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Presenilins Interactome in Alzheimer's Disease and Pathological Ageing

Michalina Maria Wężyk and Cezary Żekanowski

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Abstract

Alzheimer's disease (AD) is the most common type of dementia characterized by massive neuronal loss. Pathological hallmarks of the disease are overproduction of β -amyloid ($A\beta$) and hyperphosphorylation of tau protein accumulated into senile plaques (SPs) and neurofibrillary tangles (NFTs), respectively. SPs with cortical tau pathology are also hallmark of pathological ageing (PA). Recently, an extensive overlap has been shown between $A\beta$ levels and profiles in PA and AD brains, suggesting that PA could be a prodromal AD phase. Presenilins are major components of the γ -secretase complex involved in $A\beta$ production. Furthermore, presenilins interact with players of numerous signalling pathways important in the PA and AD. Integration of various modern research approaches would reinforce the role of presenilins signalling network in brain pathology. These approaches include high-throughput (epi)genetic and transcriptomic analyses, large-scale microscopic imaging studies, immunoaffinity purification or mass spectrometry. Comprehensive integration of these methods is necessary to update the definition of the role of presenilins in AD and PA. Hereby, we summarize the available data on presenilins' functions and interactions. We believe that the systematization of the existing knowledge will stimulate further research and will help reveal the molecular nooks and crannies in Alzheimer's disease and in pathological ageing.

Keywords: presenilins interactome, Alzheimer's disease, pathological ageing

1. Introduction

Major clinical hallmarks of Alzheimer's disease (AD) are memory loss and cognitive impairment. Pathologically, AD is manifested by overproduction of toxic intracellular β -amyloid ($A\beta$) oligomers, deposited into extracellular senile plaques (SPs), and by hyperphosphorylation of

tau protein deposited into neurofibrillary tangles (NFTs). A β is processed by the γ -secretase complex, where the most important component is presenilin [1]. There are two major types of AD: early-onset AD (EOAD), often linked with familial AD (FAD), and late-onset AD (LOAD), linked with sporadic AD (SAD). Familial EOAD represents 5–10% of all cases of AD and is associated with mutations in *PSEN1* encoding presenilin (PS1), *PSEN2* encoding presenilin 2 (PS2), and *APP* encoding amyloid β protein precursor (APP) [2, 3]. Overall, presenilins and APP mutations directly cause a production of toxic assemblies of oligomerized A β , followed by a formation of senile plaques [4]. Toxic A β forms induce apoptosis, oxidative stress, unfolded protein stress response, inflammation, or disturbances in calcium signalling, of which many are present in pathological ageing or in Alzheimer's disease.

Normal ageing results from natural maturational processes, whereas pathological ageing is related to non-normative factors such as disease or trauma to the brain. Ageing disproportionately affects frontal lobes [5]. Substantial overlap between ageing and neurodegeneration was demonstrated in several brain autopsy studies of aged people with no record of neurological diseases. These reports showed the presence of amyloid plaques, neurofibrillary tangles, Lewy bodies, inclusions of TAR DNA-binding protein 43 (TDP-43), synaptic dystrophy, and loss of neurons in most of ageing brains [6, 7]. However, unlike AD, pathological ageing usually lacks cognitive impairment despite similar senile plaque [8]. It was found that oxidative stress, commonly accompanying both ageing and AD, causes pathogenic conformational change of PS1 in neurons in vitro, which was followed by an increased ratio of A β _{42/40}. It was further concluded that this conformational shift and deregulation of PS1 precedes A β deposition in pathological ageing [9]. These data demonstrated a direct connection between presenilins and PA. Presenilins contribute to brain pathology not only by deposition of toxic A β . Both PS1 and PS2 have been found to be involved in the regulation of apoptosis in neurons induced by trophic withdrawal or A β and via Jun Kinase pathway, respectively [10]. What is more, the role of presenilins in the progression of AD and PA is underlined by their numerous functions in the adult cerebral cortex functions, including maintenance of synaptic plasticity, long-term memory, and neuronal survival, which are critical for normal ageing, healthy brain, and cognitive ability [11].

Summarizing, presenilin functions can be controlled at different cellular levels, that is, (1) gene architecture, together with the influence of damaging genetic variants, in *PSEN1* and *PSEN2*, (2) gene expression, together with corresponding regulatory protein networks, (3) protein structure with its enzymatic activity, controlled by the assembly of the γ -secretase complex with accompanying partners and by post-translational modifications (phosphorylation and ubiquitination), (4) quantity, quality and availability of numerous substrates of presenilins and finally (5) by the interaction with molecular partners involved in numerous biological processes. Hereby, we highlighted that presenilins can determine different physiological and pathological processes by the interplay with diverse signal transduction pathways and by processing of various substrates. Generally, presenilins form a signalling network, which is critical for both AD and PA. Therefore, we present below molecular players that might affect biological functions of presenilins forming together so-called presenilin interactome.

