Published in final edited form as:

Mol Neurobiol. 2018 March ; 55(3): 2275–2284. doi:10.1007/s12035-017-0487-5.

Dynamic Nature of presenilin1/ γ -Secretase: Implication for Alzheimer's Disease Pathogenesis

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Abstract

Presenilin 1 (PS1) is a catalytic component of the γ -secretase complex, responsible for the intramembraneous cleavage of more than 90 type I transmembrane proteins, including Alzheimer's disease (AD)-related amyloid precursor protein (APP). The γ -secretase-mediated cleavage of the APP C-terminal membrane stub leads to the production of various amyloid β (A β) species. The assembly of A β into neurotoxic oligomers, which causes synaptic dysfunction and neurodegeneration, is influenced by the relative ratio of the longer (A β 42/43) to shorter A β (A β 40) peptides. The ratio of A β 42 to A β 40 depends on the conformation and activity of the PS1/ γ -secretase enzymatic complex. The latter exists in a dynamic equilibrium of the so called "closed" and "open" conformational states, as determined by the Förster resonance energy transfer (FRET)-based PS1 conformation assay. Here we review several factors that can allosterically influence conformational status of the enzyme, and hence the production of A β peptides. These include genetic variations in PS1, APP and other γ -secretase components, environmental stressors implicated in AD pathogenesis and pharmacological agents. Since "closed" PS1 conformation is the common outcome of many AD-related insults, the novel assays monitoring PS1 conformation in live/intact cells in vivo and in vitro might be utilized for diagnostic purposes and for validation of the potential therapeutic approaches.

Keywords

Alzheimer's disease; Presenilin 1; γ -secretase; Amyloid β

Presenilin 1—Relevance to Alzheimer's Disease

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by memory decline and cognitive impairment. Accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in the brain and extensive neuronal loss are the major pathological hallmarks of the disease. Despite the majority of AD cases being sporadic, the disorder has a strong genetic component, and several genes have been implicated in its pathogenesis. These include *PSEN1*, *PSEN2* and *APP*, encoding for

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

presenilin 1 and 2 (PS1 and PS2), and amyloid precursor protein (APP), respectively. Based on the genetic, biochemical and neuropathological data, aberrant APP cleavage is central to the AD pathogenesis [1, 2].

The APP can be processed via two competing pathways: non-amyloidogenic and amyloidogenic. The first cleavage in the amyloidogenic pathway (Fig. 1) results in the shedding of the N-terminal ectodomain of APP and is performed by β -secretase 1 (BACE1) [3]. This yields secreted sAPP β and membrane-associated C-terminal APP fragment (β CTF/C99). The next step is the APP β CTF cleavage by PS1/ γ -secretase complex that is composed of four subunits: anterior pharynx-defective 1 (Aph1), presenilin enhancer 2 (Pen-2), nicastrin (Nct) and PS1/PS2, with the latter bearing the aspartic protease activity [4–8]. Although both PS isoforms can be incorporated into the functional γ -secretase complex, due to the higher prevalence of the familial AD (fAD) mutations within the PS1, the major focus of this review will be placed on this PS transcript.

Structure and Function of PS1/ γ -Secretase

Great progress has been made in resolving the molecular architecture of the γ -secretase although the crystal structure of the entire complex still remains unknown. It is now well established that PS1 comprises nine transmembrane helices (TMs) [9] and undergoes autoproteolytic cleavage within the large cytosolic loop domain between TM6 and TM7 to yield N- and C-terminal fragments that characterize active γ -secretase [10]. The two catalytic aspartyl residues critical for the PS1 autoproteolysis, D257 and D385, are located within the TM6 and TM7 [5]. The fAD PS1 exon 9 deletion mutant that lacks autoproteolytic cleavage site and exists as a full length PS1 holoprotein, yet possesses the γ -secretase catalytic activity, is the rare exception to the rule [11, 12].

