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Transcriptional regulation and its misregulation in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by loss of memory and cognitive function. A key neuropathological event in AD is the accumulation of amyloid-β (Aβ) peptide. The production and clearance of Aβ in the brain are regulated by a large group of genes. The expression levels of these genes must be fine-tuned in the brain to keep Aβ at a balanced amount under physiological condition. Misregulation of AD genes has been found to either increase AD risk or accelerate the disease progression. In recent years, important progress has been made in uncovering the regulatory elements and transcriptional factors that guide the expression of these genes. In this review, we describe the mechanisms of transcriptional regulation for the known AD genes and the misregualtion that leads to AD susceptibility.

Keywords: Alzheimer's disease, Transcription factors, Transcriptional regulatory element, Polymorphism, Amyloid-β

Introduction

Alzheimer's disease (AD) is an age-associated neurodegenerative disease and is the most common form of dementia in the elderly. Like many other geriatric disorders, AD appears to be multifactorial in its origin. Mounting evidence from genetic, pathological, and functional studies has shown accumulation of amyloid-β (Aβ) peptide in the aging brain [1,2]. Aβ aggregates in the forms of soluble Aβ oligomers and amyloid plaques trigger numerous pathophysiological changes that ultimately lead to cognitive dysfunction [3-5]. Aβ is a 40–42 amino-acid peptide that is generated through multiple proteolytic cleavages of the amyloid-β protein precursor (APP) [6]. The 'amyloid hypothesis' postulates Aβ as the common initiating factor in AD pathogenesis and thus places Aβ as the hot research focus in the past two decades [2]. Emerging evidences have indicated that an imbalance between production and clearance of Aβ in the brain leads to AD pathogenesis [3]. A large group of genes have been described to affect Aβ generation or clearance, which are part of the 'AD genes'.

Although it is clear that expression levels of AD genes are important in AD etiology, much remains unknown about their specific regulation [7]. Studying the regulatory elements of disease genes and their corresponding transcription factors is therefore critically important for elucidation of the disease processes [8]. This review will discuss the mechanisms of transcriptional regulation for AD genes, and the misregulation that leads to AD susceptibility.

Transcription regulation of *BACE1*

Aβ is derived from sequential cleavage of APP by β- and γ-secretase [9]. The initiation of Aβ production by BACE1 and the disease-associated increase of BACE1 level places BACE1 in the central role of AD pathogenesis [10-13]. Numerous efforts have been devoted to inhibiting BACE1 expression and activity to reduce Aβ production and its associated neuronal toxicity [14]. BACE1 is an aspartyl protease which cleaves APP at the known β-secretase sites of Asp + 1 and Glu + 11 of Aβ [15]. *BACE1* knockout mice do not produce Aβ and are free from AD-associated pathologies including memory deficits and neuronal loss [16,17]. However, detailed studies revealed specific behavioral and physiological alterations in the complete absence of BACE1 [18-20]. It was suggested that non-APP substrates that are subjected to BACE1 cleavage might be important for these specific behavioral and functional changes in *BACE1*-deficient mice [9].

The *BACE1* gene spans about 30 kilobases (kb) on chromosome 11q23.2 and includes nine exons [14]. Ever since it was first cloned in 2003, the *BACE1* gene promoter

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has attracted extensive studies [14,21]. This promoter lacks the typical CAAT and TATA boxes but has a very high GC content at its proximal region [21]. The first 600 bp of the promoter is highly conserved amongst rat, mouse and human, suggesting that this region contains important regulatory elements which modulate *BACE1* transcriptional activity [21]. A large amount of evidence shows that the *BACE1* promoter contains multiple transcription factor-binding sites and is typical of an inducible expression [14,21,22]. A number of transcription factors have been suggested to control *BACE1* transcription, including specificity protein 1 (SP1), NF-κB, hypoxia inducible factor 1α (HIF-1α), and peroxisome proliferator-activated receptor-gamma (PPAR γ), amongst others.