2. Presenilin genetic structure and transcriptional regulation network

Presenilins 1 and 2 are encoded by homologous genes *PSEN1* and *PSEN2*, located at chromosomes 14q24.3 and 1q42.1, respectively [12, 13]. The genomic sizes of *PSEN1* and *PSEN2* are largely different, and it is 70 kb for *PSEN1* and 24 kb for *PSEN2*. *PSEN1* contains 13 exons and three first exons are located in the 5' untranslated region (5'UTR) [14]. The first two exons and exon 9 of *PSEN1* could be alternatively spliced, causing structural changes to the protein [15]. *PSEN2* contains 12 exons and two first are located in the 5' UTR [16]. The alternatively spliced products in *PSEN2* include in-frame omissions of exon 8 and simultaneous omissions of exons 3 and 4 [17]. Moreover, it has been found that splicing of exon 5 in *PSEN2* occurred under hypoxic stress conditions [18]. The transcription of *PSEN1* depends on two promoters producing two mRNA transcripts of 2.7 and 7.5 kb, with different 5' UTRs [15]. *PSEN2* is also transcribed into two different transcripts of 2.4 and 2.8 kb [16].

Transcriptional regulation of presenilins might have an implication in AD and PA pathogenesis. Promoters of *PSENs* lack a TATA box but contain transcriptionally active GC. *PSEN1* promoter contains GC boxes corresponding to Sp1-like transcriptional factor, and the most active region is located between -22 and -6 bp. Transcriptional co-activator p300 with histone acetyl-transferase (HAT) activates *PSEN1* transcription. In particular in neuronal system, enhanced transcription of *PSEN1* was observed upon stimulation by N-methyl-D-aspartate (NMDA) or brain-derived neurotrophic factor (BDNF), under control of cAMP-responsive element binding (CREB). *PSEN1* expression and risk of AD and premature PA are also influenced by *PSEN1* promoter polymorphisms, found at -22C/T and -48C/T positions. Another suppressor of presenilin 1 is p53 protein that recruits other proteins to occupy *PSEN1* promoter [19]. Relatively little is known on the transcriptional regulation of *PSEN2*, where the promoter is located in a CpG island and is regulated by early growth response gene-1 (Egr-1) transcription factor, involved in learning and memory processes [20]. In addition, *PSEN2* promoter has been found to be regulated by nerve growth factor (NGF), with an NGF-responsive element localized between -403 and +13 [19]. Interestingly, parkin protein, known to be associated with Parkinson's disease, was found to act as a transcriptional factor modulating trans-activation of *PSEN1* and *PSEN2* promoters via RING1-IBR-RING2 domain and to influence γ -secretase activity [21]. The expression of both *PSEN1* and *PSEN2* was also described to be under tight control of inflammatory cytokines, including tumour necrosis factor (TNF)- α , interferon (IFN)- γ , interleukin (IL)-1 β , IL-10 or TGF- β 1 [22]. Generally, transcriptional regulation of presenilins is based on the complex signalling cascades controlling promoter's activation and requires a large variety of transcriptional factors. The dense network of signalling pathways related to the regulation of the promoters of *PSEN1* and *PSEN2* indicates numerous cellular processes that may contribute to the incidence and progression of AD and PA.

3. Presenilin structure and expression patterns

Structurally, PS1 and PS2 are integral membrane proteins of 467 and 448 amino acids, respectively [14, 15]. The homology between PS1 and PS2 is about 67%, with the highest similarity

in transmembrane domains (TMDs). PS1 and PS2 comprise nine TM, among them TM1-6 are located at N'-terminal and TM7-9 at the C'-terminal. The catalytic centre with aspartate residues is located at the cytoplasmic side of TM6 and TM7, forming large hydrophilic loop (HL) [14]. Presenilins are activated by endoproteolysis yielding N'-terminal and C'-terminal portions. Endoproteolytical cleavage of PS1 occurs at HL, with the predominant cleavage site between amino acids 291 and 292, generating 28 kDa N'-terminal and 17 kDa C'-terminal fragments [23]. Similarly, PS2 is endoproteolytically cleaved into 35 kDa N'-terminal and 20 kDa C'-terminal fragment [24]. The most common mutations of presenilins occur in gene portion encoding C'-terminal, containing proline, alanine and leucine residues, and are usually loss of function for presenilins [25]. Due to protein structure complexity, presenilins interact with different partners, which will be *described in detail in Section 6*.

Presenilins are ubiquitously expressed, with some tissue-specific differences. Generally, *PSEN1* transcript is expressed at higher levels than *PSEN2*. The expression pattern of *PSEN1* and *PSEN2* in the brain is similar and present in different brain cells, such as cortical neurons, hippocampal neurons, granule cells or neurons of amygdala [26], and different types of glial cells [27]. In neurons, presenilins are expressed in the cell body and dendrites [28] and are localized in several subcellular compartments, that is, rough endoplasmic reticulum, Golgi complex, mitochondria, and at plasma membrane [29]. Moreover, presenilins were found to be expressed in several non-nervous cells and tissues, including lymphoblasts, fibroblasts, liver, spleen, and kidney [15].