Several biochemical and in silico modelling studies aimed to address dynamic spatial arrangement of the PS1 TM domains. Using substituted cysteine accessibility method (SCAM) and crosslinking approach, it was demonstrated that PS1 hydrophilic catalytic pore is formed by TM1, TM6, TM7 and TM9 [13–15]. In addition, recent studies, focusing on the TM4 and TM5, demonstrated that these domains face the hydrophilic milieu of the catalytic pore with TM1, TM6, TM7 and TM9, and that the distance between the TM4 and TM7 correlates with the A β 42 production [16]. Further, it has been shown that TM1 and TM8 are adjacent to each other [17], and that TM2 and TM6, contributing to the formation of the initial substrate binding site, are close to TM9 [18] and present high conformational flexibility [19]. They form “gate doors”, providing access of a substrate to the catalytic site, the “hinge” of which is located within the highly dynamic loop 1 (aa 106–131) [19]. This loop cooperates with the C-terminus of PS1 to regulate the substrate recognition and gating [20]. The substrate binding model was further expanded by Fukumori and Steiner, who, by applying photoaffinity scanning, demonstrated that the extracellular and the N-terminal TM region of C99 sequentially contacts three subunits of the γ -secretase: Nct, Pen-2 and PS1 NTF. According to this stepwise binding path model, before entering the active site of the complex, C99 first interacts with the exosites in Nct and Pen-2, then is released from those and contacts exosites in PS1 NTF [21].

These findings have been complemented by the data stemming from cryo-electron microscopy (CEM) analyses, which gained insight into the near atomic structure of the TMs of PS1 incorporated into the γ -secretase complex, with up to 3.4 Å resolution [22–24]. They provided invaluable information about the assembly interfaces of the four components of the γ -secretase complex and allowed mapping the disease-linked mutations in PS1 into the two hotspots on the TMs. Furthermore, CEM studies offered structural explanation of the mechanism by which Nct may mediate the substrate recruitment, pointing towards the central role of Nct E333, Y337 and F287 in this process. Rotation of the large lobe relative to the small lobe of the γ -secretase complex, induced by the substrate binding, may result in the alignment of the Nct pocket and the active site in PS1, consequently reorienting the substrate for cleavage. Consistent with the biochemical data, these investigations support the high plasticity of the PS1 structure, which might expedite the conformational changes modulating the proximity between two catalytic aspartates [22].

Together, the structure biology data provide clear evidence for the importance of the correct spatial arrangements of the multiple components and domains within the γ -secretase for the proteolytic activity of the complex, and for the processing of the C-terminal APP stub (C99) within its transmembrane domain to release A β and amyloid intracellular domain (AICD). They also point towards molecular explanations of the variability of the exact cleavage site of the PS1/ γ -secretase, and of the multiplicity of the A β species identified. The majority of the A β (approximately 90%) appear to be non-fibrillogenic A β 40. However, the γ -cleavage yields also a smaller subset of more oligomerization prone A β 42 and A β 43 peptides, which constitute the major components of the amyloid plaques in AD brain. The high A β 42/40 ratio is directly related to the synaptic dysfunction, neuronal loss and consequent cognitive impairments in AD [25–28].

Further studies revealed the occurrence of the PS1-dependent, earlier ϵ -cleavage of the APP C99 between the Leu-49 and Val-50, homologous to the Notch site S3 cleavage [29]. This was followed by the detection of A β peptides ranging from A β 49 to 37, and spaced at about three amino acids, suggesting a step-wise cleavage model of the γ -secretase, with cleavage sites for A β 49, 46, 43 and 40 aligned on one α -helical surface of the β CTF molecule, and A β 48, 45, 42 and 38 on the other [30, 31]. These findings reinforced the idea that the type of A β peptides produced is strongly dependent on the activity and/or conformational state of the PS1/ γ -secretase complex.

Although the PS1-mediated A β production has gained the greatest attention due to high relevance to AD pathogenesis, more than 90 other proteins have been reported to serve as alternative PS1 substrates [32]. The vast majority of the PS1/ γ -secretase substrates are type I transmembrane proteins possessing large ectodomain, which undergoes proteolytic shedding, a single-pass transmembrane domain and a C-terminal cytosolic tail. The multiplicity of the PS1 substrates implicates the protein in the regulation of wide range of physiological processes. The intramembranous cleavage of APP, CD44, Notch, Delta, Jagged, E- and N-cadherin, receptor-like protein tyrosine phosphatases (RPTP), ErbB4, deleted in colorectal cancer (DCC), alcadeins, leukocyte-common antigen related (LAR), to list just a few, leads to the release of their intracellular domains (ICDs), which translocate to the nucleus to modulate the transcription of their target genes. Thus, PS1/ γ -secretase

cleavage regulates pathways involved in neuro- and astrogenesis, cell survival, apoptosis, neurite outgrowth, dendritic spine dynamics, cell adhesion and angiogenesis [33]. Furthermore, by cleaving such proteins as Na_vβ2 [34] and stromal interaction molecule 1 (STIM1) [35], PS1 regulates cell surface expression and function of voltage-gated sodium channels and store-operated calcium entry (SOCE), respectively.

