J.R. et al. (1999) Mechanism and function of signal transduction by the Wnt/beta-catenin

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

and Wnt/Ca2+ pathways. Oncogene 18, 7860-7872, PubMed ID: 20094335
49 Nagafuchi, A. (2001) Molecular architecture of adherens junctions. Curr Opin Cell Biol 13, 600-603, PubMed ID: 21428912
50 Zhou, J. et al. (1997) Presenilin 1 interaction in the brain with a novel member of the Armadillo family. Neuroreport 8, 2085-2090, PubMed ID: 97366296
51 Capell, A. et al. (1998) The proteolytic fragments of the Alzheimer's disease-associated presenilin-1 form heterodimers and occur as a 100-150-kDa molecular mass complex. J Biol Chem 273, 3205-3211, PubMed ID: 98123083
52 Yu, G.S., Lu, Y.C. and Gulick, T. (1998) Co-regulation of tissue-specific alternative human carnitine palmitoyltransferase Ibeta gene promoters by fatty acid enzyme substrate. J Biol Chem 273, 32901-32909, PubMed ID: 99047677
53 Tesco, G. et al. (1998) Abrogation of the presenilin 1/beta-catenin interaction and preservation of the heterodimeric presenilin 1 complex following caspase activation. J Biol Chem 273, 33909-33914, PubMed ID: 99069372
54 Murayama, M. et al. (1998) Direct association of presenilin-1 with beta-catenin. FEBS Lett 433, 73-77, PubMed ID: 98409316
55 Saura, C.A. et al. (2000) The nonconserved hydrophilic loop domain of presenilin (PS) is not required for PS endoproteolysis or enhanced abeta 42 production mediated by familial early onset Alzheimer's disease-linked PS variants. J Biol Chem 275, 17136-17142, PubMed ID: 20287596
56 Kashiwa, A. et al. (2000) Isolation and characterization of novel presenilin binding protein. J Neurochem 75, 109-116, PubMed ID: 20312861
57 Kang, D.E. et al. (1999) Presenilin 1 facilitates the constitutive turnover of beta-catenin: differential activity of Alzheimer's disease-linked PS1 mutants in the beta-catenin-signaling pathway. J Neurosci 19, 4229-4237, PubMed ID: 99274728
58 Noll, E. et al. (2000) Presenilin affects arm/beta-catenin localization and function in Drosophila. Dev Biol 227, 450-464, PubMed ID: 20525592
59 Kesavapany, S. et al. (2001) p35/cdk5 binds and phosphorylates beta-catenin and regulates beta-catenin/presenilin-1 interaction. Eur J Neurosci 13, 241-247, PubMed ID: 21097294
60 Nishimura, M. et al. (1999) Presenilin mutations associated with Alzheimer disease cause defective intracellular trafficking of beta-catenin, a component of the presenilin protein complex. Nat Med 5, 164-169, PubMed ID: 99128053
61 Soriano, S. et al. (2001) Presenilin 1 negatively regulates beta-catenin/T cell factor/lymphoid enhancer factor-1 signaling independently of beta-amyloid precursor protein and notch processing. J Cell Biol 152, 785-794, PubMed ID: 21167922
62 Killick, R. et al. (2001) Presenilin 1 independently regulates beta-catenin stability and transcriptional activity. J Biol Chem 276, 48554-48561, PubMed ID: 21611256
63 Xia, X. et al. (2001) Loss of presenilin 1 is associated with enhanced beta-catenin signaling and skin tumorigenesis. Proc Natl Acad Sci USA 98, 10863-10868, PubMed ID: 21437967
64 Weihl, C.C. et al. (1999) Mutant presenilin-1 induces apoptosis and downregulates Akt/PKB. J Neurosci 19, 5360-5369, PubMed ID: 99307328
65 Zhang, Z. et al. (1998) Destabilization of beta-catenin by mutations in presenilin-1 potentiates neuronal apoptosis. Nature 395, 698-702, PubMed ID: 99004850
66 Kirschenbaum, F. et al. (2001) Substitution of a glycogen synthase kinase-3beta phosphorylation site in presenilin 1 separates presenilin function from beta-catenin signaling. J Biol Chem 276, 7366-7375, PubMed ID: 21269268
67 Alberici, A. et al. (1999) Presenilin 1 protein directly interacts with Bcl-2. J Biol Chem 274, 30764-30769, PubMed ID: 99452971
68 Passer, B.J. et al. (1999) Interaction of Alzheimer's presenilin-1 and presenilin-2 with Bcl-X(L). A potential role in modulating the threshold of cell death. J Biol Chem 274, 24007-24013, PubMed ID: 99377032
69 Fannon, M. and Nugent, M.A. (1996) Basic fibroblast growth factor binds its receptors, is internalized, and stimulates DNA synthesis in Balb/c3T3 cells in the absence of heparan sulfate. J Biol Chem 271, 17949-17956, PubMed ID: 96279338
70 Maher, P. and Schubert, D. (2000) Signaling by reactive oxygen species in the nervous system. Cell Mol Life Sci 57, 1287-1305, PubMed ID: 20479890
71 Paschen, W. (2001) Dependence of vital cell function on endoplasmic reticulum calcium levels: implications for the mechanisms underlying neuronal cell injury in different pathological states. Cell Calcium 29, 1-11, PubMed ID: 21064801
72 Imaizumi, K. et al. (2001) The unfolded protein