Sp1 belongs to the Sp/KLF (Specificity protein/Krüppel-like factor) family and is amongst the first transcription factor identified to regulate *BACE1* gene expression [23,24]. Deletion analysis of *BACE1* promoter and the gel shifting assay demonstrated the functional binding site for Sp1 on the *BACE1* promoter. Subsequently, Sp1 over-expression potentiated the activity of the wild-type, but not of the Sp1-binding-site-mutant *BACE1* promoter, demonstrating an activator function for Sp1 in *BACE1* expression. Furthermore, the lack of endogenous Sp1 protein in Sp1-knockout cells markedly reduces *BACE1* promoter activity. These results clearly show that Sp1 modulates the endogenous *BACE1* expression [24]. The crucial role of Sp1 in regulation of *BACE1* expression was supported by different experimental approaches. Mithramycin A, which inhibits Sp1 binding to DNA, reduced *BACE1* expression in a dose-dependent manner [24,25]. 12/15-Lipoxygenase (12/15-LO), an enzyme widely distributed in the central nervous system, elevated the levels of *BACE1* mRNA and protein through a Sp1-mediated transcription control [26]. Considering the activation role of Sp1 for *BACE1* expression, future studies are need to illustrate the spatial and temporal expression patterns, and the transcriptional activity of Sp1 in distinct cell types of the brain. Importantly, Sp1 is known to interact with NF-kB which also regulates *BACE1* expression level, it remains to be determined whether they regulate *BACE1* gene expression in a synergistic manner [27,28].

NF-κB is a unique transcription factor that regulates *BACE1* transcription in a cell type-specific manner [29]. A detailed analysis using *BACE1* promoter constructs revealed that NF-κB acts as a repressor for *BACE1* transcription in differentiated neuronal cultures and non-activated glial cultures, but as an activator for *BACE1* transcription in activated astrocytic and Aβ-exposed neuronal cultures. The effects of NF-κB on the regulation of *BACE1* transcription are mediated by the binding of distinct NF-κB subunits. The p50/c-Rel heterodimer acts as repressor, while p50/p65, p52/c-Rel or p52/p65 acts as activator when binding to *BACE1* promoter-specific NF-

κB site. Recently, it was found that NF-κB differently regulates Aβ production under physiological and supra-physiological Aβ concentrations by modulating secretase expression [30]. Under physiological conditions, NF-κB lowers the transcriptional activity of *BACE1* promoter and triggers a repressive effect on Aβ production. However, NF-κB activates the transcription of *BACE1* promoter and enhances Aβ production under pathological context. Thus, using compounds to modulate *BACE1* expression based on NF-κB might lead to different outcomes under different conditions.

HIF-1 is a hetero-dimeric transcription factor composed of an oxygen-regulated alpha-subunit (HIF1α) and a constitutively expressed and stable beta-subunit (HIF1β) [31]. Under hypoxic conditions, HIF-1 binds to a hypoxia-responsive element (HRE) on a target gene promoter and activates gene expression [32]. A functional HRE was identified in human and mouse *BACE1* gene promoter [33,34]. Indeed, hypoxia augments β-secretase cleavage of APP by increasing *BACE1* gene transcription both in vivo and in vitro. The effect of hypoxia on *BACE1* expression is presumably mediated by HIF-1α. Over-expression of HIF-1α increased *BACE1* mRNA and protein levels, whereas down-regulation of HIF-1α reduced the level of *BACE1* expression. Consistent with these results, *BACE1* expression was reduced in the hippocampus and the cortex of HIF-1α conditional knock-out mice [34]. Additionally, hypoxia treatment markedly increased Aβ deposition and neuritic plaque formation and potentiated the memory deficit in Swedish mutant APP transgenic mice [33]. Recently, it was shown that hypoxia up-regulates *BACE1* expression through two distinct mechanisms: an early release of reactive oxygen species from mitochondria and a late activation of HIF-1α [35]. Interestingly, salidroside, which has long been used in traditional Tibetan medicine to relieve high altitude sickness, is able to attenuate Aβ accumulation via HIF-1α-mediated reduction of *BACE1* expression [36]. The link between hypoxia and *BACE1* expression provides a molecular mechanism for increased incidence of AD following cerebral ischemic and stroke injuries.