The PS1 role in the modulation of calcium homeostasis is much more complex. The protein has been demonstrated to directly interact with a number of calcium channels and pumps, including inositol triphosphate receptors (InsP3R) [36], ryanodine receptors (RyR) [37] and sarco/endoplasmic reticulum (ER) Ca²⁺ ATPase (SERCA) [38], to directly modulate their function. In addition, presenilins themselves may form a water-filled cavity, which functions as a low-conductance, passive ER Ca²⁺ leak pore [39]. Consequently, PS conditional knock-out leads to calcium dyshomeostasis, causing aberrant neurotransmitter release, which indirectly implicates PS1 in the modulation of the synaptic function [40]. The importance of PS1 for the synaptic vesicle trafficking, exocytosis and neurotransmitter release has been further strengthened by the discovery and functional characterization of the calcium-regulated interaction with synaptic vesicle release machinery protein - synaptotagmin 1 (Syt1) [41, 42].

Dynamic PS1 Subdomain Rearrangements Monitored in Situ in Intact Cells

The biochemical and structural biology studies provided invaluable insight into the organization of the PS1/γ-secretase. However, the limitation of these approaches stems from the inability to monitor dynamic changes in conformation of the PS1/γ-secretase in its native environment in intact and/or live cells. The design of the highly sensitive and reproducible Förster Resonance Energy Transfer (FRET)-based PS1 conformation assays that are uniquely suited to monitor intramolecular conformational changes of PS1 in intact cells in vitro and in vivo would allow overcoming these challenges. Such assays have been established for endogenous PS1 by co-staining two distinct epitopes on PS1 with fluorescently labelled antibodies recognizing N-terminus (NT) and loop domain or C-terminus (CT) of PS1 [11, 41, 43]. Alternatively, PS1 molecules tagged at the N-terminus and within the TM6–7 loop domain with a pair of living colour fluorescent proteins, yielding GFP-PS1-RFP or YFP-PS1-CFP FRET reporters, enabled monitoring dynamic changes of the PS1 conformation in real time in living cells [41, 44, 45]. The relative proximity between the two fluorophores tagging epitopes on the target molecule is determined by measuring FRET efficiency. The close fluorophores/subdomain proximity results in high FRET efficiency, and is revealed by shortening of the donor fluorophore lifetime or increased ratio between the intensity of the acceptor and the donor fluorophore, as detected by the Fluorescence Lifetime Imaging (FLIM) or spectral FRET, respectively.

The novel cutting-edge approach to monitor PS1 subdomain rearrangements in living cells using time-lapse imaging revealed that PS1 exists in a dynamic equilibrium of distinct conformational states – “closed” (pathogenic) and “open”, associated with higher and lower Aβ42/40 ratio, respectively [41]. This discovery opens new avenues for uncovering protective factors or pathological insults that may influence PS1/γ-secretase conformational state and progression of the amyloid pathology in AD. Specifically, the FRET-based assays

allowed to uncover how PS1 conformation is modulated by (1) maturation and assembly of the PS1/ γ -secretase complex [11, 46], (2) genetic (mutations) and pharmacological (γ -secretase modulators and inhibitors) manipulations regulating A β production and A β 42/40 ratio in particular [44, 47–49], (3) interactions with other proteins [41, 50] and (4) endogenous factors, implicated in AD pathogenesis, such as ageing [43], calcium overload [51], increased production of reactive oxygen species (ROS) [52, 53] and impaired synaptic activity [41, 45] (Fig. 2).

