

Transcriptional regulation of the presenilin-1 gene: implication in Alzheimer's disease

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1. ABSTRACT

Two (amyloid and presenilin) hypotheses have been proposed to explain the pathogenesis of Alzheimer's disease (AD). According to amyloid hypothesis, the main amyloid plaques which are hallmark of AD are generated by β - and γ -secretase mediated proteolytic processing of amyloid precursor protein (APP). The amyloid hypothesis does not adequately address the pathogenesis of the disease, however, since transgenic mice that express the pathologic mutations of the APP and presenilin-1 (PS1) genes produce amyloid plaques but fail to exhibit neurodegeneration and memory loss observed in AD patients. According to presenilin hypothesis, loss of essential functions of PS due

to decreased PS expression or mutations in the PS genes better explains the pathogenesis of AD. Recent studies have revealed that forebrain specific conditional knockouts of PS1 and PS2 genes (cPSKO) cause both neuronal degeneration and memory loss without evidence of formation of amyloid plaques. Another potential mechanism for the pathogenesis of AD may reside at the transcriptional regulation of the presenilin-1 gene. In this review, a detailed analysis of transcription factors that regulate PS1 transcription will be discussed. An in depth understanding of the regulatory mechanism of PS1 transcription can identify the targets that can potentially be used in therapeutic intervention of AD.

3. INTRODUCTION

Both the early-onset and the late-onset of Alzheimer's disease (FAD and AD respectively) affect millions of people throughout the world. The late onset of the disease is sporadic and affects people in the 6th or 7th decades of their lives (1). The early-onset of the disease is genetically linked and affects people between 3rd and 4th decades of their lives (1), and thus called familial AD or FAD. Mutations in the coding regions of genes encoding amyloid precursor protein (APP) (2,3), presenilin-1 (PS1) (4,5), and presenilin-2 (PS2) (4,6-8) have been shown to be the pathogenic cause of FAD. Most of the early-onset AD (FAD) is due to mutations in the coding region of the PS1 gene (4,5). Mutations in the promoter regions of the PS1 gene also appear to cause susceptibility to both AD and FAD (9). Conditional knockout of presenilins in the adult mouse brains leads to progressive memory loss and neurodegeneration in mice similar to AD pathology in humans (10). On the contrary, overproduction of amyloid β -peptide ($A\beta$) in transgenic mouse model system failed to produce neurodegeneration (11). These data suggest that loss of essential functions of presenilins could be the primary cause of dementia and neurodegeneration in AD without the production of amyloid plaques. PS1/PS2 is the catalytic subunit of γ -secretase (12). Mutations in PS1 or PS2 gene may cause the pathogenesis of FAD either by altering the proteolytic processing of β -amyloid precursor protein (APP) to produce $A\beta_{42}$ instead of normal $A\beta_{40}$ (13-16) or loss of essential functions of PS leading to neurodegeneration and memory loss (10,17). Therefore, PS1 gene regulation may play a crucial role in the development of FAD and AD. Covalent modifications of histone tails by acetylation control regulation of gene transcription (18-23). Ets transcription factors play a critical role in trans-activation of the PS1 gene (24,29). Co-activator p300 appears to interact with Ets transcription factors and co-activate PS1 transcription (25). Zinc finger protein ZNF237 (30) and chromodomain helicase DNA-binding protein CHD3 (31) interact with Ets transcription factor ERM and inhibit PS1 transcription and PS1 protein level. Since p300 has intrinsic histone acetyl transferase (HATs) activity CHD3 is a part of the histone deacetylase (HDACs) complex, acetylation of histones by p300 and deacetylation of histones by CHD3 may potentially play important roles in the regulation of PS1 expression and γ -secretase activity. Therefore, transcription factors that regulate PS1 expression may be potential drug targets for the treatment of AD.

3. DISCUSSION

3.1. Amyloid hypothesis of Alzheimer's disease and presenilin-1 protein

3.1.1. Amyloid hypothesis of Alzheimer's disease

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive decline in memory, judgment, ability to reason, and intellectual function (17). AD is also the most common cause of both neurodegeneration and dementia (17). Neuronal and synaptic loss is also an essential neuropathological feature common to AD (17). AD is

accompanied by wide range of neuropathological features including extracellular amyloid plaques and intra-cellular neurofibrillary tangles (32-40). The cause of AD is still very much unknown and no cure is available to treat these patients. AD afflicts approximately 5 millions American adults (1). More than 100,000 victims die annually due to complications of AD making it the fourth leading cause of death in adults after heart disease, cancer, and stroke (1). Complications associated with AD usually result in death within 10 years of onset. The baby boom generation, now in their middle age, will enter into their old age in the next few years, and the number of AD patients is projected to increase substantially. The health care cost to treat these patients will be astronomical.

Amyloid hypothesis of AD is based on the detection of cerebral cortical amyloid plaques consisting of 40- and 42-residue amyloid β -peptide ($A\beta_{40}$ and $A\beta_{42}$) which are derived from sequential proteolytic processing of amyloid precursor protein APP by β - and γ -secretase (33,35,36). Another feature of the AD pathology is the generation of neurofibrillary tangles due to hyperphosphorylation of tau protein (35,36,41). In the current review we will not focus on the roles of neurofibrillary tangles and tau phosphorylation that might be causative of AD.

3.1.2. Structure and topology of presenilin-1 (PS1) protein

PS1 and PS2 are integral membrane proteins localized mainly in the endoplasmic reticulum and, to a lesser extent, in the Golgi compartment (5,42). PS1 probably contains eight transmembrane domains (TM), with both the N- and C-terminal domains, as well as the large hydrophilic loop between TM6 and TM7, toward the cytoplasm (Figure 1) (43). PS1 is involved in a variety of physiological processes such as mammalian embryogenesis, CNS development, neuronal survival, intracellular cell signaling, cell death, and the pathogenesis of AD (44-48). The PS1 gene was originally discovered because of its pathological role in the development of presenile (onset before 65 years of age) Alzheimer's disease. Indeed, because of its critical role in AD, the gene was dubbed "presenilin".

3.1.3. PS1 is the catalytic subunit of the γ -secretase complex

The γ -secretase (Figure 1) is an unusual aspartyl protease required for the intramembranous cleavage of variety of type 1 integral membrane proteins including APP and Notch 1 receptor (32,33). Processing of Notch 1 by γ -secretase is essential for Notch signaling, a critical factor in vertebrate development, neurogenesis, as well as synaptic remodeling and plasticity in postmitotic neurons (33,49-51). The γ -secretase also plays a central role in the pathogenesis of AD, because the amyloid β -protein ($A\beta_{40}$) which forms plaques in the brains of AD patients, is generated by sequential cleavage of APP by β - and γ -secretases (Figure 2). The γ -secretase is an equimolecular complex of four noncovalently associated integral membrane proteins, PS1, nicastrin, Aph-1, and Pen-2 (Figure 2)(52,53). Mutation of either of two conserved

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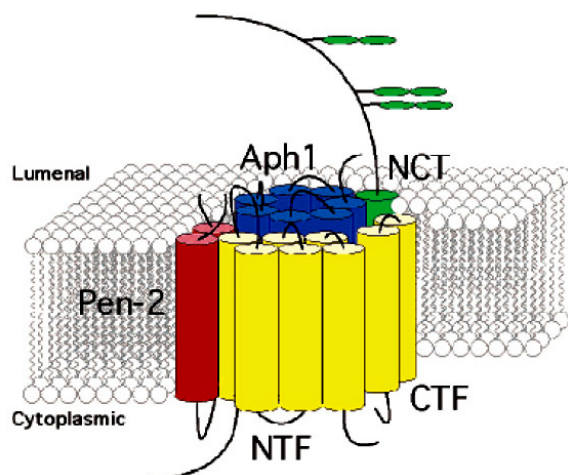