Peroxisome proliferator-activated receptor-gamma (PPARγ) is a ligand-activated nuclear transcription factor that has two isoforms, PPARγ1 and PPARγ2 [37,38]. These isoforms are produced by alternative splicing of the same gene. PPARγ can form heterodimers with retinoid X receptors (RXR) and binds to PPAR-responsive element (PPRE) upon ligand activation [39]. The *BACE1* gene promoter also contains PPRE and mutagenesis of the PPRE increased *BACE1* gene promoter activity by abolishing PPARγ binding to PPRE [40]. Over-expression of PPARγ has been shown to reduce *BACE1* gene promoter activity. These results suggest a repressive role of PPARγ on *BACE1* expression. Interestingly, brain extracts from

AD patients showed that both PPARγ levels and binding to PPRE on the *BACE1* gene promoter was decreased [40]. Pro-inflammatory cytokines decrease PPARγ mRNA level and this effect was suppressed by non-steroidal anti-inflammatory drugs (NSAIDs). Intriguingly, NSAIDs were shown to modulate *BACE1* transcription by repressing its promoter activity specifically through PPARγ [40]. Indeed, epidemiological evidence suggests that a strong inflammatory reaction is present in AD brains and long-term treatments with NSAIDs decrease the risk for AD [41]. PPARγ could be herein a major regulatory factor for modulating inflammation. The activation of PPARγ by agonists such as certain NSAIDs could open a prospective avenue for AD therapy.

Transcription regulation of *APOE*

Apolipoprotein E (ApoE) is a major cholesterol carrier in the brain [42,43]. ApoE is primarily produced by astrocytes and its function is to deliver lipids to neurons through the binding of cell surface ApoE receptors [44]. Human ApoE exists as three polymorphic alleles: ε2, ε3 and ε4 [43]. These three isoforms differ from each other by a single amino acid, resulting in different protein structures, lipid association and receptor binding [45-47]. The ε4 allele of the ApoE is the strongest genetic risk factor for late-onset AD (LOAD) [48]. Individuals with one ε4 allele are 3–4 times more likely to develop AD than those without ε4 allele [49]. Interestingly, the rare ε2 allele has a protective effect against AD compared with the ε3 allele [50].

In addition to the polymorphisms at the ε2/ε3/ε4 locus, changes in *APOE* expression level have been reported to be associated with AD, although the results remain controversial [51]. ApoE levels have been found to be increased in the cerebrospinal fluid (CSF), plasma and frontal cortex of AD patients [52-54]. However, other studies have observed either no change or a decrease in the ApoE levels of AD patients [55-58]. Such discrepancies may be related to confounding factors interfering with sample handling and/or analyses, of which remains to be clarified. Indeed, one study pinpointed that the hydrophobic character of ApoE resulted in adsorption to different types of test tubes commonly used for collection of CSF at lumbar puncture, resulting in falsely low levels [58]. More recently, two groups showed consistent results that reducing human ApoE level attenuates amyloid deposition in mutant human APP transgenic mouse model, regardless of isoform status [59,60]. Thus, overall *APOE* expression level plays an important role in AD pathology, although the exact correlation remains controversial.

APOE expression is regulated by nutritional, developmental and hormonal factors which bind to its proximal promoter region [61-63]. In contrast to *BACE1*, the 5'-flanking sequence of *APOE* harbors a functional TATA box [64]. Multiple cis-acting positive and negative regulatory elements have been mapped to the 5'-flanking sequence of *APOE*, including AP-2, PPARγ and liver X receptor (LXR) [65-68].

AP-2 is an astrocyte-associated transcription factor whose expression can be strongly and rapidly induced by cyclic AMP (cAMP) [69]. Retinoic acid (RA) is also known to regulate the transcriptional activity of *AP-2* gene [70]. Interestingly, the activity of the proximal *APOE* promoter in astrocytes is up-regulated by cAMP and RA synergistically [65]. Sequence analysis and footprinting technique revealed the existence of two binding sites for AP-2 in the *APOE* promoter which might mediate the stimulatory effect of cAMP and RA [65]. Mutations in these regions markedly impaired the trans-stimulatory effect of AP-2 on *APOE* expression [65]. These results indicate the existence of functional AP-2 sites in the promoter region of ApoE. The AP-2 transcription factor family consists of five isoforms (α, β, γ, δ and ε), with α- and β-isoform abundantly expressed in the brain [71,72]. Interestingly, a recent study observed that Aβ induced a time-dependent increase in *APOE* mRNA in astrocytes which was mediated by AP-2β [73]. The transcriptional up-regulation of *APOE* level by Aβ may be a neuro-protective response against Aβ-induced cytotoxicity, consistent with ApoE's role in cytoprotection.