4. Presenilin biological functions

Presenilins are aspartyl proteases and constitute a subunit of γ -secretase complex involved in the processing of APP and producing various A β peptides (*described in Section 5*). Besides that, presenilins are involved in numerous biological processes, playing various molecular functions in distinct subcellular compartments. Presenilins reprocess more than 90 substrates [30]. Presenilin substrates are involved in various signalling pathways, and several examples are provided in subsequent text.

Receptor tyrosine-protein kinase erbB-4 (ErbB4) processing by presenilins leads to enhanced spine formation through activation of Rac signalling [31]. Furthermore, presenilin-dependent cleavage of ErbB4 interplay is crucial for signal transduction during cells maturation [32]. Importantly, ErbB4 is involved in EGF/neuregulin signalling crucial for cell proliferation, differentiation, apoptosis, oligodendrocyte maturation, angiogenesis, synapse formation, LTP, and nerves myelination [33]. Another presenilin substrate of great biological importance is E-cadherin, which misprocessing affects transcriptionally regulated genes downstream of E-cadherin, involved in cell adhesion [34]. Next to that, glutamate receptor proteolysis performed by γ -secretase complex was found to be crucial for synaptic transmission [35]. Furthermore, VEGF receptor proteolysis and phosphorylation controlled by presenilins were reported to be important for angiogenesis, what could have further consequences in damages of brain areas by interfering with oxygen and energy supply [36]. Presenilin substrates selection

is also a way of modulation of cell signalling and processing of presenilins' substrates regulated by the γ -secretase substrate-recruiting factors (γ SSRFs) [37]. This establishes a complex signalling network of the process important in brain, thus in PA and AD.

Summarizing, presenilin biological functions and resultant interactome are not merely attributed to the γ -secretase activity and APP processing. Diversity of presenilin substrates is reflected by numerous biological implications including postsynaptic Ca^{2+} signalling, synaptogenesis, neurites outgrowth, lipid metabolism, cell adhesion, axon guidance, cell growth, regulation of dendritic spines, angiogenesis, LTP or glutamate synaptic transmission [30 (Tables 1 and 2), 38, 39]. In this regard, the amyloid cascade is complemented with the above-listed processes disturbed in AD. Similarly, pathological ageing is manifested by a loss of protein homeostasis, DNA damage, lysosomal dysfunction, epigenetic changes, immune deregulation, or disturbed calcium homeostasis [6]. Altogether, AD and PA might result from presenilin-dependent processes or presenilins' interactomes.

5. Presenilin substrate APP and production of toxic β -amyloid peptides

$\text{A}\beta$ peptides are generated from amyloid β -precursor protein (APP) by enzymatic digestion involving the activity of α -, β - and γ -secretases. Amyloidogenic cleavage of APP is started by β -secretase, which generates a 100-kDa-soluble N-terminal fragment and membrane-bound 12-kDa C-terminal fragment (C99), which is further cleaved by γ -secretase, yielding the APP intracellular domain (AICD) and 40, 42, up to 56 amino acids $\text{A}\beta$ peptides. C99 cleavage by γ -secretase is inaccurate and results in numerous different $\text{A}\beta$ species, but those ending at position 40 ($\text{A}\beta_{1-40}$) are the most abundant and considered as physiological (~80–90%), followed by less abundant but toxic 42 ($\text{A}\beta_{1-42}$, ~5–10%). The second cleavage, which takes place within the hydrophobic transmembrane domain (TMD) and is regulated by intramembrane proteolysis (RIP), has been attributed to the γ -secretase complex with presenilins, as the catalytic component. The γ -secretase is a membrane-bound protease complex consisting of four components: nicastrin, anterior pharynx-defective 1 (APH-1) and presenilin enhancer 2 (PEN-2) and presenilin (1 or 2) forming aspartyl protease subunit and activity centre of the complex [40, 41].

As mentioned above, PA patients are characterized by the presence of amyloid deposits. However, PA is manifested by fewer-cored plaques and there is little or no neuritic pathology or neurofibrillary tangles in the cortex. Moreover, the species of $\text{A}\beta$ peptides in PA differs from AD brains. It has been demonstrated that $\text{A}\beta_{1-40}$ levels were 20-fold higher in AD brains compared to PA brains, whereas $\text{A}\beta_{1-42}$ levels were only twofold higher [42]. Overall, several studies suggested quantitative and qualitative differences in the amyloid deposits between PA and AD brains [43]. It can be concluded that a wide spectrum of harmful effects of $\text{A}\beta$ species, peptides, oligomers or plaques coincides with the disturbed presenilin signalling. These data demonstrate both common and different mechanisms of AD and PA, with the contribution presenilin, whose functions influence qualitative and quantitative status of amyloid.

6. Presenilin interactome: implementation in AD and PA

Numerous studies have been conducted in order to identify proteins interacting with PS1 and PS2. Majority of these studies have focused on the key signalling cascades specific for AD, as well as for PA, that is, oxidative stress, generation of free radicals or inflammatory processes. The best studied presenilin partners are components of γ -secretase complex (nicastrin, APH-1 and PEN-2), presenilin substrates (APP, Notch) and proteins involved in a regulation of cell death, calcium homeostasis and cell adhesion. It should be stressed that the knowledge on full PS interactome is crucial for more detailed definition of the pathomechanisms of AD and PA, and further studies are needed to complement this image.