Figure 1. Schematic of the four candidate members of the γ -secretase complex. PS1 or PS2 contains two intramembrane aspartates that constitute the probable active sites. The membrane topology of Presenilin-1 (PS1) (yellow), nicastrin (NCT) (green), Aph-1 (blue), and Pen-2 (red) are also depicted. The $-NH_2$ (NTF) and $-COOH$ (CTF) terminal fragments of PS1 are marked (43)

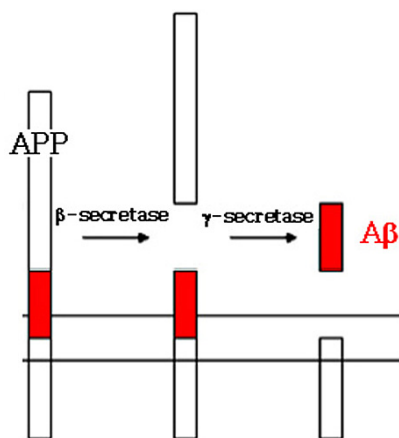


Figure 2. Proteolytic processing of APP by β - and γ -secretase. APP is first cleaved by β -secretase to produce APP-CTF β = C99. (red-white). Cleavage of APP-CTF β (or C99) by γ -secretase generates AICD (white) and A β peptide (red).

transmembrane aspartate residues in PS1, Asp257 (in TM6) and Asp385 (in TM7) substantially reduces A β production (Figure 2) (12). Therefore, transmembrane aspartate residues are critical for γ -secretase activity. The γ -secretase activity is greatly reduced and secretion of A β_{40} is strongly inhibited in brain cultures from living PS1^{-/-}embryos suggesting a direct role of PS1 in the amyloidogenic processing of APP (54).

3.1.4. Different risk factors in the pathogenesis of late-onset Alzheimer's disease (AD)

There are two types of AD; late onset and early onset. Late-onset AD (> 60 years) comprises the majority of AD cases. The apoE4 allele of the apolipoprotein E

(apoE) (55-57) and a common mutation in the gene encoding α_2 -macroglobulin (α_2M) (58) are associated with a significant proportion of cases with late-onset AD. Recently a gene called SORL1 (sortilin-related receptor) has been linked to the late onset or sporadic form of AD (59). The SORL1 gene is robustly associated with an increased risk of AD. The protein made by the SORL1 gene is called SORLA or LR11. The protein product SORLA of the SORL1 gene appears to regulate protein movements through the cell (59). Mutations in the SORL1 gene cause the reduction of its protein product SORLA which in turn increases the risk of developing AD. One possible mechanism is that lack of SORLA may direct the trafficking of APP to compartments in cells that contains enzymes to process APP to generate neurotoxic A β peptide which forms plaques to cause AD. If this hypothesis about the function of SORLA is proven to be right, this will identify the cause of AD and this will help identify and develop treatment for people at risk of AD.

3.1.5. PS1 gene mutations cause early-onset familial Alzheimer's disease (FAD): Early-onset familial AD or presenile AD

(onset at age 30-50 years) is an aggressive form of devastating memory disorder that strikes in middle age and is primarily inherited as an autosomal dominant trait (familial AD or FAD). Estimates of the proportion of AD cases that are genetically based have varied widely from as low as 10% to as high as 40 or 50% (5,8,37). Some investigators believe that almost all cases of AD will be shown eventually to have genetic determinants (8). Mutations within three genes have been found to cause FAD. (A) Point mutations in the β -amyloid precursor protein (APP) gene on chromosome 21 cause only 10% of all early-onset AD (2,3), and less than 0.1% of all AD cases. (B) Mutations in the PS2 gene are implicated in the pathogenesis of FAD (4,6,8). (C) 70% of all FAD cases are due to mutations in the coding region of the PS1 gene (4,5). More than 140 different mutations have been found within the coding region of the PS1 gene (heterozygous) (4).

3.1.6. PS1 gene mutations cause abnormal processing of β -amyloid precursor protein leading to early onset Alzheimer's disease (FAD)

The principal component of amyloid in senile plaques of AD patients is an ~ 4 kDa peptide A $\beta_{42/43}$ derived from APP (60-64). An altered APP processing has been proposed to result in generation of amyloidogenic protein fragments A $\beta_{42/43}$ instead of A β_{40} (Figure 2)(13,14). Overexpression of the FADPS1 gene in transgenic mice leads to increases in the cerebral production and/or deposition of amyloidogenic A $\beta_{42/43}$ peptides (14-16). Indeed significantly elevated levels of A $\beta_{42/43}$ were found in plasma and conditioned media of primary fibroblasts of patients with chromosome 14-associated FAD (14-16,65,66). Studies indicate that cultured neurons making just normal amounts of FADPS1 protein look healthy but are still more easily pushed into apoptosis by various forms of stress (67). Therefore, it may be the case that mutation of PS1 is not the critical event leading to FAD. Rather, it is the real quantity of mutated PS1 protein that may be the culprit. When mutated PS1 protein exceeds a critical

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threshold concentration, then FAD results. Hence downregulation of FAD-associated PS1 expression in neurons may potentially reduce the risk of early-onset of the disease. These results provide strong evidence for a direct link between altered proteolytic processing of APP and PS1 mutations that modify γ -secretase function causing early-onset FAD.

3.1.7. PS1 gene mutations are associated with increased levels of calcium in the endoplasmic reticulum in the brains of FAD patients

Two pathogenic mechanisms for PS1 mutations (FADPS1) that cause early onset familial Alzheimer's disease (FAD) have been proposed. One mechanism involves altered γ -secretase-mediated processing of amyloid precursor protein (APP) resulting in increased production of neurotoxic $A\beta_{1-42}$. Second mechanism is associated with increased levels of calcium in the endoplasmic reticulum (ER) (68). Increased calcium in ER leads to the enhancement of the intracellular Ca^{+2} levels due to release from ER causing neuronal apoptosis. Fluctuations of intracellular Ca^{+2} levels also produce highly consistent alterations in intracellular calcium signaling pathways, which include a potentiation of the phosphoinositide/calcium signaling cascade and deficits in capacitative calcium entry. Proteolytic fragment AICD generated by sequential processing of APP by β - and γ -secretase was found to rescue Ca^{+2} deficits present in APP^{-/-} cells (68). Blast search suggests that AICD may associate with other transcription factors (CP2/LS/LBP1) to form transcriptionally active complex and may regulate the expression of ER calcium ATPase which is responsible for transporting Ca^{+2} from cytosol to the lumen of the ER. Presenilin-1 (PS1) is the catalytic subunit of the γ -secretase complex. Pathologic mutations in the PS1 gene may enhance PS1/ γ -secretase activity resulting in increased production of AICD and enhancement of the intercellular Ca^{+2} levels.

3.2. Presenilin hypothesis of Alzheimer's disease

3.2.1. Decreased expression of presenilins causes neuronal apoptosis

There is a significant decrease in PS1 and PS2 content in neurons from brain areas adversely affected by late-onset Alzheimer's disease (69,70). Takami *et al.* provided convincing evidence that expression of PS1 mRNA is markedly decreased in the hippocampus of AD patients compared to non-demented controls (70). This reduction of PS1 mRNA was particularly marked in pathologically affected areas where numerous plaques and tangles existed. The above data indicate that decreased expression of the PS1 gene may lead to neuronal apoptosis causing Alzheimer's disease.

