Alzheimer’s disease (AD) is characterized by progressive decline in cognitive functions associated with depositions of aggregated proteins in the form of extracellular plaques and neurofibrillary tangles in the brain. Extracellular plaques contain characteristic fibrils of amyloid β peptides (Aβ); tangles consist of paired helical filaments of the microtubuli-associated protein tau. Although AD manifests predominantly at ages above 65 years, rare cases show a much earlier onset of disease symptoms with very similar neuropathological characteristics. In 1995, two homologous genes were identified, in which mutations are associated with dominantly inherited familial forms of early onset AD. The genes therefore were dubbed presenilins (PS) and encode polytopic transmembrane proteins. At this time the role of these proteins in the pathogenesis of AD and their biological function in general were completely unknown. However, individuals carrying PS mutations showed alterations in the composition of different length variants of Aβ peptides in blood and cerebrospinal fluid, which indicated the potential involvement of presenilins in the metabolism of Aβ. After 20 years of intense research, the roles of presenilins in Aβ generation as well as important functions in biological processes have been identified. Presenilins represent the catalytic components of protease complexes that directly cleave the amyloid precursor protein (APP) but also many other proteins with important physiological functions. Here, the progress in presenilin research from basic characterization of their cellular functions to the targeting in clinical trials for AD therapy, and potential future directions, will be discussed.

Online address: http://www.molmed.org
doi: 10.2119/molmed.2015.00163

INTRODUCTION

Alzheimer’s disease (AD) is a growing burden in aging societies and represents a major challenge in the treatment of common diseases. Currently, effective therapies that prevent progression of, or even cure, the disease are not available. Thus, the understanding of the etiology of this devastating disease is critical for future development of therapeutic or preventive strategies.

At the neuropathological level, AD is diagnosed by the combined occurrence of extracellular plaques and neurofibrillary tangles consisting of aggregated amyloid β peptides (Aβ) and hyperphosphorylated tau, respectively (1,2). Strong evidence from biochemical and molecular biological experiments as well as genetic findings indicates a critical role of Aβ aggregates in the pathogenesis of AD (3–5).

Aβ peptides have been isolated from extracellular plaques and vascular deposits from AD and Down syndrome brains and characterized by amino acid sequencing (6,7). The demonstration that the Aβ amino acid sequence is part of a much larger precursor protein already suggested that proteolytic processing would be involved in the generation of this peptide and was instrumental for subsequent work at the molecular, cell biological and in vivo level (8).

Aβ derives from the amyloid precursor protein (APP) by proteolytic processing involving specific proteases that were termed β- and γ-secretase (Figure 1).

β-Secretase initiates Aβ generation by cleavage of APP within its ectodomain, thereby resulting in the secretion of a soluble form of APP (sAPP) and a corresponding C-terminal fragment (CTF) that is still inserted into cellular membranes (1,9). As this cleavage occurs in front of the first aspartate residue of the Aβ domain, the resultant CTF contains the full Aβ peptide sequence, which partly comprises the transmembrane domain of APP. The subsequent processing of the APP CTF by γ-secretase within the transmembrane domain eventually leads to the generation and secretion of Aβ into extracellular fluids (10,11).

IDENTIFICATION OF PRESENILIN GENES IN EARLY ONSET FAMILIAL AD

Genetic analyses of families with mendelian inheritance of early onset AD allowed the identification of causative gene mutations by positional cloning.
The first gene identified was the APP gene itself (12), giving strong support for the amyloid hypothesis (13). In 1995, mutations in two previously uncharacterized homologous genes were identified that comprise up to 40% of all early onset familial AD (FAD) cases (14–16). Briefly, after their identification, the two genes were named presenilins (PSEN) 1 and 2. The roles of respective presenilin proteins (PS1 and PS2) in the pathogenesis of AD or their biological function were enigmatic at this time. PSEN genes are ubiquitously expressed in different tissues and show considerable conservation between mammalian and other organisms. Initial studies with plasma and primary fibroblasts of mutation carriers showed elevated levels of secreted Aβ42, while levels of Aβ40 and APP synthesis were not significantly changed compared with those from controls (17). Aβ42 has a higher aggregation propensity than Aβ40 and appears to be a critical player in triggering the deposition of amyloid plaques (3–5). Notably, plasma Aβ42 levels were also increased in presymptomatic PS mutation carriers. These results were subsequently confirmed in other cellular models as well as in transgenic mice and already suggested that presenilins could affect the metabolism of APP or Aβ itself (18–22).