PS1 Conformation in Familial and Sporadic AD

A number of missense mutations displaying extreme allelic heterogeneity, and hence scattered widely from the N- to the C-terminus of PS1 has been identified as causative of AD (<http://www.alzforum.org/mutations>). However, it remains unresolved how exactly all these mutations lead to observed neuropathology and cognitive impairments [54]. In general, most of the PS1 mutations cause an increase in the A β 42/40 ratio by either decreasing the A β 40 or elevating the A β 42 production. The increased A β 42/40 ratio rather than total A β level appears to be central to AD pathogenesis [25, 26]. Several mechanisms of action for PS1 mutations have been proposed, including aberrant PS1 endoproteolysis impairing PS1 activity [55], alterations in calcium homeostasis via over-stimulation of the InsP3R gating by mutant PS1 [36] or disruption of PS1 function as a calcium-leak channel [39], and aberrant membrane integration and catalytic site conformation of the mutated PS1 [56], to name just a few. Moreover, it has been reported that all tested fAD mutations, but not non-pathogenic E318G PS1 polymorphism, alter PS1 conformation in vitro and in vivo. The pathogenic mutation-triggered conformational shift of PS1 is characterized by greater proximity between the fluorophores labelling PS1 N-terminus and PS1 C-terminus/TM6–7 loop domain [11, 43, 44]. It has been suggested that pathogenic PS1 mutations can act not only *in cis* but also *in trans* to alter function of the wild type protein by causing it to adopt an altered conformation with deleterious catalytic activity and substrate specificity [57].

Although fAD offers a unique model to gain insight into molecular pathomechanisms and aetiology of AD, it represents only less than 5% of all AD cases [58]. Intriguingly, the pathogenic rearrangement of the subdomain organization similar to that of fAD mutant PS1 has been reported for wild type PS1 in sporadic AD, where PS1 in “closed” conformation is predominantly found in the vicinity of amyloid plaques [43]. This suggests a link between the PS1 conformational state and reported altered microenvironment surrounding the plaques, characterized by the calcium overload, accumulation of reactive oxygen species (ROS), oligomeric A β and neurotoxicity [59–62]. Importantly, the recent report demonstrates a reciprocal interrelationship between PS1 and oligomeric A β . The exposure of neurons to the increased A β 42/40 ratio (oligomeric A β) results in the increase in the intracellular calcium levels and consequent shift of PS1 towards the pathogenic state [51]. This may point towards the existence of the vicious circle exacerbating and promoting the spread of the amyloid pathology within the brain.

Another factor implicated in AD pathogenesis is the accumulation of ROS in the brain. This stems from the age-related imbalance between excessive ROS production and the antioxidant defence mechanisms [63]. The accumulating superoxide anions can cause

protein modifications or react with fatty acids leading to the membrane damage and production of reactive aldehydes, such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE) [64, 65]. Importantly, accumulation of ROS can alter PS1/ γ -secretase function. It has been shown that nitrotyrosination of PS1 strengthens association of the two PS1 endoproteolytic NTF/CTF fragments that form catalytic centre of the enzyme [53]. Moreover, lipid peroxidation product HNE attaches to nicastrin and causes a shift of the PS1/ γ -secretase towards the “closed” pathogenic state associated with increased A β 42/40 ratio [52, 66].

In addition to accumulation of the ROS, impairments in calcium handling have been implicated in AD pathogenesis [67–70]. A link between altered calcium homeostasis and altered conformation of PS1 has been recently reported. Calcium ionophore or KCl-mediated calcium influx into primary neurons results in a dynamic, rapid and reversible phosphorylation of PS1 at the specific residues that leads to the PS1 subdomain reorganization [41, 71]. Mechanistically, calcium influx activates cAMP-dependent protein kinase (PKA), which phosphorylates PS1 at several serine residues, with serine 367 being critical for the pathogenic PS1 conformational shift. This change in the enzyme architecture translates into a shift in the production of A β species towards the longer, more fibrillogenic A β 42. The observed in sAD brains hyperphosphorylation of PS1 may contribute to the amyloid deposition in the sporadic cases, in the absence of PS1 mutation [71].