3.2.2. Certain mutations in the PS1 gene can cause neurodegenerative dementia without $A\beta$ accumulation

In contrast to AD, frontotemporal dementia (FTD) is a neurodegenerative disease without accumulation of $A\beta$ plaques in the brains of affected patients (17). PS1 mutations (L113P, G183V, and ins R352) have been identified to be present in families with FTD without amyloid pathology (17). Neuronal and synaptic loss is the

common pathological feature for both AD and FTD. Mouse models of AD in which mutated PS1 and APP are overexpressed to overproduce $A\beta$ peptide failed to produce neurodegeneration (11). On the contrary, conditional knockout of PS1 and PS2 in adult mouse brains ultimately leads to progressive neurodegeneration accompanied by loss of synapses, dendrites, and neurons, memory loss and tau hyperphosphorylation without the formation of amyloid plaques (10,17). These data support the hypothesis that loss or decreased of PS functions (either by mutations or deletion) leads to synaptic dysfunction, and altered signaling which can cause neuron degeneration, gliosis, and tau hyperphosphorylation. Thus these data support that loss of presenilin functions is a better model for the pathogenesis of AD than the amyloid model of AD.

3.2.3. A hypothetical mechanism by which loss of PS functions may cause neurodegenerative dementia without $A\beta$ accumulation

Conditional knockout of PS1 and PS2 in the adult cerebral cortex were carried out and PS expression was inhibited at 4 weeks of age and neurodegeneration was very prominent at the same time (10). By 9 months more than 25% of cortical neurons are lost. Neurodegeneration of these mice are preceded by memory loss, reduction in NMDA receptor mediated long term potentiation, diminished expression of CRE-dependent (cAMP response element-dependent) gene expression such as c-fos and BDNF gene expression (10). Transcription activator CREB (CRE-binding protein) binds to CRE and enhances the expression of genes containing CRE. Co-activator of CREB, called CBP (CREB-binding protein) interacts with CREB and co-activates target gene expression containing CRE. Expression of c-fos and BDNF genes are regulated by CREB and CBP (10). Studies of forebrain specific PS1^{-/-} PS2^{-/-} cKO postnatal mice suggest that expression of CREB, CBP, and their target genes (e.g. c-fos, BDNF) is drastically reduced confirming the role of presenilins in the expression of CRE-dependent genes and neurodegeneration. Data from these studies suggest that inhibition of CRE-dependent gene expression leads to neurodegeneration without $A\beta$ accumulation. PS cDKO mice have reduced long term potentiation (LTP) which is a measured of memory. LTP deficit in these mice reflects a potential reduction of NMDA receptor mediated response. Also, PS1 is involved in the transport of NMDA receptor subunits (NR1, NR2A, NR3A) and to the cell surface which is required for NMDA receptor mediated memory formation and LTP (10,71). Therefore, inhibition of PS function in these mice may hinder this transport process resulting in the loss of memory. Western blot analysis suggests that total cortical levels of NR1, NR2A, and NR2B are unchanged but the expression of NR1 and NR2A is drastically reduced synaptosome preparations of PS cDKO mice (10). Thus it appears that physical association of PS with NMDA receptor subunits are required for normal NMDA receptor mediated LTP and memory formation. CaMKII plays a central role in synaptic plasticity or LTP (10). NMDAR-mediated responses regulate the localization, levels of expression, and modulate the activity of CaMKII. Correlation of deficit in NMDAR responses and the reduction of CaMKII activity

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in PS cDKO mice confirm the roles of NMDAR and CaMKII to the impairments synaptic plasticity, learning, and memory in these mice (10). The major conclusion of the study of PS cDKO mice is that pathologic mutations in the PS genes may alter the functions of PSs similar to those of loss of function of PS and thus may cause disease by partial loss of PS functions.

3.2.4. Wild type PS1 but not M146L mutant PS1 activates CREB-binding protein CBP by a mechanism involving MAPK pathways

cAMP response elements (CRE) are present in the promoter of many neuronal genes including c-fos and BDNF genes (10). CRE-binding protein (CREB) binds to CRE and regulate target gene expression in response to cAMP-dependent pathway. The coactivator of CREB (called CREB-binding protein CBP) promotes transcriptional activation by linking DNA binding transcription factors with the basal transcription factors. We have previously discussed that inactivation of CREB and CBP by inactivation of PS functions leads to memory loss and neurodegeneration in mice (10). From these results it was hypothesized that pathogenic mutations in the PS1 gene may cause inactivation of CBP resulting in the pathogenesis of early onset *alzheimer's* disease. It was previously hypothesized that Notch is processed by PS-containing gamma secretase to produce Notch intracellular domain (NICD). NICD then migrates to the nucleus and associates with DNA binding transcription factor CBF-1 and activate the expression of the CBP gene which contains CBF-1 binding site. Loss of PS function inhibits Notch processing and generation of NICD leading to inactivation of CBP and repression of CRE-containing genes (10) that are involved in neuronal survival and formation of memory.

In a parallel investigation it was shown that wild type PS1 stimulates the transcriptional activity of CBP whereas PS1 M146L pathogenic mutant did not produce such an effect (72). This experimental finding supports the loss of function hypothesis due to pathogenic FAD mutations in the PS1 gene. The proposed mechanism by which PS1 regulates transcriptional activity of CBP is different from the mechanism proposed by Saura *et al* (10). It was shown that wild type PS1 activates PI3K, p38MAPK, and p42/p44 MAPK pathways which activates CBP by phosphorylation which is translocated to the nucleus to promote expression of CRE-containing genes (72). On the contrary PS1 M146L mutant fails to activate CBP and thus CBP can not be translocated to the nucleus to promote CRE-containing genes. Therefore, PS1 M146L mutant may have partial loss of function and may reduce the expression of CRE-dependent genes such as c-fos or BDNF resulting in memory loss and neurodegeneration. The mechanisms by which PS1 activates MAPK pathways remain to be determined.

3.3. Transcriptional regulation of the presenilin-1 gene

3.3.1. The PS1 gene is regulated in neurons

To date very little is known about the promoter structures and the transcriptional regulation of the PS2 gene (73). Most of the studies are focused on the

transcriptional regulation of the human PS1 gene. The PS1 gene is regulated during development (74), aging (75), and brain injury (76). PS1 gene expression is also upregulated during development and *in situ* hybridization studies of mouse embryos reveal a neuronal expression pattern of PS1 mRNA that overlaps with the expression of Notch homologues (75). There is a significant decrease in PS1 content in neurons from brain areas adversely affected by AD (70) and also during aging (74). Thus, PS1 gene is not only involved in AD pathology but also appears to regulate broader process of brain development and response to injury. PS1KO in postmitotic neurons causes impairments of memory followed by age-dependent neurodegeneration (10).