**INITIAL CHARACTERIZATION OF PRESENILIN PROTEINS**

Early cell biological and biochemical studies aimed to characterize the subcellular localization and metabolism of PS proteins. As expected from the primary structure of PS1 and PS2, both proteins were found to be localized in different membrane compartments of cells (23–25). PS proteins were predominantly localized in the endoplasmic reticulum (ER) and the Golgi compartment. It was debated whether PS proteins could also reach additional compartments (see below). In our initial study, we also found colocalization of PS proteins with APP in the Golgi compartment (24). A binding of PS proteins with APP was later shown by coimmunoprecipitation studies (26,27).

A second part of our initial study was focused on the characterization of potential posttranslational modifications with the aim to identify potential molecular mechanisms that could regulate presenilin function. Using a heterologous expression system with transient overexpression of cDNAs encoding full-length PS1 or PS2, the proteins were detected at their expected molecular weight of about 50 kDa. Metabolic labeling with 32P-orthophosphate revealed phosphate incorporation selectively into the PS2 full-length protein (24). Consistent with the presence of consensus recognition sites for casein kinases, we found that PS2 could indeed be phosphorylated by protein kinases CK1 and CK2 in vitro (24,28). Additional modifications, like glycosylation or sulfation, were not detected.

In contrast to the overexpressed PS proteins, very little if any endogenous protein could be detected at the expected molecular weight. A very important finding was that endogenously expressed PS1 proteins were detected as 30-kDa N-terminal fragments (NTF) and 20-kDa C-terminal fragments (CTF), which indicated a specific endoproteolytic

![Figure 1](https://example.com/image1.png)

**Figure 1.** Schematic showing the proteolytic processing of APP and the composition of the γ-secretase complex. (A) APP is a type I transmembrane protein. β-Secretase cleaves at the N-terminus of the Aβ domain (red), resulting in the secretion of soluble APP (APPs-β) and generation of a C-terminal fragment (APP CTFβ). Subsequent cleavage of this fragment by γ-secretase liberates Aβ and the APP intracellular domain (AICD) from cellular membranes. (B) Composition of the γ-secretase complex. Presenilins represent the catalytically active proteins in the complex. Critical aspartate residues within the active site of presenilins are indicated by yellow stars. Nicastrin, Aph-1 and Pen-2 mediate assembly, substrate recognition and subcellular transport of the γ-secretase complex. See text for details.
processing step of the full-length proteins (29–32). We also found respective NTF and CTF of endogenously expressed PS1 in cultured cells (33). Interestingly, the PS1 CTF was found to undergo regulated phosphorylation within the hydrophilic loop region by protein kinase C, which could be stimulated by activation of muscarinic acetylcholine receptors (33,34). Since the full-length PS1 protein is not phosphorylated, these data suggested a specific regulation at the level of proteolytically processed PS1. The phosphorylation of the PS1 CTF affected its mobility in sodium dodecyl sulfate–polyacrylamide gel electrophoresis gels, suggesting a conformational change. PS2 was found to be phosphorylated in both its NTF and CTF. In contrast to the regulated phosphorylation of the PS1 CTF by protein kinases A (PKA) and C (PKC), PS2 NTF and CTF undergo constitutive phosphorylation by protein kinases CK1 and CK2 (28). However, at this time the biological function of PS proteins and the role of phosphorylation was enigmatic (see below).