6.1. The γ -secretase complex partners

Direct partners of presenilins are the components of the γ -secretase complex, namely nicastrin, APH-1 and PEN-2 [44]. Nicastrin associates with the complex comprising PS1-C' terminal and APH-1 [45]. Nicastrin is required for the assembly of presenilin complexes to mediate Notch signalling and for processing and trafficking of β -amyloid precursor protein and thus plays a role in amyloid plaque formation [46]. Proper signalling between presenilin and nicastrin is important not only for processing of APP and accumulation of A β peptides but also for synaptic plasticity [47]. The next component of γ -secretase complex is PEN-2, a membrane protein with two predicted transmembrane domains, both N' and C' terminals are in extracellular space and with hydrophilic cytosolic loop [48]. PEN-2 binds to the fourth transmembrane domain of PS and helps to stabilize the γ -secretase complex after PS endoproteolysis [49]. Together with APH-1, PEN-2 is indispensable for Notch signalling [50], exhibiting thus similar properties like nicastrin. Importantly, mutations in TM4 reduced PS1-PEN-2 interaction which was further accompanied by an increased A β 42 production and disrupted the endoplasmic reticulum calcium homeostasis [51]. The final component of γ -secretase complex is APH-1, a protein composed of seven transmembranes with N-terminus and large loops at cytosolic side [52]. APH-1 contains a conserved GXXXG motif that may be involved in interactions with other subunits of the complex [53]. APH-1 together with nicastrin forms a stable complex that constitutes a scaffold prior to the generation of the full presenilin complex [54]. APH-1 directly interacts with both immature and mature forms of the presenilins and nicastrin and this is indispensable for γ -secretase activity [55]. According to that described above, presenilin biological functions are regulated by complex assembly.

6.2. Mitochondrial interactome of presenilins

The γ -secretase complex was found in mitochondria [56]. Since A β is not a substrate for mitochondrial γ -secretase complex, its mitochondrial implication may be related to cell death signalling, switching between necrosis and apoptosis depending on ATP levels [56]. Moreover, PS2 was found to modulate ER-mitochondria juxtaposition and interactions, and that was enhanced in the case of PS2 mutations [57]. In detail, the components of γ -secretase complex were found in mitochondria-associated ER membranes (MAMs) with lipid raft-like domain [58]. Mutations in presenilin 1 were found to impair the IP3 receptor- and voltage-dependent calcium

transport, as well as Ca^{2+} -dependent mitochondrial proteins transport, and this was followed by a mitochondrial dysfunction, reduced patients' motor coordination and $\text{A}\beta$ aggregation with ultimate dementia [59]. Presenilin 1 was found to interact with mitochondrial intramembrane cleaving protease, called presenilin-associated rhomboid-like protein (PARL), which could promote changes in mitochondrial morphology [60]. Next to mitochondrial membrane residing proteins, presenilins interact with immunophilin FKBP38 forming macromolecular complexes, which promoted anti-apoptotic protein Bcl-2 sequestration into endoplasmic reticulum and Golgi apparatus compartments [61]. Importantly, AD-linked presenilin mutants enhanced the pro-apoptotic activity by reducing levels of mitochondrial Bcl-2 [62]. In the light of above, presenilins and other elements of the γ -secretase complex located in mitochondria establish a novel type of cellular signalling and interacting network.

6.3. Hif-1 α interaction

Hypoxia-inducible factor 1 α (Hif-1 α), which upregulates γ -secretase activity, was recently identified as PSs partner [63]. Hif-1 α is related to ubiquitin-mediated proteolysis, induction of angiogenesis, inflammation or increase of vascular tone. Villa et al. [63] showed that Hif-1 α acts as a subunit of γ -secretase activity, which is distinct from its canonical role as a transcription factor. Moreover, hypoxia-induced cell invasion and metastasis were improved by either γ -secretase inhibitors or a dominant-negative Notch coactivator, indicating essential role of γ -secretase/Notch signalling [63]. These data provided the molecular mechanism for an increased incidence of AD and PA following cerebral ischaemic injuries and strokes [64]. In addition, cells lacking presenilin 1 were characterized by an impaired induction of HIF-1 α in response to hypoxia. Furthermore, presenilin 1 and HIF-1 α physical interaction may protect HIF-1 α from degradation through proteasome. Additionally, M146V Psen1 mutation impaired metabolic induction of HIF-1 α [65]. These data suggest that PS1 regulates the induction of HIF-1 α .