3.3.2. Ets transcription factors bind to several the proximal promoter elements of the human PS1 gene and activate PS1 transcription

Deletion mapping of the human PS1 promoter delineated the most active fragment from -118 to +178 in relation to the transcription start site in human neuroblastoma SK-N-SH cells (Figure 3) (28). However, the promoter appears to be utilized in alternative way in SK-N-SH and SH-SY5Y cells (28). Altering the Ets motif at -10 eliminates 80% of transcription in SK-N-SH cells whereas the same mutation has only minor effecting SH-SY5Y cells. Conversely, mutation on the Ets element at +90, which eliminates 70% of transcription in SH-SY5Y cells, has a lesser effect in SK-N-SH cells. In both cell types a promoter including mutations at both -10 and +90 Ets sites loses over 90% transcription activity indicating the crucial importance of these two Ets motifs. Several Ets factors that recognize specifically the -10 Ets motif by yeast one-hybrid selection including avian erythroblastosis virus E26 oncogene homologue 2 (Ets2), Ets-like gene 1 (Elk-1), Ets translocation variant 1 (ER81) and Ets related molecule (ERM) (26,27). Ets2, ER81, and ERM specifically bind to the -10 Ets element and transactivate PS1 transcription in transient transfection assay whereas Elk-1 inhibits PS1 transcription (26,27). It has also been shown that ERM specifically recognizes Ets motifs on the PS1 promoter located at -10 as well as +90, +129, and +165 and activates PS1 transcription with promoter fragments containing or not the -10 Ets sit (28).

3.3.3. p300 protein interacts with Ets transcription factor Ets2 and co-activates PS1 transcription

p300 protein is a global transcriptional co-activator of many eukaryotic genes. p300 is known to interact with Ets transcription factors Ets1 and Ets2. Ets1/Ets2 factor binds specifically to the -10 Ets element and activates PS1 transcription. p300 enhances the activation of PS1 transcription by Ets1 and Ets2 suggesting that p300 is a co-activator of the PS1 gene (25).

3.3.4. Zinc finger protein ZNF237 interact with ERM transcription factor and inhibit PS1 transcription

Using the C-terminal 415 amino acid of ERM as bait for yeast two hybrid selection in a human brain cDNA library two proteins were identified which interact with Ets transcription factor ERM (30,31). One of the interacting proteins was ZNF237 (30), a member of the

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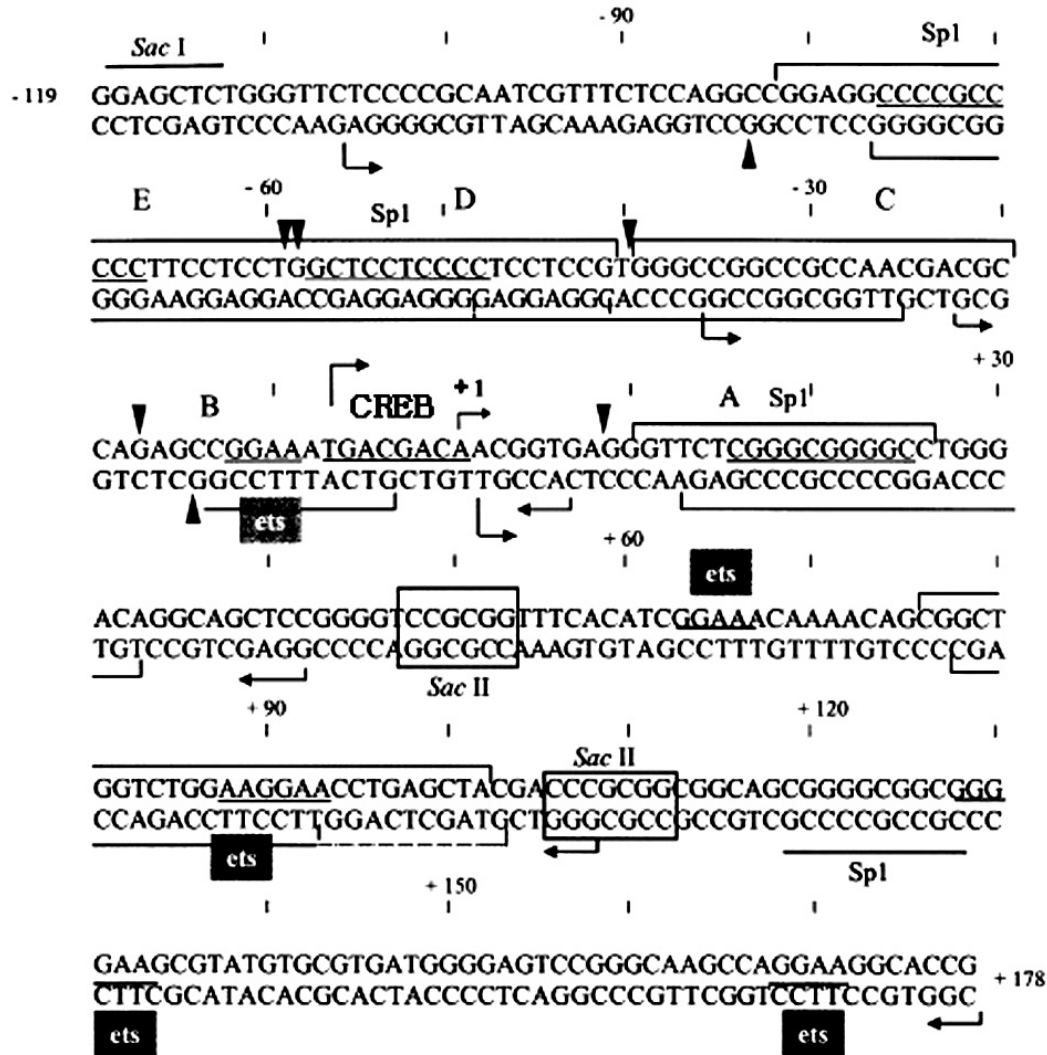


Figure 3. PS1 promoter. The sequences from -119 to +178 flanking the major transcription initiation site (+1) in sk-n-sh cells included in the PS1CAT reporter fusion vector are shown. The binding sites for known transcription factors Sp1 and Ets are indicated with brackets defined by footprinting with SK-N-SH cells (24) as well as site C which correspond to an unknown binding protein. Arrowheads indicate the position of DNase I hypersensitive sites observed in footprinting experiments. The Ets and Sp1 consensus motifs are underlined. Arrows indicate the end points of 5' or 3'-deletions. -10 and +90 Ets binding sites are important for PS1 transcription (24).

myeloproliferative and mental retardation motif (MYM) gene family (77). ZNF237 is widely expressed in different tissues in eukaryotes under several forms derived by alternative splicing, including a large 382 amino acid form containing a single MYM domain, and 2 shorter forms of 208 and 213 amino acids respectively that do not contain MYM domain. Both the 382 as well as the 208 amino acid forms are expressed in SK-N-SH cells but not in SH-SY5Y cells. Both these ZNF237 forms interact with ERM and repress the transcription of PS1 in SH-SY5Y cells. Both the C-terminal and N-terminal deletion indicate that the N-terminal 120 amino acid region of ZNF237 is required for interaction with ERM in yeast, and single amino acid mutations show that residues 112 and 114 of ZNF237 play an important role. The repression of transcription in SH-

SY5Y cells also appears to require the N-terminal portion of ZNF237 and was affected by mutations of the amino acid 112 of ZNF237 (30).