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

response and Alzheimer's disease. Biochim Biophys Acta 1536, 85-96, PubMed ID: 21299066

73 Janicki, S. and Monteiro, M.J. (1997) Increased apoptosis arising from increased expression of the Alzheimer's disease-associated presenilin-2 mutation (N141I). J Cell Biol 139, 485-495, PubMed ID: 97477394

74 Wolozin, B. et al. (1996) Participation of presenilin 2 in apoptosis: enhanced basal activity conferred by an Alzheimer mutation. Science 274, 1710-1713, PubMed ID: 97094374

75 Katayama, T. et al. (1999) Presenilin-1 mutations downregulate the signalling pathway of the unfolded-protein response. Nat Cell Biol 1, 479-485, PubMed ID: 20056448

76 Niwa, M. et al. (1999) A role for presenilin-1 in nuclear accumulation of Ire1 fragments and induction of the mammalian unfolded protein response. Cell 99, 691-702, PubMed ID: 20084441

77 Sato, N. et al. (2000) Upregulation of BiP and CHOP by the unfolded-protein response is independent of presenilin expression. Nat Cell Biol 2, 863-870, PubMed ID: 20582444

78 Siman, R. et al. (2001) Endoplasmic reticulum stress-induced cysteine protease activation in cortical neurons: effect of an Alzheimer's disease-linked presenilin-1 knock-in mutation. J Biol Chem 276, 44736-44743, PubMed ID: 21576212

79 Bursztajn, S. et al. (1998) Overexpression in neurons of human presenilin-1 or a presenilin-1 familial Alzheimer disease mutant does not enhance apoptosis. J Neurosci 18, 9790-9799, PubMed ID: 99042056

80 Zhang, Y. et al. (2002) Selective cytotoxicity of intracellular amyloid beta peptide1-42 through p53 and Bax in cultured primary human neurons. J Cell Biol 156, 519-529, PubMed ID: 21686200

81 Yang, A.J. et al. (1998) Loss of endosomal/ lysosomal membrane impermeability is an early event in amyloid Abeta1-42 pathogenesis. J Neurosci Res 52, 691-698, PubMed ID: 98331981

82 Kim, J. et al. (1996) Integration of positional signals and regulation of wing formation and identity by Drosophila vestigial gene. Nature 382, 133-138, PubMed ID: 96317584

83 Hamada, Y. et al. (1999) Mutation in ankyrin repeats of the mouse Notch2 gene induces early embryonic lethality. Development 126, 3415-3424, PubMed ID: 99396706

84 Ferri, K.F. and Kroemer, G. (2001) Organelle-specific initiation of cell death pathways. Nat Cell Biol 3, E255-263, PubMed ID: 21571932

85 Tan, S., Schubert, D. and Maher, P. (2002) Oxytosis: A novel form of programmed cell death. Curr. Topics Med. Chem. 1, 497-506

86 Buxbaum, J.D. et al. (1998) Calsenilin: a calcium-binding protein that interacts with the presenilins and regulates the levels of a presenilin fragment. Nat Med 4, 1177-1181, PubMed ID: 98442695

87 Carrion, A.M. et al. (1999) DREAM is a Ca2+-regulated transcriptional repressor. Nature 398, 80-84, PubMed ID: 99176420

88 Leissring, M.A. et al. (1999) Alzheimer's presenilin-1 mutation potentiates inositol 1,4,5-trisphosphate-mediated calcium signaling in Xenopus oocytes. J Neurochem 72, 1061-1068, PubMed ID: 99155081