6.4. Presenilin interactome of tetraspanin-enriched microdomains (TEMs)

Tetraspanin-enriched microdomains (TEMs) consist of proteins and lipids crucial for coordination of many biological processes, including cell adhesion, proteolysis, cell motility or sorting to exosomes [66]. A series of proteins transiently interacting with the γ -secretase complex were found in TEM network. Moreover, the disruption of TEM inhibited $\text{A}\beta$ production [67]. The study of Wakabayashi and co-workers showed an interaction of γ -secretase complex with tetraspanin proteins, that is, CD81, Upk1b and CD9 and cell surface immunoglobulin superfamily proteins EWI-2 and EWI-F [67]. Another research evidenced that the association of TEM with γ -secretase complex is needed for an enhancement of its proteolytic activity [68]. These data also confirmed a localization of γ -secretase in the raft-like domains [69]. All the above studies revealed that the integrity of tetraspanin microdomains is crucial for presenilins and γ -secretase signalling. In addition to TEM, presenilin complex and its interactive network were shown to be located predominantly in a specialized sub-compartment of ER, spatially and biochemically connected to mitochondria, called mitochondria-associated ER membranes (MAMs). MAM is a lipid raft-like structure, enriched in anionic phospholipids, cholesterol

and sphingomyelin. MAM is involved in cholesterol and phospholipid metabolism, calcium homeostasis and in mitochondrial function and dynamics. MAM function was altered and ER-mitochondrial connectivity is significantly increased in AD. The authors of these findings proposed the “MAM-AD hypothesis” with a central role of ER-mitochondrial-presenilin network in AD pathogenesis [70]. Schon and Area-Gomez [71] reported a large list of genes encoded in MAM, including genes involved in the regulation of apoptosis process, maintenance of calcium signalling, inflammatory response (formation of inflammasomes) or protein ubiquitination. In addition, they discovered that a MAM function in cholesteryl ester and phospholipid synthesis was overactive in AD. According to Schon and Area-Gomez [71], MAM is an unexplored research area, and its importance is vastly underestimated in brain pathology, both AD and PA.

6.5. Recent findings on presenilin interactome

The large list of molecular partners of presenilins supports their extended significance in AD and PA. Testing whole presenilin interactome, instead of selected signalling pathway, is highly recommended due to the fact that any brain pathologies are extremely complex diseases, where causative and susceptibility genes are highly interconnected [72]. Novel PSEN-related genes were discovered through high-throughput immunoaffinity (co-IP and pull-down) studies [73, 74]. Novel findings on PS1 partners involved ST13, GCDH, ECSIT and CDC37 proteins, and novel PS2 partners were PDCD4, DYNC1H1 and ECSIT. These interactions together with the already known might provide a novel and holistic insight into the molecular pathways interconnection underlying various brain pathologies. Soler-López and co-workers also indicated and confirmed a physical connection between apolipoprotein E (APOE) and PS1 [73, 74]. Direct evidence on APOE and PS1 binding provided a novel insight into the pathogenic role of APOE as a regulator of PS1 in APP cleavage. Furthermore, Soler-López et al. also confirmed an interaction between PS1 and PS2, previously suggested to cooperate as part of the γ -secretase complex in APP cleavage [73, 74]. The direct binding of APP with both PS1 and PS2, confirmed by co-IP, had been previously suggested [75]. These results provided a fresh perspective on the possible functions of presenilin in the process of brain degeneration in AD or PA.

Furthermore, the interaction of presenilin with ECSIT components (evolutionarily conserved signalling intermediates in Toll pathway) could constitute a molecular link between oxidative stress, inflammation and mitochondrial dysfunction in AD. Supporting the idea of the implication of presenilins' interactome in oxidative stress response, another component of redox signalling, glutaryl-CoA dehydrogenase (GCDH), also interacts with PS. Moreover, the association of ECSIT with APOE was shown to bind A β in its oxidized form Ref. [76]. Another novel example of presenilin interaction partners is the member of the tumour necrosis factor receptor-associated factor (TRAF) family. More precisely, presenilin full-length holo-proteins were suggested to be novel substrates of TRAF6-mediated Lysine-63-linked ubiquitination. Furthermore, TRAF6 induced PS1 gene transcription in a JNK-dependent manner. Notably, TRAF6-mediated ubiquitination of presenilin did not affect γ -secretase enzyme activity, but likely regulated presenilin function in calcium signalling. TRAF6 deficiency coincided with reduced PS1 ubiquitination,

protein levels and Ca^{2+} leakage from ER, suggesting that ubiquitination may be an important regulatory post-translational modification of presenilin function [77]. On the other hand, TRAF6 is involved in nerve growth factor (NGF)-dependent phosphorylation, ubiquitination and association of tropomyosin receptor kinase A (TrkA) with p75NTR, thereby promoting cell survival and differentiation. Under pathological conditions in AD or PA, pro-NGF stimulation can lead to nitrosylation of TrkA, thereby impairing its ubiquitination and downstream signalling which results in apoptosis [78]. In addition, presenilin ubiquitination was shown to be controlled by ubiquitin 1. In detail, ubiquitin 1 promoted the formation of PS1-positive aggregates [79, 80]. Furthermore, PS1 ubiquitination was found to demand Cdc4 component of the SCF ubiquitin E2-E3 ligase complex (Skp1-Cdc53/CUL1-F-box protein) and formation of this complex was followed by an increase in $\text{A}\beta$ production [81]. Overall, the above-described scientific reports present a large spectrum and different aspects of presenilin interactome, important for brain functions thus implemented in brain pathological ageing or degeneration.