3.3.5. Chromodomain helicase DNA binding protein 3 (CHD3) interact with ERM transcription factor and inhibit PS1 transcription

The second protein identified by yeast two hybrid selection using the C-terminal 415 amino acid of ERM as bait is chromatin remodeling factor CHD3/ZFH (31). The clones contained the C-terminal region of CHD3 starting from amino acid 1676. This C-terminal fragment (amino acids 1676 -2000) repressed the transcription of the PS1 gene in transfection assays and PS1 protein expression from the endogenous gene in SH-SY5Y cells. In cells

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transfected with both CHD3 and ERM the activation of PS1 transcription by ERM was eliminated with increasing levels of CHD3. Progressive N-terminal deletions of CHD3 fragment (amino acids 1676 to 2000) indicated that sequences crucial for repression of PS1 as well as interactions with ERM in yeast 2-hybrid assays are located between amino acid 1862 and 1877. This was correlated by the effect of progressive C-terminal deletions of CHD3 which indicated that sequences required for repression of PS1 lie between amino acids 1955 and 1877. Similarly, deletion to amino acid 1889 eliminated binding in yeast 2-hybrid assays. Testing various shorter fragments of ERM as bait indicated that the region essential to bind CHD3/ZFH is contained in the amino acid region 96 to 349 which contains the central inhibitory DNA binding domain (CIDD) of ERM. N-terminal deletions of ERM indicated that residues between amino acids 200 and 343 are required for binding to CHD3 (1676-2000) and C-terminal deletions of ERM indicated that amino acids 279 to 299 are also required. Furthermore, data from chromatin immunoprecipitation (ChIP) indicate that CHD3/ZFH indeed interacts with the PS1 promoter *in vivo* (31).

3.3.5. Regulation of PS1 transcription by acetylation of histones

Gene expression can be affected by changes in chromatin structure and the packaging of DNA into nucleosomes (histone-DNA complex) (18-23). Each nucleosome comprises ~146 bp of DNA wrapped around a histone core (H2A-H2B-H3-H4)₂. The acetylation of lysine residues on histone tails by histone acetyl transferase (HATs) neutralizes their charges and decreases the affinity for DNA and thus facilitates transcription of genes located in these regions (18-23). On the contrary, deacetylation of these lysine residues by histone deacetylase (HDACs) restores high affinity of histones for DNA and therefore, can decrease the accessibility of genes to transcriptional machinery (18-23). In addition, the Swi/Snf class of proteins can cause ATP-dependent disruption of nucleosome structure by helicase activity at a promoter, and enhance the binding of transcription factors to their binding sites (18-23). Therefore, actions of HATs, HDACs, and Swi/Snf proteins lead to nucleosome movement, changes of chromatin conformation, and profound transcriptional activation (or repression) of a gene (18-23). Ets2, ER81, and ERM activate PS1 transcription (24-27) and p300 is a co-activator of Ets2 (25). Transcription factor ERM interacts with its co-repressor CHD3 in yeast two-hybrid selection assay (31). Since p300 has intrinsic HAT activity and CHD3 is a component of the histone deacetylase (HDACs) complex, chromatin remodeling by acetylation and deacetylation of histones may play a critical role for PS1 regulation. Transfection SH-SY5Y cells with CHD3 expression vector inhibits PS1 transcription and PS1 protein expression as well as increased recruitment of CHD3 into the PS1 promoter (31). These data suggest that chromatin remodeling and deacetylation of histones by CHD3-containing HDAC may play a crucial role in the repression of PS1 transcription. Therefore, HDAC inhibitors may potentially be used to augment PS1 expression and to treat neurodegenerative diseases including AD.

3.3.6. A mutation in the PS1 core promoter is associated with an increased risk of Alzheimer's disease

A mutation (-22C>T promoter polymorphism) in the PS1 core promoter has been shown to correlate with the increased risk of AD and FAD (9). This pathologic promoter mutation was discovered on the basis of the published *in vitro* results to show that Ets transcription factors play a critical role in PS1 transcription (24). Reporter assay shows a neuron-specific 2-fold decrease in promoter activity for the -22C risk allele (9). Therefore, homozygosity at -22C allele appears to cause decrease in PS1 expression in AD (9). The -22C>T mutation also affects the binding of Ets factor (s) at the -10Ets site (9) suggesting that regulation of PS1 transcription by Ets factors is critical for the pathogenesis of AD and FAD. This discovery suggests that regulation of PS1 transcription by Ets factors would play a critical role in the pathogenesis of AD.

3.3.7. Activated cAMP-response element-binding protein (CREB) regulates expression of human PS1 in SK-N-SH cells

In a separate studies, it was shown that a putative cAMP-response element (CRE) TGACGACA spanning the PS1 promoter sequence (-7 to +1) also controls the expression of the PS1 gene (Figure 3) (78). Electrophoretic mobility shift and antibody supershift assays were performed to show that this CRE binds to CRE-binding protein (CREB) upon stimulation of SK-N-SH neuroblastoma cells with NMDA (78). Stimulation of SK-N-SH cells with NMDA also resulted in activation of CREB (increased phosphorylation at ser-133) and increased PS1 reporter expression and PS1 protein level (78). Similarly treatment of SK-N-SH cells with brain derived neurotrophic factor (BDNF) activated CREB and also increased PS1 expression in a dose dependent manner (78). Activation of CREB by phosphorylation at ser-131 is mediated by MAP kinase pathway. It was demonstrated that constitutive expression of MEK resulted in activation of CREB and PS1 expression which can be blocked by treatment of SK-N-SH cells with MEK inhibitor U0126 (78). These data suggest that activation of NMDA receptor may activate CREB to enhance PS1 expression and neuronal function. This finding is contradictory to what is observed in PS cDKO mice study in which it was demonstrated that inhibition of PS functions lead to reduced transport of NMDAR subunits (NR1, NR2A), decreases activity of CaMKII, decreased expression of CREB, CBP, and CRE-containing genes (c-fos and BDNF), which are involved in neuronal survival, memory formation, and LTP (10).

4. IMPORTANCE IN DRUG DEVELOPMENT TARGETING PS1 TRANSCRIPTION

According to amyloid hypothesis, increased PS1/ γ -secretase activity due to overexpression of the FADPS1 gene would lead to increased production of A β ₄₂ and deposition of amyloid plaques in the brains of FAD patients. In this scenario, overexpression of ZNF237 and CHD3 may reduce amyloid burdens. This possibility could be tested using APP Tg model of AD in which Swedish

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mutation of APP has been overexpressed under the control of PDGF- β promoter (79). These APPTg mice develop A β ₄₂ plaques at the age of 6 months and have all the pathological features of AD (79). Roles of ZNF237 or CHD3 in the inhibition of PS1/ γ -secretase activity, reduction of A β ₄₂ and amyloid production can be tested by neuron-specific conditional expression of ZNF237 or CHD3 in the brains of APPTg mice. If it is demonstrated that ZNF237 and/or CHD3 reduces amyloid load in the brains of APPTg mice, small molecules that activate the transcription of ZNF237 or CHD3 can be developed to test their efficacy in APPTg mouse models of AD. Positive results may lead to use those small molecules in preclinical and clinical human trials for the treatment of AD and FAD.

On the other hand, according to presenilin hypothesis, loss of PS functions may cause neurodegeneration and memory loss in AD. In that event, stimulation of PS1 expression by HDAC inhibitors may potentially be used to treat AD patients (23).

5. CONCLUSION

This review provides a general understanding of two prevailing but contradictory amyloid and presenilin hypotheses which are thought to participate in the pathogenesis of Alzheimer's disease. Each of these hypothesis explains many features of the disease. One drawback of the presenilin hypothesis is that it is primarily based on the conditional PSKO mouse models that turn off the expression of presenilins (10). This observation suggests that transcriptional inhibition of PS genes may be based on decreased mRNA levels in AD patients. Although, consistent with this hypothesis, the levels of PS1 and PS2 mRNAs are reduced in the brains of AD patients, complete absence of gene expression has not been shown in any patient so far (70). Therefore, there is a need to better understand the mechanisms of transcriptional regulation of the PS1 gene and dissect the role of PS1 transcription in the pathogenesis of AD.