Pharmacological Modulation of the A β 42/40 Ratio

The findings of the “closed” pathogenic conformational change in PS1/ γ -secretase during ageing and in the AD brain open new opportunities for pharmacological modulation of the PS1 domains spatial arrangements. Failure of the clinical trials using γ -secretase inhibitors (GSI) to reduce A β production has proven that inhibition of the overall PS1/ γ -secretase activity results in undesirable side effects. This was mainly due to the lack of GSI's selectivity for the APP-directed γ -secretase activity and interference with the processing of the numerous γ -secretase substrates. Furthermore, since the relative ratio of the longer to shorter A β species rather than absolute A β amount is implicated in the AD pathogenesis, the efforts have been placed on modulation of the γ -secretase cleavage site. Non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, sulindae sulphide, flurbiprofen and ibuprofen, have been the first compounds reported to selectively reduce production of the toxic A β 42 species while increasing the levels of A β 38 and not affecting the A β 40 amount [72–74]. The most critical aspect of these compounds is their ability to modulate specific A β specie production without affecting the APP ϵ -cleavage and the homologous S3 cleavage site on Notch [75]. A number of these compounds have been tested for their effect on the conformation of PS1/ γ -secretase. It was found that NSAIDs that selectively decrease the A β 42 production consistently alter PS1 conformation by extending the distance between fluorophores labelling PS1 N- and C-termini in vitro and in vivo [48]. Importantly, the effect of NSAIDs on PS1 conformation was cyclooxygenase (COX) inhibitors independent, since aspirin did not modulate the APP cleavage and did not affect the arrangement of the PS1 domains [44, 48].

Despite the promising data on the A β 42-lowering properties, NSAIDs do not meet the pharmacological profile requirements for successful AD therapeutics. The relatively poor selectivity of NSAIDs and the reduced blood brain barrier (BBB) penetration lead to the need for a toxic high concentration to achieve therapeutic efficacy [76]. Moreover, clinical trial data from the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) did not support the hypothesis that NSAIDs, such as naproxen and celecoxib reduce the risk of AD. On the contrary, application of the drugs may lead to several cardiovascular complications due to COX2 inhibition, with celecoxib increasing the risk of death when compared to the placebo control [77]. The obstacles presented by NSAIDs have been at least partially surmounted with the application of medicinal chemistry, and several classes of the next generations γ -secretase modulators (GSMs) have been developed and proved efficient in vitro and in vivo [74, 78–81]. The prerequisite for the successful sign of the novel GSMs would be the detailed understanding of their interactions with the enzyme and the substrate. At present, NSAIDs and new generation GSMs that modulate A β 42/40 ratio have been reported to target either PS1/ γ -secretase or APP [73, 79, 82–88]. It has been also demonstrated that mutations within the luminal border of the APP substrate transmembrane domain alter conformation of the PS1/ γ -secretase [89] and its sensitivity to GSMs [90]. The interrelationship between APP and PS1/ γ -secretase may suggest that structural modifications within the substrate and/or other PS1/ γ -secretase interacting proteins might allosterically modulate the conformation of the enzyme and affect the A β production.

Modulation of PS1 Conformation by Interacting Proteins

PS1 interacts with several proteins, including other members of the γ -secretase complex (Aph1-a/-b, Nct and Pen -2), its substrates (e.g., APP and N-cadherin) and non-substrates (e.g. Syt1). These intra- and inter- γ -secretase complex interactions, modulating the conformation of PS1, may serve as novel potential drug targets and warrants greater attention.

It has been reported that genetic manipulations targeting either γ -secretase complex or the APP substrate affect the A β species produced and alter the A β 42/40 ratio [89, 91, 92], Predominant incorporation of Aph1-b vs. Aph1-a into the γ -secretase complex results in conformational change of the PS1 towards the pathogenic state [44, 46] and concomitant increase in the A β 42/40 ratio [75]. Similarly, greater proximity between the fluorescently labelled NT and loop domain of PS1 and increased A β 42/40 ratio have been observed in cells expressing modified Pen-2, N-terminus of which was elongated by fusion with the Flag-tag [44, 92].

Not only specific assembly of the γ -secretase complex itself but also substrate recruitment and its presentation to the complex play important roles in the modulation of the PS1/ γ -secretase subdomain architecture and in the subsequent production of the distinct A β peptides. It has been demonstrated that V44, L49, M51 and L52 residues of the C99 TMD constitute the predominant PS1 interaction sites [93], and that I716F and V717I mutations within APP (corresponding to I43 and V44 in C99) alter the APP positioning within the membrane by bringing its C-terminus closer to the lipid bilayer [94]. This mis-positioning within the membrane influences the way APP is presented to the PS1/ γ -secretase. It leads to

the reduction in the distance between the APP CT and PS1 loop domain, and promotion of the “closed” PS1 conformation [89, 94]. On the other hand, A β 42-lowering substitutions within the APP (V715F and L720P) promote “open” PS1 conformation and shift the γ -secretase cleavage away from the A β 42 production [47]. The importance of the substrate presentation to the PS1/ γ -secretase complex has been further strengthened by the data demonstrating that after the initial binding to PS1/ γ -secretase, the APP must undergo a translocation and/or conformational change in order to access the active site of the enzyme and undergo proteolysis [95].