6.6. Presenilins and synaptic transmission

One of the most important pathologies of brain degeneration or pathological ageing is disturbed synaptic transmission. It is believed that the impairment of synaptic function accounts for pathological ageing or degeneration independently on SP deposition. Recently, presenilins were proposed to participate in neurotransmitter release in the γ -secretase function-independent manner. It was reported that presenilins are essential for regulating neurotransmitter release like glutamate, and its inhibition is mediated by a depletion of ER Ca^{2+} storage and a block of intracellular Ca^{2+} release [82]. Importantly, PS1 knockout and PS1-M146V neurons did not exhibit synaptic strengths. On the other hand, synaptic activity was found to modulate PS1 activity and $\text{A}\beta_{40/42}$ ratio via altering PS1 conformation [83]. Additionally, it has recently been demonstrated that the interaction of PS1 with synaptic vesicle-associated protein, synaptotagmin 1 (Syt1), implicated novel synaptic functions of PS1, and both proteins modulated each other's functions in neurons via direct activity-triggered interaction, and the PS1-Syt1 complexes were crucial for exocytosis at the synapses and safeguarding of PS1 conformation [84]. Overall, mounting evidence points to a role of presenilins in synaptic transmission. It is clear that the interplay between presenilins and synaptic activity could originate from presenilins γ -secretase activity.

6.7. Other aspects of interactomes of presenilins 1 and 2

PS1 and PS2 can exhibit distinct from γ -secretase activities [85]. For instance, it has been demonstrated that autophagy and lysosomal proteolysis required presenilin 1 [86], as well as presenilin 2 through a γ -secretase-independent mechanism [87]. Further detailed analyses revealed novel interactions of the γ -secretase core complex with a molecular machinery targeting synaptic vesicles to cellular membranes, and with the H^{+} -transporting lysosomal ATPase macrocomplex [88]. Importantly, lysosomal dysfunction is also associated with many age-related pathologies like Parkinson's and Alzheimer's disease, as well as with a decline in lifespan. Conversely, targeting lysosomal functional capacity is emerging as a means to promote longevity [89]. Another example of γ -secretase-independent interaction is the catenin/

cadherin network that was almost exclusively found associated with PS1. In detail, catenin $\alpha 2$, catenin $\beta 1$ and plakophilin 4, as well as the cadherins 2 and 11, were repeatedly and strongly enriched in the PS1-specific sample [90]. On the other hand, an intramembrane protease, signal peptide peptidase (SPP), predominantly co-purified with PS2-containing γ -secretase complexes and was observed to influence A β production [90]. Another interesting interaction was found between PS2 and DREAM protein [91]. The Ca²⁺-binding protein DREAM regulates gene transcription and activity of potassium channels in neurons. DREAM interaction with PS2 might have implication in the regulation of the Ca²⁺ content in endoplasmic reticulum. The transient co-expression of DREAM and presenilin 2 potentiated the decrease of endoplasmic reticulum Ca²⁺ observed in presenilin-overexpressing cells. This could be due to a direct effect of DREAM on presenilin 2 as the two proteins interacted in a Ca²⁺-independent fashion. Finally, an example of an interaction unique to PS2 is the DRAL protein. DRAL is an LIM-only protein containing four LIM domains and an N-terminal half LIM domain. The PS2-DRAL interaction was confirmed using yeast two-hybrid and immunoaffinity studies, suggesting that DRAL functioned as an adaptor protein that links PS2 to an intracellular signalling [92]. This paragraph outlines the differences between PS1 and PS2, and cautions against correct attributing of a given interactome with disease phenotype.

7. Pathological ageing and Alzheimer's disease in the *omic* era

The above-presented insight on the presenilins' interactome provides important information about the background of pathological ageing and neurodegeneration. Nevertheless, the protein interactome is still only a small fragment recognized by the systemic biology. Thus, there is a need to integrate interactome data with other high-throughput data. The importance of integration of different parts of biological systems is stressed by the fact of becoming an ageing society. Undoubtedly, the ageing is one of the major risk factors for various diseases, ranging from cancer, cardiovascular diseases, type 2 diabetes (T2D) and ending with Alzheimer's disease. This creates a long list of ageing-related diseases (ARDs). In this regard, a recognition of the whole functional network linking ageing and ARD becomes one of the key tasks of current medical science. In the era of *omics* research, publicly available domains allow comparison of genomics, transcriptomics, proteomics, metabolomics, miRomics, epigenomics, regulomics (regulatory genomics), microbiomics, and lipidomics with particular disease [93]. These criteria are met by the 'GeroNet' research model, an approach that is targeting the relationship between ageing and hundreds of ARD [94]. These studies indicated several subnetworks associated with ageing, including 'response to reduced oxygen levels' or 'cell cycle checkpoints'. Importantly, the GeroNet model has helped to identify several genes that may play a key role combining pathological ageing and Alzheimer's disease, including the top five most significant STAT3, P53, FOS, BCL2 and NFKB1. The next example of integration of several omics research is analysis of the genes associated with longevity and ageing, collected in Ageing Gene/Interventions database (<http://www.kaeberleinlab.org/ageid>) and in GenAge database, which can be useful for the research on different interactome networks in AD or PA. Another recent *omic* approach was presented in the studies on inflammaging with