If amyloid hypothesis turn out to be correct, then drugs can be developed that target the transcription factor(s) that regulate PS1 transcription. Since PS1 has many potential targets (such as Notch signaling), it will be a challenge to regulate PS1 levels or activity in a manner that would be non-toxic. The targeting the PS1 gene would involve chronic partial (30-40%) inhibition of the PS1/ γ -secretase by augmenting HDAC (CHD3) activity or ZNF237 activity. By using statin drugs, this strategy has already been accomplished for another vital enzyme, HMGCoA reductase that lowers cholesterol but does not cause side effects. Although γ -secretase inhibitors may have potential side effects due to their ability to inhibit Notch signaling, some inhibitors are currently being studied for the treatment of AD. It is hoped that such strategies will slow and/or prevent familial AD (FAD) or AD without inducing significant side effects.

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7. REFERENCES

1. Alzheimer's disease facts and figures. Alzheimer's disease association, p1-7 (2007)
2. Karlinsky, H, G Vaula, J.L.Haines, J. Ridgley, C. Bergeron, M. Mortilla, R.G. Tupler, M.E. Percy, Y. Robitaille, N.E. Noldy, T. C. Yip, R.E. Tanzi, J.F. Gusella, R. Becker, J.M. Berg, M.McLachlan, D. R. Crapper & P.H. St. George-Hyslop: Molecular and prospective phenotypic characterization of a pedigree with familial Alzheimer's disease and a missense mutation in the codon 717 of the β -amyloid precursor protein gene. *Neurology* 42, 1445-1453 (1993)
3. Shoji M, T.E. Golde, J. Ghiso, T.T.Cheung, S. Estus, L.M. Shaffe, X-D. Cai, D. M. McKay, R. Tintner, B. Frangione & S. G.Younkin: Production of the Alzheimer amyloid beta protein by normal proteolytic processing. *Science* 258, 126-129 (1992)
4. Sherrington R, E.I. Rogaev, Y. Liang, E.A. Rogaeva, G. Levesque, M. Ikeda., H. Chi, C. Lin, G. Li, K. Holman, T. Tsuda, L. Mar, J-F. Foncin, A.C. Bruni, M.P. Montesi, S. Sorbi, I. Rainero, L. Pinessi, L. Nee, I. Chumacov, D. Pollen, A. Brookes, P. Sanseau, R.J. Polinsky, W. Wasco, H.A.R. Da Silva, J.L. Haines, M.A. Patricak-Vance, R.E. Tanzi, A.D. Roses, P.E. Fraser, J.M. Rommens & P.H. st George-Hyslop: Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 375, 754-760 (1995)
5. Haass C: Presenilins: Genes for life and death. *Neuron* 18, 687-690 (1997)
6. Levy-Lahad E, E.M. Wysman, E. Nemens, L. Andeson, K.A.B. Goddard, J.L. Weber, T.D. Bird & G.D. Schellenberg: Candidate gene for chromosome 1 familial Alzheimer's disease locus. *Science* 269, 973-977 (1995)
7. Rogaev E.I., R. Sherrington, G. Levesque, M. Ikeda, Y. Liang, H. Chi, C. Lin, K. Holman, T. Tsuda, L. Mar, S. Sorbal, B. Nacmias, S. Placentini, L. Amaducci, I. Chumakov, D. Cohen, L. Lennfelt, P.E. Fraser, J.M. Rommens & P.H. st George-Hyslop: Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* 376, 775-778 (1995)
8. Selkoe D. J: Translating cell biology into therapeutic advances in Alzheimer's disease. *Nature* 399 (suppl), A23-A31(1999)
9. Theuns J, J. Remacle, R. Killick, E. Corsmit, X. Vennekens, Y. Huylebroeck, M. Cruts & C. Van Broeckhoven: Alzheimer's-associated C alleles of the promoter polymorphism -22C>T causes a critical neuron-specific decrease of presenilin 1 expression. *Human Mol. Genetics* 12, 869-877(2003)
10. Saura C.A, S-Y. Choi, V. Beglopoulos, S. Malkani, D. Zhang., B.S. Shankaranarayana Rao, S. Chattarji, R.J.