The accessibility of the APP to the active site is also regulated by nicastrin. It has been recently reported that nicastrin’s ectodomain extends about 25 Å from the TMDs of γ -secretase, directly above the substrate binding pocket of PS1, and hence provides a steric block that regulates access of the substrate to γ -secretase active site [96]. In line with that substrates with shorter neo-ectodomains (e.g., C83 vs. C99) appear to be preferred by the PS1/ γ -secretase [97].

The substrate-enzyme interrelation is not only limited to APP. It has been demonstrated that N-cadherin interacts with the PS1 loop domain and promotes PS1 cell-surface expression [98]. Overexpression of N-cadherin results in enhanced A β production, likely caused by the greater accessibility of APP to the γ -secretase catalytic site, whereas the A β 42/40 ratio was decreased. The A β 42/40 ratio reduction was linked to PS1 adopting the “open”, protective conformational state either due to increased interaction with N-cadherin and/or altered subcellular localization [50, 99]. The synaptic N-cadherin, its involvement in the formation of synaptic contacts and regulation of the neuron-specific functions, such as synaptic plasticity [100], would suggest that the PS1-N-cadherin interaction might be targeted for the synapse-specific modulation of the PS1 conformation and thus the A β 42/40 ratio.

The synapse-specific mechanisms of the modulation of the PS1 conformation were further demonstrated by the discovery of the synaptic activity/calcium influx-triggered interaction between PS1 and a synaptic vesicle protein-synaptotagmin 1 (Syt1). Importantly, knock-down of Syt1 in PC12 cell line or peptide-based inhibition of the PS1-Syt1 binding result in a shift of PS1 towards the pathogenic “closed” conformation, and concomitant increase in the A β 42/40 ratio [41, 42]. These data underscore important role of PS1 at the synapse and may help to understand how impaired PS1 structure and function may lead to local increase in the A β 42/40 ratio, followed by synaptic accumulation of the toxic amyloid oligomers and neurodegeneration.

Conclusion

The scientific technological advancements and the design of the novel cutting-edge research approaches to investigate intramolecular structural rearrangements at a single cell level in real time enabled the discovery of the dynamic conformational changes of PS1. This, followed by uncovering of the PS1/ γ -secretase modulatory pathways, may provide deeper understanding of AD pathogenesis and promote the design of novel therapeutic approaches. The data from preclinical and clinical studies demonstrate that γ -secretase modulators are promising agents to be applied in the AD therapy, especially at the early, “prodromal” stages

of the disease. These compounds are known to allosterically modulate conformation of PS1/ γ -secretase by shifting it towards the “open”, non-pathogenic state, which strongly correlates with the reduction in the ratio of longer to shorter A β species. Therefore, monitoring PS1 conformation might serve as a read-out for the efficacy of the drugs targeting γ -secretase. The ease of the PS1 conformation FRET assay makes it suitable for the use in high-throughput fluorescence microscopy or flow cytometry screenings of the libraries of compounds in vitro to determine their therapeutic potential. The most efficient drugs can be further validated in vivo by employing the recently developed two-photon imaging of the GFP-PS1-RFP FRET-reporter probe in the brain of a living mouse [71] and correlating the conformational changes in PS1 with the improvements in behaviour, synaptic functions and amyloid pathology in AD mouse models.

Furthermore, since recent studies demonstrated that AD-related pathological changes (calcium dyshomeostasis, mitochondrial dysfunctions and oxidative stress, all of which affect PS1 conformation) are observed not only in the brain but also in the easily accessible peripheral cells [101], detecting pathogenic PS1 conformational changes in the patient-derived lymphocytes, monocytes or fibroblasts may serve as a novel biomarker for AD. This might facilitate early AD detection, monitoring of its progression, and provide an opportunity for the development and evaluation of the potential personalized treatments.

Acknowledgments

Funding This work was supported by the National Institutes of Health (AG15379 and AG044486 to OB).

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Fig. 1. Schematic representation of the amyloid precursor protein (APP) processing. The schematic image presents the amyloidogenic pathway of the APP processing via β - and γ -secretases

Fig. 2. Schematic representation of the modulation of PS1/ γ -secretase conformation. The schematic image presents the dynamic changes in the subdomain architecture of PS1 triggered by genetic and environmental factors