propagation of pro- and anti-inflammatory mediators in a dynamic manner from cell to cell and from organ to organ, supplemented by glycomics data [95]. Additionally, other wide-genomic studies revealed longevity and age-related functional biological networks, underlining the importance of neuronal development, autophagy and other processes associated with Alzheimer's diseases [96]. Furthermore, the integration of various systemic biology data has revealed common mechanisms associated with genomic instability and reduced capacity to DNA repair for both ageing and neurodegeneration. [97, 98]. Genomic instability is also influenced by a number of epigenetic changes that can be associated with both ageing and AD. These epigenetic changes occur at different levels, for example, histone methylation pattern, replacement of the canonical histones by rare variants of histones or regulated by an altered expression of non-coding RNA [99]. Indeed, there are studies confirming a decrease in genome-wide DNA methylation occurring in both ageing and AD patients [100]. Significantly, epigenetic regulation of the presenilins 1 and 2 was found to be pivotal in the development of the cerebral cortex of mice [101]. This epigenetic regulation of PS1 and PS2 was controlled by the acetylation and methylation of histone H3K9/14 and this was associated with further differential expression of PS1 and PS2, as well as their interacting protein partners. These data indicated that multiple levels of epigenetic regulation may be involved in controlling the formation of amyloid beta. Given epigenetic context, interestingly, dietary supplementation with B group vitamins restored methylation of promoters of presenilin 1, APP and BACE1 and slowed down the progression of AD [102]. In addition, this was associated with a decrease in oxidative stress and a delay in the accumulation of neurological symptoms in transgenic mice with beta amyloid pathology [102]. Generally, the methylation status of all the elements of presenilins' interactome may be suitable for future research on ageing and AD. Supplementing the above data, an important matter in the era of omics research is the use of appropriate computational and mathematical models. One example is weighted gene co-expression network analysis method (WGCNA), which by the use of large omics data may predict gene-gene, protein-protein, or gene-miRNA interaction nature [103]. In particular, the WGCNA method was used to organize gene expression data into a functionally significant structure, in order to indicate the modules of co-expressed genes and novel gene signatures associated with Alzheimer's disease [104].

Overall, ADs or PAs are systemic diseases based on the interplay of several cellular networks. Thus, it should be noted that conducting the research only on individual protein factors, as the studies on presenilins and processing of APP, is only a part of the holistic homeostatic insight on these pathological states and such comprehensive approach is still missing in the discussion. Due to wide-range nature of ageing and degeneration process, the conducted studies should be more non-deterministic, without a concrete causation and particular trigger (gene, protein pathway). The holistic approach should include the response to DNA repair with cell cycle and genome integrity checkpoints, proteostasis, unfolded protein response, protein-folding chaperone networks, ER-associated degradation/ubiquitin proteasome system, endolysosomal network, autophagy, inflammatory response and other stress-response networks. This can be accomplished by integration of various omics data and can be fulfilled when supported by latest methods and research approaches including next-generation sequencing, modern neuroimaging or high-throughput computational bioinformatic studies. Complexity

and multi-level nature of the network of genes, proteins, their interactomes and relationships with ageing-related disease processes present in both AD and PA have been reported in several recent review papers [94, 98, 105–107]. This and other reviews underline the importance of the integration of different biological data provided for the process of brain degeneration, in both PA and AD, and other neurodegeneration disorders with dementia.

8. Challenges of the future

The aim of the future will be to develop an accurate map of omic data of the ageing process. This is associated with the problem of collection of the samples for multiomics data from a human across lifespan. Second, the factors that can be a source of a noise in the omic data should be identified, including information on the ethnicity, personal immunological history or parameters of lifestyle (dietary habits, physical activity and microbiological status). Comprehensive of integrative interactomics of (epi)gene-protein-pathways axis would demand more advanced and consolidated computational, mathematical and bioinformatic tools. These methods should integrate the data obtained with a use of various methodological approaches and engines, from different biological range and integrate the statistical power for all of them. Further aspects, which require to be consolidated or demand additional computational approaches, are related to the source material (tissues and cells) used for omics analyses. These and other criteria must be met to be able to pinpoint the cause and prevent a decline in cognitive skills, so important in everyone's life.

9. Summary

Neurodegeneration in AD or PA is a multiparametrical process. Thus, there is a need of not only for an establishment of the most complete genetic background but also to pinpoint the functional implications of this knowledge. Despite strong efforts of the recent research, based mostly on modern technologies, including GWAS and WES, it is still a largely unknown domain. It is very likely that expanding the interactomes PS1 and PS2 will help to emerge the complex biological processes accompanying processing of many substrates of presenilins. The broad spectrum of γ -secretase substrates and interacting proteins has invoked the analogy to γ -secretase 'secretosome' or 'proteasome of the membrane'. The complexity of the interactome of presenilin 1 is implicated in a number of molecular functions, manifested in different cell components and implicated in a variety of biological processes, crucial for Alzheimer's disease and pathological ageing, and is depicted in a schematic presentation of this chapter (**Figure 1**). Additionally, it is important to take into account environmental factors, for example, psychological circumstances might affect gene expression profile via epigenetical mechanisms, and thus presenilins interacting network, with further functional implications. In conclusion, the understanding of existing genetic mechanisms together with presenilin functions leading to brain degeneration in AD or PA is crucial for better understanding of molecular bases of these pathologies and facing them in the future.