THE HUNT FOR PRESENILIN FUNCTION

Early insight into the physiologic function of PS proteins came from studies with Caenorhabditis elegans. Mutants of the PS homologue sel-12 in these organisms revealed an egg-laying defective phenotype closely resembling the lin-12/notch phenotype (35). Interestingly, this phenotype could be rescued by expression of the human wild-type, but not FAD mutant PS1 or PS2 (36,37). Deletion of the PS1 gene in mice led to early postnatal or late embryonic lethality associated with skeletal deformation, impaired somitogenesis and brain development (38,39). Some of these effects were similar to those in Notch mutant mice. A double knockout of both PS1 and PS2 closely resembled the Notch knockout phenotype with early embryonic lethality (40). However, PS2 knockout mice were viable and fertile and produced only mild phenotypes associated with pulmonary fibrosis and hemorrhage at higher age (40). Like APP, Notch is a type I membrane protein and has important functions in cell fate decision and differentiation during development and also during adulthood (41,42). These findings demonstrated that presenilins play fundamental physiological roles, potentially related to the function of Notch.

PS knockout mice and cells were also instrumental for understanding the role of these proteins in APP metabolism. Using neurons from PS1 knockout mice, it was demonstrated that deficiency of PS1 decreased the cleavage of APP CTFs that derive from APP by α- or β-secretory processing, and thus, the generation of Aβ (43). Interestingly, mutation of two aspartate residues localized in transmembrane domains 6 and 7 of human PS1, which are also highly conserved in PS2 and other orthologs of other species, also prevented cleavage of APP CTFs and Aβ generation. The combined evidence suggested that PS proteins themselves might exert catalytic activity and represent a novel class of aspartyl proteases that could mediate intramembrane cleavage of APP, a characteristic feature proposed for γ-secretase (8,44). Importantly, PS proteins were also shown to mediate cleavage of Notch and thereby release the Notch intracellular domain from cellular membranes to allow its nuclear translocation and transcriptional regulation of target genes (45–47).

Previous cell biological and biochemical studies suggested that γ-secretase–dependent cleavage of APP and Notch might occur at the plasma membrane or endocytic compartments (48–52). This contrasted with the predominant localization of presenilins in the ER and early Golgi compartment, thereby raising debate about a “spatial paradox” on the differential localization of presenilins and γ-secretase activity and whether presenilin could represent γ-secretase at all (53). However, other studies demonstrated the presence of presenilins (and γ-secretase) in different secretory and endocytic compartments as well as at the plasma membrane (54–56).

PRESENILINS AS THE CORE COMPONENT OF THE γ-SECRETASE COMPLEX

As mentioned above, presenilins are mainly found as stable N- and C-terminal fragments, whereas the full-length proteins appear to be instable (29,31,32,57,58). Several early studies suggested that PS NTF and CTF exist in larger complexes, probably together with additional components (59–61). Protein interaction studies then revealed that PS proteins could associate with members of the catenin family together with glycogen synthase kinase 3β (GSK3β) and tau (62–65). Whether this interaction affects the activity of γ-secretase remains unclear (see below).

The first protein identified to be critically involved in γ-secretase activity of presenilin was a type I protein called Nicastrin (66). Functional screens for Notch signaling in C. elegans led to the identification of two additional proteins called anterior pharynx defective 1 (aph-1) and presenilin-enhancer-2 (pen-2) (67). Later studies showed that these three proteins together with presenilins are required and sufficient to constitute the active γ-secretase complex (68,69) (Figure 1). While presenilins represent the catalytically active component of the γ-secretase complex, the other proteins mediate complex assembly, subcellular trafficking and substrate recognition (70–73).

Besides APP and Notch, more than 90 substrate proteins for γ-secretase have been identified (74). The vast majority of them, like APP and Notch, are type I membrane proteins. However, a physiological role for the cleavage of most proteins remains to be determined. Given the high number of substrates, γ-secretase might also play a more general role in the degradation of type I membrane proteins (74,75). Cleavage of the transmembrane domain could liberate extracellular peptides and intracellular domains from cellular membranes for further degradation.