89 Leissring, M.A. et al. (2000) Calsenilin reverses presenilin-mediated enhancement of calcium signaling. Proc Natl Acad Sci USA 97, 8590-8593, PubMed ID: 20359751

90 Meyers, M.B. et al. (1998) Sorcin associates with the pore-forming subunit of voltage-dependent L-type Ca2+ channels. J Biol Chem 273, 18930-18935, PubMed ID: 98334621

91 Ito, E. et al. (1994) Internal Ca2+ mobilization is altered in fibroblasts from patients with Alzheimer disease. Proc Natl Acad Sci USA 91, 534-538, PubMed ID: 94119921

92 Etcheberrigaray, R. et al. (1998) Calcium responses in fibroblasts from asymptomatic members of Alzheimer's disease families. Neurobiol Dis 5, 37-45, PubMed ID: 98368168

93 Hasegawa, H. et al. (1996) DOCK180, a major CRK-binding protein, alters cell morphology upon translocation to the cell membrane. Mol Cell Biol 16, 1770-1776, PubMed ID: 96239533

94 Chen, Q. et al. (2001) Presenilin binding protein is associated with neurofibrillary alterations in Alzheimer's disease and stimulates tau phosphorylation. Am J Pathol 159, 1597-1602, PubMed ID: 21552769

95 Chen, Q., Kimura, H. and Schubert, D. (2002) A novel mechanism for the regulation of amyloid precursor protein metabolism. J Cell Biol 158, 79-89, PubMed ID: 22100008

96 Morimoto, T. et al. (1998) Involvement of amyloid precursor protein in functional synapse formation in cultured hippocampal neurons. J Neurosci Res 51, 185-195, PubMed ID: 98129474

97 Mileusnic, R. et al. (2000) APP is required during an early phase of memory formation. Eur J Neurosci 12, 4487-4495, PubMed ID: 20571423