Transcriptional regulation of the presenilin-1 gene

- Kelleher III, E.R. Kandel, K. Duff, A. Kirkwood & J. Shen: Loss of presenilin function causes impairments of memory and synaptic plasticity followed by age-dependent neurodegeneration. *Neuron* 42, 23-36 (2004).
11. Irizarry M.C, M. McNamara, K. Fedorchak, K. Hsiao & B.T. Hyman: *J Neuropathology Exp Neurol* 56: 965-973 (1997)
12. Wolfe M.S, W. Xia, B. L. Ostaszewski, T. S.Diehl, W. T.Kimberly & D. J Selkoe: Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and γ -secretase activity. *Nature* 398, 513-522 (1999)
13. Sisodia S.S, E.H. Koo, K. Beyreuther, A.Unterback & D.L.Price: Evidence that a beta-amyloid protein in Alzheimer's disease is not derived by normal processing. *Science* 248, 492-495 (1990)
14. Duff K, C. Eckman, C.Zehr, X. Yu., C-M.Prada, J.Perez-tur, M. Hutton, L. Buee, Y. Harigaya, D. Yager, D. Morgan, M.N. Gordon, L.Holcomb, L. Refolo, B. Zenk, J. Hardy & S. Younkin: Increased amyloid- β 42 (43) in brains of mice expressing presenilin 1. *Nature* 383, 710-712 (1996)
15. Borchelt D.R, G.Thinakaran, C.B.Eckman, M. K. Lee, F. Davenport, T. Ratovitsky, C-M. Prada, G. Kim, S. Seekins, D. Yager, H. H. Slunt, R. Wang, M. Seeger, A. I. Levey, S. E. Gandy, N. G. Copeland, N. A. Jenkins, D. L. Price, S. G. Younkin & S. S. Sisodia: Familial Alzheimer's disease-linked presenilin 1 variants elevate A β 1-42/1-40 ratio *in vitro* and *in vivo*. *Neuron* 17, 1005-1013 (1996)
16. Borchelt D.R, T.Ratovitski, J.Van Lare, M.K. Lee, V. Gonzales, N.A. Jenkins, N.G.,Copeland, D.L.Price & S.S. Sisodia: Accelerated amyloid deposition in the brains of transgenic mice coexpressing mutant presenilin 1 and amyloid precursor proteins. *Neuron* 19, 939-945 (1997)
17. Shen J & R.J. Kelleher III: The presenilin hypothesis of Alzheimer's disease: Evidence for a loss-of-function pathogenic mechanism. *Proc. Natl. Acad. Sci. USA* 104:403-409 (2007)
18. Khochbin S & H-Y. Kao: Histone deacetylase complexes: functional entities or molecular reservoirs. *FEBS Letters* 494, 141-144 (2001)
19. Narlikar G. J, H-Y. Fan & R.E. Kingston: Cooperation between complexes that regulate chromatin structure and transcription. *Cell* 108, 475-487 (2002)
20. Emerson B. M: Specificity of gene regulation. *Cell* 109, 267-270 (2002)
21. Naar A. M, B. D.Lemon & R. Tjian: Transcriptional coactivator complexes. *Annu. Rev. Biochem* 70, 475-501 (2001)
22. Tong J. K, C. A. Hassig, G. R. Schnitzler, R. E. Kingston & S. L: Schreiber. Chromatin deacetylation by an ATP-dependent nucleosome remodelling complex. *Nature* 395, 917-921 (1998)
23. Langley B, J.M. Gensert, M. F. Beal & R.R.Ratan: Remodeling chromatin and stress resistance in the central nervous system: Histone deacetylase inhibitors as novel and broadly effective neuroprotective agents. *Current Drug Targets-CNS & Neurological disorders* 4, 41-50 (2005)
24. Pastorcic M & H.K.Das: An upstream element containing an ETS binding site is crucial for transcription of the human presenilin-1 gene. *J. Biol. Chem* 274, 24297-24307 (1999)
25. Pastorcic M & H.K. Das: Regulation of transcription of the human presenilin-1 gene by Ets transcription factors and the p53 protooncogene. *J. Biol. Chem* 275, 34938-34945 (2000)
26. Pastorcic M & H.K. Das: Ets transcription factors ER81 and Elk1 Regulate the transcription of the human presenilin 1 gene promoter. *Mol. Brain. Res* 113, 57-66 (2003)
27. Pastorcic M & H.K. Das: An abbreviated procedure for the cloning and identification of Ets transcription factors regulating the expression of the human presenilin 1 gene. *Brain. Res. Protocols* 12, 35-40 (2003)
28. Pastorcic M & H.K. Das: Alternative initiation of transcription of the human presenilin 1 gene in SH-SY5Y and SK-N-SH cells: the role of Ets factors in the regulation of presenilin 1. *Eur. J. Biochem* 271, 4485-4494 (2004)
29. Mitsuda N, A.D. Roses & M.P.Vitek: Transcriptional regulation of the mouse presenilin-1 gene. *J. Biol. Chem* 272, 23489-23497 (1997)
30. Pastorcic M & H.K. Das: Analysis of transcriptional modulation of the presenilin 1 gene promoter by ZNF237, a candidate binding partner of the Ets transcription factor ERM. *Brain Res* 1128, 21-32 (2007)
31. Pastorcic M & H.K. Das: The C-terminal region of CHD3/ZFH interacts with the CIDDD region of the Ets transcription factor ERM and represses transcription of the human presenilin 1 gene. *FEBS J* 274, 1434-1448 (2007)
32. Annaert W & B. De Strooper: A cell biological perspective on Alzheimer's disease. *Annu. Rev. Cell Dev. Biol* 18, 25-51 (2002)
33. Selkoe D & R. Koplan: Notch and presenilin: regulated intramembrane proteolysis links development and degeneration. *Annu. Rev. Neurosci* 26, 565-597 (2003)
34. Arendt T, M.K. Bruckner, H. J. Gertz & L. Marcova: Cortical distribution of neurofibrillary tangles in Alzheimer's disease matches the pattern of neurons that retain their capacity of plastic remodeling in the adult brain. *Neuroscience* 83, 991-1002 (1998)
35. Das H.K & H. Lal: Pathogenesis of Alzheimer's disease: current status on apolipoprotein E4 gene research. *Rev. Neurosciences* 7, 277-283 (1996)

Transcriptional regulation of the presenilin-1 gene

36. Das H.K & H. Lal: Genes implicated in the pathogenesis of Alzheimer's disease. *Frontiers in Biosciences* 2, 253-259 (1997)
37. R. Katzman : Alzheimer's disease. *N. Eng. J. Med* 314, 964-967 (1986)
38. Price D. L: New perspectives on Alzheimer's disease. *Annu. Rev. Neurosci* 9, 489-512 (1986)
39. Muller-Hill B & K. Beyreuther: Molecular biology of Alzheimer's disease. *Annu. Rev. Biochem* 58, 287-307 (1989)
40. Blessed G, B.E. Tomlinson & R. Roth: The association between quantitative measures of dementia and senile changes in the cerebral gray matter of elderly subjects. *Brit. J. Psychiatry* 114, 797-811 (1968)
41. Roush W: Protein studies try to puzzle out Alzheimer's tangles. *Science* 267, 793-794 (1995)
42. Doan A, G. Thinakaran, D.R Borchelt, H. H Slunt, T. Ratovitsky, M.Podlisy, D. J Selkoe, M. Seeger, S. E Gandy, D. Price S & Sisodia: Protein topology of presenilin1. *Neuron* 17, 1023-1030 (1996)
43. Fraering, P. C, M. J. LaVoie, W. Ye, B. L. Ostaszewski, W. T. Kimberly, D. J. Selkoe & M. S. Wolfe: Detergent-dependent dissociation of active gamma-secretase reveals an interaction between Pen-2 and PS1-NTF and offers a model for subunit organization within the complex. *Biochemistry* 43, 323-333 (2004).
44. Price D.L & S.S. Sisodia: Mutant genes in familial Alzheimer's disease and transgenic models. *Annu. Rev. Neurosci* 21, 479-505 (1998)
45. Wong P.C, H. Zheng, H. Chen, M. W. Becher, D.J.S.Sirinathsinghji, M.E. Thumbauer, H.Y. Chen., D.L. Price, L.H.T.Van der Ploeg & S.S. Sisodia: Presenilin 1 is required for Notch 1 and Dll 1 expression in the paraxial mesoderm. *Nature* 387, 288-291(1997)
46. Levitan D, T.G. Doyle, D. Brousseau, M.K. Lee, G. Thinakaran, H.H. Slunts, S.S. Sisodia & I. Greenwald: Assessment of normal and mutant human presenilin function in *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. USA* 93, 14940-14944 (1996)
47. Shen J, R.T. Bronson, D.F. Chen, W. Xia, D.J. Selkoe & S. Tonegawa: Skeletal and CNS defects in Presenilin-1 deficient Mice. *Cell* 89, 629-639 (1997)
48. Davis J.A, S. Naruse, H. Chen, C. Eckman, S. Younkin, D.L. Price, D.R. Borchelt, S.S. Sisodia & P.C. Wong: An Alzheimer's disease-linked PS1 variant rescues the developmental abnormalities of PS1-deficient embryos. *Neuron* 20, 603-609 (1998)
49. Artavanis-Tsakonas S, M.D. Rand & R. J. Lake: Notch signaling: cell fate control and signal integration in development. *Science* 284, 770-776 (1999)
50. Berezovska O, P. McLean, R. Knowles, M. Frosh, Lu F.M., S.E. Lux & B.T: Hyman. Notch 1 inhibits neurite outgrowth in postmitotic primary neurons. *Neuroscience* 93, 433-439 (1999)
51. Berezovska O, M. Q. Xi & B.T: Hyman. Notch is expressed in adult brain, is coexpressed with presenilin-1 and is altered in Alzheimer's disease. *J. Neuropathol & Neurol* 57, 738-795 (1998)
52. De Strooper B: Aph-1, Pen-2, and nicastrin with presenilin generate an active γ -secretase complex. *Neuron* 38, 9-12 (2003)
53. Kimberly W.T, M. J. LaVoie, B.L. Ostaszewski, W. Ye, M.S. Wolfe & D.J. Selko: γ -secretase is a membrane protein complex composed of presenilin, nicastrin, aph-1, and pen-2. *Proc. Natl. Acad. Sci. USA* 100, 6382-6387(2003)
54. De Strooper B, P. Saftig, K. Craessaerts, H. Vandersticheles, G. Guhde, W. Annaert, K.V. Figura & F. Van Leuven: Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein. *Nature* 391, 387-390 (1998)
55. Corder E.H, A.M. Saunders, W.J. Strittmatter, D.E. Schmechel, P.C. Gaskell, G.W. Small, A.D. Roses, J.L. Hainse & M. A. Pericak-Vance: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 261, 921-923 (1993)
56. Rebeck G.W, J.S. Reiter, D.K. Strickland & B.T. Hyman: Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptors interactions. *Neuron* 11, 575-580 (1993)
57. Strittmatter W.J, A.M. Saunders, D. Schmechel, M. Pericak-Vance, J. Enghild, G.S. Salvesen & A.D: Roses. Apolipoprotein E: high-avidity binding to beta amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc. Natl. Acad. Sci. USA* 90 (5), 1977-1981 (1993)
58. Blacker D, M.A. Wilcox & N.M. Laird: Alpha-2 macroglobulin is genetically associated with Alzheimer's disease. *Nat. Genet* 19, 557-360 (1998)
59. Rogueva E, Y. Meng, J. H. Lee, Y. Gu, T. Kawarai, F. Zou, T. Katayama, C.T Baldwin, R. Cheng, H. Hasegawa, F. Chen, N. Shibata, K. L Lunetta, R. Pardossi-Piquard, C. Bohm, Y. Wakutani, L. A. Cupples, K. T. Cuenco, R. C. Green, L. Pinessi, I. Rainero, S. Sorbi, A. Bruni, R. Duara, R. P. Friedland, R.Inzelberg, W. Hampe, H. Bujo, Y-Q, O. M. Andersen, T. E. Willnow, N. Graff-Radford, R. C. Petersen, D. Dickson, S. D. Der, P. E. Fraser, G. Schmitt-Ulms, S. Younkin, R. Mayeux, L. A. Farrer & P.H. St George-Hyslop: The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nat.Genet* 39 (2), 168-177 (2007)
60. Selkoe D. J: Biochemistry of altered brain proteins in Alzheimer's disease. *Annu. Rev. Neurosci* 12, 463-490 (1989)