EFFECT OF FAD-ASSOCIATED MUTATIONS

Since the identification of mutations in the presenilins as a major cause of fami-
ial early onset AD, the effect of such mutations on the generation of Aβ and activity of γ-secretase has been of prime interest. Today, more than 200 different mutations in PS1 and PS2 have been identified (www.alzforum.org/mutations). As described above, the common effect of FAD-associated mutations is an increased ratio of Aβ42/Aβ40 peptides. However, it is still unclear whether all of the pathogenic mutations act similarly. Although some of the mutations studied so far might increase the production of Aβ42, most mutations decreased the secretion of Aβ40 peptides (76,77). PS FAD–associated mutations also decrease the secretion of Aβ40 more strongly than Aβ42 in induced pluripotent or embryonic stem cell–derived human neurons, further supporting a partial loss of γ-secretase function of PS FAD mutants (78,79).

Whether the mutations cause a gain of function (increased production of Aβ42) or a loss of function (decreased production of Aβ40) is of great importance considering the development of drugs that modulate γ-secretase activity for treatment or prevention of AD (see below). γ-Secretase cleaves the APP CTF initially at the interface of the transmembrane domain and the cytoplasmic domain, thereby liberating the APP intracellular domain (AICD) fragment from the cytosol. This so-called ε-cleavage, however, can occur at least at two different positions leading to the generation of “long” Aβ peptides (Aβ48 or Aβ49). Elegant and comprehensive analyses on the subsequent processing steps indicate that γ-secretase processes these long Aβ peptides in steps of three amino acids, leading to two product lines that could end at Aβ42 and Aβ40, respectively (48→45→42 or 49→46→43→40) (80). It is interesting that certain transition-state analogs used as γ-secretase inhibitors led to accumulation of longer Aβ species in vitro, suggesting they affect the “productivity” of γ-secretase. A similar effect has also been observed for certain γ-secretase mutations (80).

**PRESENILINS MIGHT EXERT γ-SECRETASE-INDEPENDENT FUNCTION**

Since their identification, presenilins have also been related to biological functions that might be independent from their activity in γ-secretase, including the regulation of apoptosis, cellular calcium homeostasis, protein transport and signaling (81,82).

**Apoptosis**

A screen for genes that inhibit T-cell receptor–induced apoptosis revealed a cDNA fragment encoding the C-terminal amino acids 346–449 of PS2, suggesting that PS2 might exert an anti-apoptotic function (83). However, overexpression of PS2 full-length rather than promoted apoptosis in neuronally differentiated PC12 cells (62). While the exact role of PS2 in the regulation of apoptosis was enigmatic, additional support for a connection of PS proteins to apoptosis came from the observation that both PS1 and PS2 are cleaved by caspases-3 and -7, two important proteases in the execution phase of programmed cell death (84–87).

Building on the initial observations on the phosphorylation of PS2 (24), we assessed a potential role in the regulation of apoptosis. Phosphorylation sites within the PS2 CTF were identified at Ser327 and Ser330 (88). Interestingly, both sites are localized directly at the cleavage sites for caspases. The phosphorylation of PS2 CTF at these sites strongly decreased the caspase-mediated processing and also retarded the progression of apoptosis (88). A very similar effect was also identified at the phosphorylation of the PS1 CTF at Ser346 (89).

In addition to the phosphorylation of Ser346 by PKA or PKC, the PS1 CTF can be phosphorylated at Ser357 and Ser359 by GSK3β (90,91). Phosphorylation of these sites strongly decreased the caspase-mediated processing and also retarded the progression of apoptosis (88). A similar effect was also identified at the phosphorylation of the PS1 CTF at Ser346 (89).

In addition to the phosphorylation of Ser346 by PKA or PKC, the PS1 CTF can be phosphorylated at Ser353 and Ser357 by GSK3β (90,91). Phosphorylation at these sites strongly decreased the interaction of PS1 with β-catenin (92). This finding was consistent with the initial identification of β-catenin as an interaction partner of PS1 (64,93). The function of PS1 in β-catenin metabolism and signaling appears to be independent of its catalytic activity (90,94–96). Additional phosphorylation sites have also been identified. However, mutations of the respective sites did not affect APP processing (97). Whether the phosphorylation of the respective sites did not affect the subcellular transport, activity of γ-secretase or additional functions remains to be determined.