98 Schubert, D. (1991) The possible role of adhesion

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

in synaptic modification. Trends Neurosci 14, 127-130, PubMed ID: 91263254
99 Georgakopoulos, A. et al. (1999) Presenilin-1 forms complexes with the cadherin/catenin cell-cell adhesion system and is recruited to intercellular and synaptic contacts. Mol Cell 4, 893-902, PubMed ID: 20101232
100 Beher, D. et al. (1999) Proteolytic fragments of Alzheimer's disease-associated presenilin 1 are present in synaptic organelles and growth cone membranes of rat brain. J Neurochem 72, 1564-1573, PubMed ID: 99196498
101 Baki, L. et al. (2001) Presenilin-1 binds cytoplasmic epithelial cadherin, inhibits cadherin/p120 association, and regulates stability and function of the cadherin/catenin adhesion complex. Proc Natl Acad Sci USA 98, 2381-2386, PubMed ID: 21126893
102 Singh, N. et al. (2001) The role of Alzheimer's disease-related presenilin 1 in intercellular adhesion. Exp Cell Res 263, 1-13, PubMed ID: 21099585
103 Feng, R. et al. (2001) Deficient neurogenesis in forebrain-specific presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces. Neuron 32, 911-926, PubMed ID: 21603136
104 Yu, H. et al. (2001) APP processing and synaptic plasticity in presenilin-1 conditional knockout mice. Neuron 31, 713-726, PubMed ID: 21453755
105 Dewji, N.N. and Singer, S.J. (1997) Cell surface expression of the Alzheimer disease-related presenilin proteins. Proc Natl Acad Sci USA 94, 9926-9931, PubMed ID: 97420786
106 Schwarzman, A.L. et al. (1999) Endogenous presenilin 1 redistributes to the surface of lamellipodia upon adhesion of Jurkat cells to a collagen matrix. Proc Natl Acad Sci USA 96, 7932-7937, PubMed ID: 99324166
107 Levesque, G. et al. (1999) Presenilins interact with armadillo proteins including neural-specific plakophilin-related protein and beta-catenin. J Neurochem 72, 999-1008, PubMed ID: 99155075
108 Takashima, A. et al. (1998) Presenilin 1 associates with glycogen synthase kinase-3beta and its substrate tau. Proc Natl Acad Sci USA 95, 9637-9641, PubMed ID: 98356210
109 Zhang, W. et al. (1998) Interaction of presenilins with the filamin family of actin-binding proteins. J Neurosci 18, 914-922, PubMed ID: 98099802
110 Dumanchin, C. et al. (2000) Presenilins interact with Rab11, a small GTPase involved in the regulation of vesicular transport. Human Molec. Genet. 8, 1263-1269
111 Scheper, W. et al. (2000) Alzheimer's presenilin 1 is a putative membrane receptor for rab GDP dissociation inhibitor. Hum Mol Genet 9, 303-310, PubMed ID: 20076327
112 Imafuku, I. et al. (1999) Presenilin 1 suppresses the function of c-Jun homodimers via interaction with QM/Jif-1. J Cell Biol 147, 121-134, PubMed ID: 99439762
113 Johnsingh, A.A. et al. (2000) Altered binding of mutated presenilin with cytoskeleton-interacting proteins. FEBS Lett 465, 53-58, PubMed ID: 20088797
114 Prihar, G. et al. (1999) A novel candidate presenilin-1 interacting protein containing tetratricopeptide repeats. Neuroreport 10, 1409-1415, PubMed ID: 99308662
115 Ray, W.J. et al. (1999) Evidence for a physical interaction between presenilin and Notch. Proc Natl Acad Sci USA 96, 3263-3268, PubMed ID: 99179050
116 Smine, A. et al. (1998) Regulation of brain G-protein go by Alzheimer's disease gene presenilin-1. J Biol Chem 273, 16281-16288, PubMed ID: 98298141
117 Stabler, S.M. et al. (1999) A myristoylated calcium-binding protein that preferentially interacts with the Alzheimer's disease presenilin 2 protein. J Cell Biol 145, 1277-1292, PubMed ID: 99296618
118 Van Gassen, G. et al. (1999) Alzheimer's disease associated presenilin 1 interacts with HC5 and ZETA, subunits of the catalytic 20S proteasome. Neurobiol Dis 6, 376-391, PubMed ID: 99459106
119 Xu, X. et al. (1999) Identification of a novel PSD-95/Dlg/ZO-1 (PDZ)-like protein interacting with the C terminus of presenilin-1. J Biol Chem 274, 32543-32546, PubMed ID: 20020213
120 Smith, S.K. et al. (2000) Identification of syntaxin 1A as a novel binding protein for presenilin-1. Brain Res Mol Brain Res 78, 100-107, PubMed ID: 20351558
121 Pack-Chung, E. et al. (2000) Presenilin 2 interacts with sorcin, a modulator of the ryanodine receptor. J Biol Chem 275, 14440-14445, PubMed ID: 20261572
122 Annaert, W.G. et al. (2001) Interaction with telencephalin and the amyloid precursor protein predicts a ring structure for presenilins. Neuron 32, 579-589, PubMed ID: 21576526
123 Tanahashi, H. and Tabira, T. (2000) Alzheimer's

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press

disease-associated presenilin 2 interacts with DRAL, an LIM-domain protein. Hum Mol Genet 9, 2281-2289, PubMed ID: 20458893

124 Zhang, S.X., Guo, Y. and Boulianne, G.L. (2001) Identification of a novel family of putative methyltransferases that interact with human and Drosophila presenilins. Gene 280, 135-144, PubMed ID: 21601112

125 Mah, A.L. et al. (2000) Identification of ubiquilin, a novel presenilin interactor that increases presenilin protein accumulation. J Cell Biol 151, 847-862, PubMed ID: 20530664

Further reading, resources and contacts

The Alzheimer Research Forum website is the leading scientific resource for emerging research developments in Alzheimer's disease, and includes sections on clinical trials and Alzheimer's disease patents.

http://www.alzforum.org

The Alzheimer's Association (the leading US Alzheimer's disease foundation) website provides patient support.

http://www.alz.org/

Alzheimer's Disease International provides a global perspective on the disease.

http://www.alz.co.uk

Features associated with this article

Figures

Figure 1. Schematic diagram of the amyloid precursor protein and its cleavage to give β-amyloid (fig001dss)
Figure 2. Schematic diagram of presenilin 1 (fig002dss).
Figure 3. Summary of some known presenilin-mediated pathways (fig003dss).

Table

Table 1. Current state of knowledge on proteins that interact with presenilin 1 (PS1) and PS2 (tab001dss).

Citation details for this article

Qi Chen and David Schubert (2002) Presenilin-interacting proteins. Exp. Rev. Mol. Med. 22 August, http://www.expertreviews.org/02005008h.htm

Accession information: (02)00500-8a.pdf (short code: txt001dss); 22 August 2002
ISSN 1462-3994 ©2002 Cambridge University Press

https://doi.org/10.1017/S1462399402005008 Published online by Cambridge University Press