Transcriptional regulation of the presenilin-1 gene

61. Masters C.L, G. Simms, N.A. Weinman, G. Multhaup, B. L. McDonald & K. Beyreuther: Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc. Natl. Acad. Sci. USA* 82, 4245-4249 (1985)
62. Kang J, H.G. Lemaire, A. Unterback, J.M. Salbaum, C. L. Masters, K.-H. Grzeschik, G. K. Multhaup, K. Beyreuther & B. Muller-Hill: The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. *Nature* 325, 733-736 (1987)
63. Tanzi R.E, J.F. Gusella, P.C. Watkina, G.A. Bruns, P. St. George-Hyslop, M.L. Van Keuren, D. Patterson, S. Pagan, D.M. Kurntt & R.L. Neve: Amyloid β protein gene: cDNA, mRNA distribution and genetic linkage near the Alzheimer's locus. *Science* 235, 880-884 (1987)
64. Goldgabar D, M.I. Lerman, O.W. McBride, U. Saffiotti & D.C. Gajdusek: Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease. *Science* 235, 877-880 (1987)
65. Scheuner D, C. Eckman, M. Jensen, X. Song, M. Citron N. Suzuki, T.D. Bird, J. Hardy, M. Hutton, W. Kukull, E. Larson L. Levy-Lahad, M. Viitanen, E. Peskind, P. Poorkaj, G. Schellenberg, R. Tanz, W. Wasco, L. Lannfelt, D. Selkoe & S. Younkin: Secreted amyloid β -protein similar to senile plaques of Alzheimer's disease is increased *in vivo* by presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. *Nat. Med* 2, 864-870 (1996)
66. Mehta N.D, L.M. Refolo, C. Eckman, S. Sanders, D. Yager, J. Perez-Tur, S. Younkin, K. Duff, J. Hardy & M. Hutton: Increased A β 42(43) from cell lines expressing presenilin 1 mutations. *Ann. Neurology* 43, 256-258 (1998)
67. M. Barinaga: Is apoptosis key in Alzheimer's disease? *Science* 281, 1303-1304 (1998)
68. Leissring A.M, P.M. Murphy & M.F. LaFerla: A physiologic signaling for the γ -secretase-derived intracellular fragment of APP. *Proc. Natl. Acad. Sci. USA* 99, 4697-4702 (2002)
69. McMillian P, J. Leverenz, P. Poorkaj, G. Schellenberg & D. Dorsa: Neuronal expression of STM2 and mRNA in human brain is reduced in Alzheimer's disease. *J. Histochem. Cytochem* 44, 1215-1222 (1996)
70. Takami K, K. Terai, A. Matsuo, D. Walker & P. McGeer: Expression of presenilin-1 and -2 mRNAs in rat and Alzheimer's disease brains. *Brain Res* 748, 22-130 (1997)
71. Frotini M.E: γ -secretase-mediated proteolysis in cell-surface-receptor signaling. *Nat. Rev. Mol. Cell Bio* 3, 673-684 (2002)
72. Francis Y.I, A. Stephanou & D.S.Latchman: CREB-binding protein activation by presenilin 1 but not by its M146L mutant. *Neuroreport* 9:917-921 (2006)
73. Pennypacker K.R, R. Fuldner, R. Xu, H. Hernandez, D. Dawbarn, N. Mehta, J. Perez-Tur, M. Baker & M. Hutton: Cloning and characterization of the presenilin-2 gene promoter. *Mol Brain. Res* 56, 57-65 (1998)
74. Hartman H, J. Busciglio, K. Bauman, M. Staufenbiel & B. Yankner: Developmental regulation of presenilin-1 processing in the brain suggests a role in neuronal differentiation. *J. Biol. Chem* 272, 14505-14508 (1997)
75. Lee M.K, H.H. Slunt, L. J. Martin, G. Thinakaran, G. Kim G., S.E. Grandy, M. Seeger, E. Koo, D. Price & S. Sisodia: Expression of presenilin 1 and presenilin-2 (PS-1 and PS-2) in human and murine tissues. *J. Neurosci* 16, 7513-7525 (1996)
76. Cribbs D.H, L.S. Chen, C.W. Cotman, & F.M. LaFerla. Injury induces presenilin-1 expression in mouse brain. *Neuroreport* 7, 1773-1776 (1996)
77. Sohal J, A. Reiter, J.M. Goldman & N.C.P: Cross. Cloning of ZNF237, a novel member of MYM gene family that maps to human chromosome 13q11-q12. *Cytogenet Cell Genet* 89, 24-28 (2000)
78. Mitsuda N, N. Ohbutaka, M. Tamatani, Y-D. Lee, M. Taniguchi, K. Namikawa, H. Kiyama, A. Yamaguchi, N. Sato, K. Sakata, T. Ogihara, M.P. Vitek & M. Tohyama: Activated cAMP-response element-binding protein regulates neuronal expression of presenilin-1. *J. Biol. Chem.* 276, 9688-9698 (2001)
79. Mucke L, E. Masliah, G-Q Yu, M. Mallory, E. M. Rockenstein, G. Tatsuno, K. Hu, D. Kholodenko, K. Johnson-Wood & L. McConlogue: High-level neuronal expression of abeta 1-42 in wild type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. *J. Neuroscience* 20, 4050-4058 (2000)

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