**Calcium Homeostasis**

The polytopic transmembrane structure with 9 predicted transmembrane domains led to the speculation that PS proteins could exert channel activity. Interestingly, studies with heterologous expression systems and neurons from transgenic mice as well as with FAD patient–derived fibroblasts revealed a role of PS proteins in Ca2+ signaling. Cells endogenously expressing FAD mutant PS1 or PS2 showed increased release of Ca2+ from ER stores and also altered activity and expression of inositol trisphosphate (IP3) and ryanodine receptors (98–102). However, the molecular mechanisms underlying these observations are still under debate.

PS proteins could interact with these receptors and regulate their gating properties and/or subcellular localization. In addition, PS-dependent effects on the expression and turnover of these Ca2+ channels have also been described (100–102). Because PS FAD mutants also affect the proteolytic processing of APP and the ratio of Aβ42/40, cytosolic Ca2+ levels could also be affected by increased membrane perturbation by aggregated forms of Aβ. In addition, the APP intracellular domain generated by γ-secretase activity could also alter the expression of IP3 and ryanodine receptors by transcriptional regulation (103,104). The Notch ICD has also been shown to regulate Ca2+ signaling in hippocampal neurons and thereby affect synaptic plasticity, learning and memory, and Ca2+-dependent cell death (55).

The PS proteins themselves might also function as Ca2+ channels. Tu et al. have shown that PS proteins represent low conduction ER leak channels (105). Inter-
Interestingly, this function is exerted selectively by full-length PS without or prior to assembly into the γ-secretase complex (105). However, other studies did not show altered Ca\(^{2+}\) leak from the ER by PS mutations (100,106–109).

Although the exact mechanisms that contribute to PS-dependent Ca\(^{2+}\) signaling remain to be determined, aberrant Ca\(^{2+}\) mobilization from ER or other cellular stores might affect synaptic plasticity, and thus learning and memory. Elevated cytosolic Ca\(^{2+}\) concentrations could sensitize neurons to Aβ-mediated toxicity and other stressors and promote neuronal degeneration and cell death (100–112).

**PROTEIN TRANSPORT AND METABOLISM**

Several studies also indicate that PS could affect subcellular transport and degradation of select proteins. In PS knockout cells, the transport of TrkB was found to be reduced (113). In addition, the targeting of telencephalin and v\(_{0}\)ATPase to endosomal and lysosomal compartments is impaired in PS-deficient cells (114,115). Interestingly, some indications suggest that these effects are independent of the catalytic activity of γ-secretase. Whether and how these mechanisms contribute to the impairment of lysosomal function, and thus also autophagy, is debated and requires further investigation (116–118). In general, the differentiation of γ-secretase activity dependent and independent PS function is challenging (82), and might require knockin models with inactive PS proteins at the endogenous expression level.

**TRANSLATIONAL ASPECTS**

Given the fundamental role of γ-secretase in the production of Aβ, this protein complex is considered as an interesting target in AD therapy or prevention. Different inhibitors have been developed that efficiently decrease Aβ generation *in vitro* and in mouse models of AD. Consequently, several clinical (phase II and III) trials have been performed and are ongoing (http://www.alzforum.org/therapeutics) (119). Unfortunately, so far no trial has shown beneficial effects on cognitive performance. Rather, detrimental outcomes were observed (120). This might at least in part be due to the broad substrate spectrum of γ-secretase and its important physiological functions that would also be affected by strong inhibition of its enzymatic activity (121,122). It needs to be kept in mind that presenilins are essential not only for embryonic development, but also in adulthood. The conditional deletion of PS proteins in neurons prevents Aβ generation but leads to age-dependent neurodegeneration in mouse brain and early death (123).