Proliferator-activated receptor gamma (PPARγ) and liver X receptors (LXRs) form obligate hetero-dimers with retinoid X receptors (RXRs) and are reported to regulate *APOE* transcription [66,68]. Indeed, the LXR agonists GW3965 and TO901317 were reported to increase *APOE* expression in astrocytes, enhance Aβ clearance and ameliorate the memory deficit in amyloid mouse model [66,67]. Similar to LXRs, PPARγ agonists such as pioglitazone and ciglitazone can also induce *APOE* expression and rescue the behavioral deficits in AD mouse model [39,68]. In addition, RXR activation by numerous compounds has shown to increase *APOE* level, likely through activation of RXR and PPAR signaling pathways [74,75]. Owing to their ability to enhance *APOE* gene expression and promote Aβ degradation, LXRs, PPARs, and perhaps RXRs, serve as an attractive therapeutic target for AD.

While rarely-detected on the *BACE1* gene promoter, polymorphisms within the proximal promoter of the *APOE* gene lead to changes in ApoE level by altering gene transcription [76]. Four promoter polymorphisms have been identified and their association with AD risk has been investigated, including −491 (A/T transversion), −427 (T/C transition), −219 (G/T transversion, also known as the Th1/E47cs polymorphism), +113 (C/G transversion, also termed IE1) [77-80]. These polymorphisms are proposed to affect the transcriptional activity of ApoE gene by altering the binding of transcription factors [81]. Among them, the −491 A/T polymorphism has been the most

thoroughly investigated and shown to robustly affect ApoE level. The A to T substitution at −491, and the T to G substitution at −219, resulted in a 63% decrease and a 169% increase of the *APOE* promoter activity, respectively [81]. Epidemiological studies have shown that the −491 T allele was associated with a decreased risk for AD, while the −219 T allele was associated with an increased risk for AD occurrence, independently of the ε2/ε3/ε4 polymorphism [82]. These data suggest that these promoter polymorphisms are functional in nature. In addition to the polymorphism within the coding region, uncovering the polymorphism within the *APOE* promoter might be also beneficial to predict AD risk.

Transcription regulation of other AD genes

APP belongs to the type I transmembrane proteins, encompassing a long extracellular domain, a hydrophobic transmembrane domain, and a short C-terminal intracellular domain [6]. The human *APP* gene is located on the long arm of chromosome 21 and contains at least 18 exons [83]. APP is abundantly expressed in the neuronal cells of the central nervous system; and the mechanisms controlling *APP* gene expression have been extensively studied [8,84-88]. The *APP* promoter is devoid of typical TATA and CAAT boxes, but contains a strong initiator element surrounding the major transcription start site [89]. The promoter sequences of *APP* gene are highly conserved among species, and share numerous binding sites for regulatory transcription factors [85,86,90,91]. The *APP* promoter activation is mainly governed by two GC-rich elements, the −93/−82 fragment (APBβ) which is bound by CCCTC-binding factor (CTCF) and the −65/−41 fragment (APBα) which is bound by stimulating protein 1 (SP1) and the upstream stimulatory factor (USF) [92-96]. Further, numerous stress factors could activate *APP* transcription which is mediated by heat-shock factor 1 (HSF-1) binding to the heat-shock element (HSE) at position −317 [97]. Another transcription factor NF-κB was found to specifically recognize two identical sequences at −2250/−2241 and −1837/−1822 on *APP* promoter. In neural cells that were treated with either the inflammatory cytokine interleukin-1beta (IL-1β) or the excitatory amino-acid glutamate, NF-κB up-regulated the transcriptional activity of the *APP* promoter [98,99]. Rac1, a member of the Rho family GTPases, was shown to stimulate the transcription of *APP* promoter in the region between −233 and −41 bp [100]. In primary hippocampal neurons, over-expression of the dominant-negative Rac1 mutant or the presence of Rac1 inhibitors decreased the levels of *APP* mRNA, indicting Rac1 could be a potential drug target for AD therapy [100]. Other regulatory elements includes the binding sites for activator protein 1 (AP1), cAMP-responsive element-binding protein (CREB) and 'GATA' binding factor 1 (GATA1) [101].