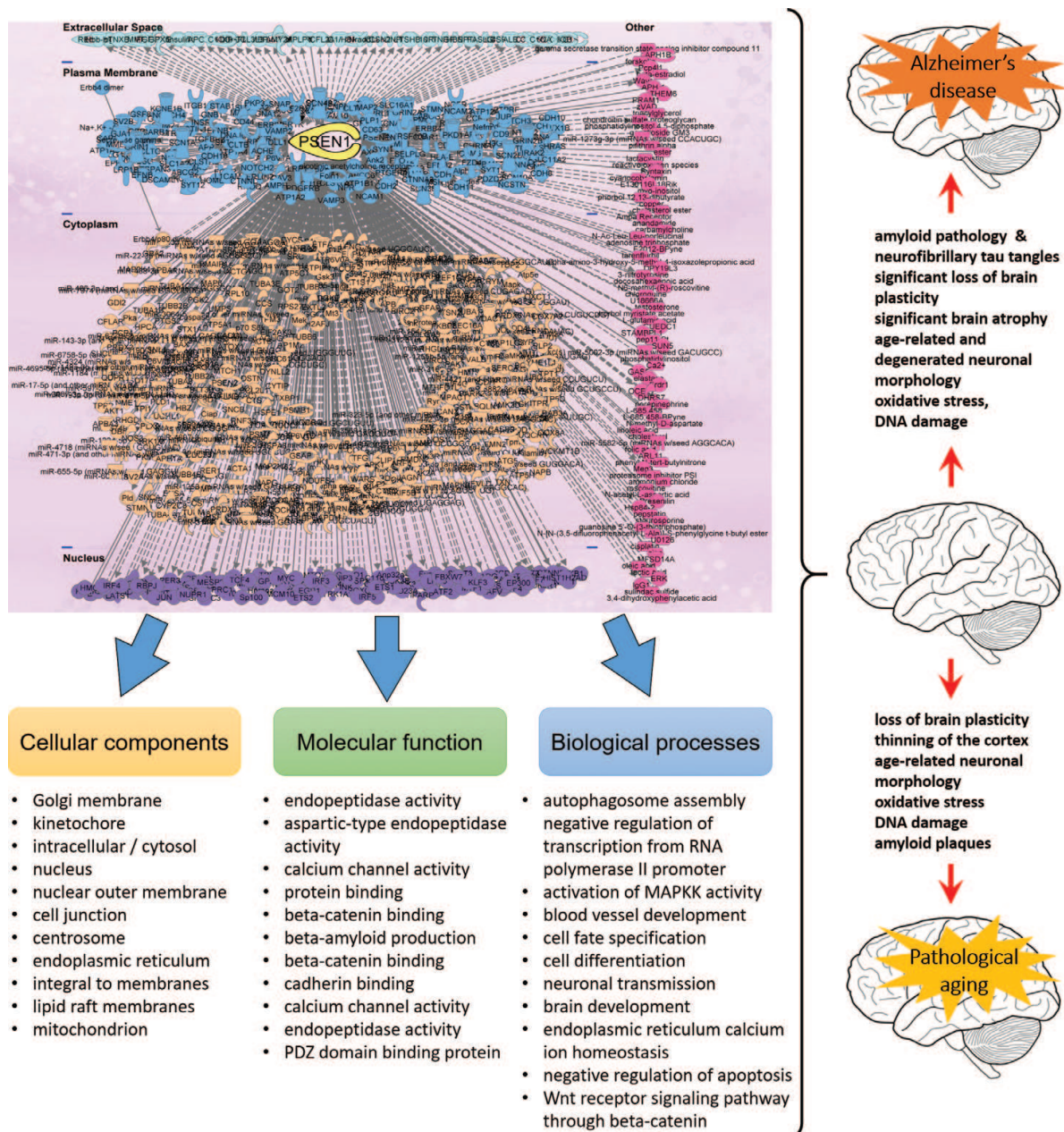


Figure 1. The interactome of presenilin 1 in Alzheimer's disease and in pathological ageing. Presenilin 1 interactome was generated using Ingenuity Pathway Analysis software (www.ingenuity.com). Presenilin 1 interactome is implicated in a number of molecular functions, cell components and biological processes of presenilin 1, according to GeneCards®: The Human Gene Database. Presenilin 1 interaction network with its functional consequences are crucial both for Alzheimer's disease and for pathological ageing brains.

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Author details

Michalina Maria Węzyk^{1,2*} and Cezary Żekanowski¹

*Address all correspondence to: mwezyk@imdik.pan.pl

1 Department of Neurodegenerative Disorders, Laboratory of Neurogenetics, Mossakowski Medical Research Centre Polish Academy of Sciences, Warsaw, Poland

2 Department of Neurology, Warsaw Medical University, Warsaw, Poland

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