It is important to note that these findings and the sobering outcome of the clinical trials does not mean that γ-secretase is not a potential target for future AD therapy. Careful consideration of dosing and the development of more selective compounds that could target individual γ-secretase complexes or activities will help in future approaches. Indeed, the identification of compounds that could modulate γ-secretase specificity or processivity rather than generally inhibit its enzymatic activity holds great promise for future drug development targeting γ-secretase. Here, the observation that certain nonsteroidal anti-inflammatory drugs (NSAIDs) could selectively decrease the production of Aβ42, without affecting Aβ40, was instrumental for the development of γ-secretase modulators (GSMs) (124). However, as with the γ-secretase inhibitors, GSMs have not proven beneficial in the treatment of AD so far (125).

**FUTURE CONSIDERATIONS**

Despite the strong progress that has been made in presenilin and γ-secretase research in the past 20 years, we can only surmise the complex biological and pathophysiological roles of this enzyme. Further research will help to elucidate the functional relevance of the γ-secretase-mediated cleavages of individual protein substrates in different cell types and organs. We still know very little about the transcriptional, posttranscriptional and posttranslational mechanisms that regulate expression, trafficking and activity of presenilins and their complex partners. The existence of two major isoforms of PS (PS1 and PS2) and Aph-1 (Aph-1a and Aph-1b), several additional splice variants, and posttranslational modifications allows the formation of several distinct γ-secretase complexes that might have distinct, albeit partially redundant biological activities.

Notably, γ-secretase also regulates the metabolism of other important risk factors of AD, like apolipoprotein E (126) and the triggering receptor expressed on myeloid cells 2 (Trem2) (127,128). Thus, it will be interesting to assess whether γ-secretase contributes to the pathogenesis of AD not only via the generation of Aβ, but also by affecting additional pathways involved in the pathogenesis of the most common late onset form of AD.

The recent progress in elucidation of the molecular structure of the γ-secretase complex (129–131) will also allow rational drug designing to improve the characteristics of compounds to modulate γ-secretase function for future targeting of this enzyme in AD therapy or prevention.

**ACKNOWLEDGMENTS**

I am grateful to my colleagues for interesting discussions and fruitful collaborations. Especially, I would like to thank C Haass for initiation of and guidance through presenilin research for many years. I also thank previous and current lab members for their excellent work and stimulating discussions.

The lab is or was supported by grants of the German Research Foundation (DFG), the German Federal Ministry for Education and Research (BMBF), the Mizutani Foundation, and the Hans and Ilse Breuer Foundation.

**DISCLOSURE**

The author declares he has no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.
ROLE OF PRESENILINS IN HEALTH AND DISEASE

REFERENCES

41. Kaether C, et al. (2002) Presenilin-1 affects traf-
ficking and processing of betaAPP and is tar-
ged in a complex with nicastrin to the plasma
53. Wang Y, et al. (2004) Involvement of Notch sig-
naling in hirpoepoietic syncytial plasticity. Proc.
secretase with lipid rafts in post-Golgi and endo-
some membranes. J. Biol. Chem. 279:44495–54.
55. Podlisny MB, et al. (1997) Presenilin proteins un-
dergo heterogeneous endoproteolysis between
Thr291 and Ala299 and occur as stable N- and C-
terminal fragments in normal and Alzheimer
the degradation of familial Alzheimer’s disease-
linked presenilin 1 and potentiate A beta 42 re-
the Alzheimer’s disease-associated presenilin-1
form heterodimers and occur as a 100–150-kDa mo-
disease-associated presenilin-1 is controlled by
proteolytic degradation and complex formation.
59. thinakaran g, et al. (1997) evidence that levels of
presenilins (PS1 and PS2) are coordinately regu-
lated by competition for limiting cellular factors.
2 in apoptosis: enhanced basal activity conferred
brain with a novel member of the Armadillo
family. Neuroreport. 8:1489–94.
component of a high molecular weight intracel-
lar complex that contains beta-catenin. J. Biol.
with glycan synthase kinase-3beta and its sub-
64. Yu G, et al. (2000) Nicastrin modulates presenilin-
mediated notch/glp-1 signal transduction and
for Notch pathway signaling, gamma-secretase
cleavage of betaAPP, and presenilin protein ac-
67. Kimberly WT, et al. (2003) Gamma-secretase is a
membrane protein complex comprised of prese-
68. Takasugi N, et al. (2003) The role of presenilin co-
422:438–41.
gamma-secretase: a complex story of GxGD-type
horizons for presenilins and gamma-secretases in
71. St George-Hyslop P, Fraser PE. (2012) Assembly of
the presenilin gamma-/epsilon-secretase com-
72. Haapasalo A, Kovacs DM. (2013) The many sub-
strates of presenilin/gamma-secretase. J. Alzheimers
Biol. 5:499–504.
74. Wolfe MS. (2007) When loss is gain: reduced pre-
senilin proteolytic function leads to increased
Abeta42/Abeta40. Talking Point on the role of
presenilin mutations in Alzheimer disease.
75. Shen J, Kelleher RJ III. (2007) The presenilin hy-
pothesis of Alzheimer’s disease: evidence for a
loss-of-function pathogenic mechanism. Proc.
76. Mertens J, et al. (2013) APP processing in human
pluripotent stem cell-derived neurons is resistant
to NSAID-based gamma-secretase modulation.
Stem Cell Reports. 1:491–8.
Presenilin-1 L166P mutant human pluripotent stem
cell-derived neurons exhibit partial loss of gamma-secretase activity in endogenous amyloid-beta generation. Am. J.
Pathol. 180:2404–16.
78. Morishima-Kawashima M. (2014) Molecular me chanism of the intramembrane cleavage of the beta-carboxyl terminal fragment of amyloid pre
cursor protein by gamma-secretase. Front. Physiol.
5:463.
mediates phosphorylation of the gamma-secretase-derived intracellular fragment of amyloid beta protein.
lates its cleavage by caspases and retards
secretase activity, which truncates amyloid beta-
peptide after its presenilin-dependent genera-
82. Kirschbaum F, Hsu SC, Cordell B, McCarthy
JV. (2001) Glycogen synthase kinase-3beta regu-
lates presenilin 1 C-terminal fragment levels.
83. Kirschbaum F, Hsu SC, Cordell B, McCarthy
JV. (2000) Nicastrin modulates presenilin-
mediated phosphorylation regulates the interac-
tion with beta-catenin and its nuclear signaling.
J. Biol. Chem. 276:7366–75.
84. Prager K, et al. (2007) A structural switch of pre-
senilin 1 by glycan synthase kinase 3beta-me-
diated phosphorylation regulates the interact-
ion with beta-catenin and its nuclear signaling.
catenin by mutations in presenilin-1 potentiates
associated with Alzheimer disease cause defec-
tive intracellular trafficking of beta-catenin, a
component of the presenilin protein complex.
Nat. Med. 5:164–9.
87. Kang DE, et al. (1999) Presenilin 1 facilitates the
constitutive turnover of beta-catenin: differen-
tial activity of Alzheimer’s disease-linked PSI
mutants in the beta-catenin-signaling pathway.
paired phosphorylation of beta-catenin inde-
dent of axin: implications for beta-catenin
ilin-1 phosphotases: implication for gamma-
secretase activity and Abeta production. J. Neu-
rochem. 133:409–21.
beta-amyloid precursor protein counteracts the
proapoptotic action of mutant presenilin-1 by ac-
tivation of NF-kappaB and stabilization of calci-
testifies and elevated luminal calcium con-
tent in mutant presenilin-1 knockin mice. J. Cell
93. LaFerla FM. (2002) Calcium dyshomeostasis
and intracellular signalling in Alzheimer’s dis-
94. Mattson MP. (2010) ER calcium and Alzheimer’s
95. Leisering MA, et al. (2002) A physiologic signal-
ning role for the gamma -secretase-derived intra-

INVITED REVIEW ARTICLE

MOL MED 21 (SUPPLEMENT 1), S41–S48, 2015 | WALTER | S47