Interestingly, copper depletion significantly reduced *APP* gene expression by acting on the region between −490 and +104 of *APP* promoter [102]. In addition, promoter polymorphisms have been found to modulate APP expression and therefore increase susceptibility to AD, including −877 T/C, −955A/G [103].

Presenilin genes (*PSEN1* and *PSEN2*) encode highly homologous integral membrane proteins which are the catalytic subunits of γ-secretase [104-106]. *PSEN* mutations cause abnormal processing of APP and lead to early onset AD [107-109]. Therefore, *PSEN* gene regulation may play a crucial role in the development of AD. Both *PSEN*s are expressed primarily in neurons [110,111]. Their promoters lack a TATA box but contain transcriptionally active GC boxes [112,113]. To date, most studies are focused on the transcriptional regulation of *PSEN1*; little is known about the transcriptional control of *PSEN2*. Deletion mapping of the human *PSEN1* promoter delineated the most active region between −22 and −6 which controls over 90% of *PSEN1* promoter activity [114]. Ets transcription factors bind to this region and activate *PSEN1* transcription [115]. Intriguingly, co-activator p300 appears to interact with Ets transcription factors and co-activate *PSEN1* transcription [115]. Zinc finger protein (ZNF237) and chromodomain helicase DNA-binding protein (CHD3) interact with Ets transcription factor ERM and inhibit *PSEN1* transcription [116,117]. Since p300 has intrinsic histone acetyltransferase (HAT) activity and CHD3 is a component of the histone deacetylase (HDACs) complex, chromatin modification by acetylation and deacetylation may play a critical role for *PSEN1* transcription regulation [118]. In a separate study, cAMP-responsive element-binding protein (CREB) was shown to bind *PSEN1* promoter upon stimulation by N-Methyl-D-aspartate (NMDA) or brain-derived neurotrophic factor (BDNF), and enhance *PSEN1* transcription [119]. Further, IL-1β and Aβ42 peptide synergistically activated *PSEN1* gene expression and the effect could be enhanced by hypoxia. At least two promoter polymorphisms (−22C/T, −48C/T) have been found to modulate *PSEN1* expression and AD risk [120,121]. On the *PSEN2* promoter, a functional nerve growth factor (NGF) binds to its responsive element and leads to twofold up-regulation of *PSEN2* transcription [122]. Early growth response gene-1 (Egr-1) binds to *PSEN2* promoter, and *PSEN2* level is increased three-fold by over-expression of Egr-1, or by 12-O-tetradecanoylphorbol-13-acetate (TPA) which increases Egr-1 level [123].

Recently, studies from two independent groups of researchers suggested that rare variants in the *TREM2* (triggering receptor expressed on myeloid cells 2) gene are associated with an increased risk of late-onset AD [124,125]. *TREM2* encodes a single-pass type I membrane receptor that regulates cell activity through a

transmembrane signaling adapter protein called TYROBP (also called DAP12) [126]. In the brain, TREM2 is dominantly expressed in microglia and performs two important roles: suppresses inflammatory reactivity and mediates the phagocytosis of cell debris [127,128]. Impaired function of the TREM2 gene may therefore affect the inflammatory processes and the clearance of amyloid plaques, ultimately leading to increased risk for AD. Interestingly, TREM2 expression in microglia was reduced more than 8-fold after Aβ treatment [129], which indicates that increasing TREM2 level might be beneficial for AD therapy. Regulation of TREM2 transcription especially in microglia remains largely unknown. Identifying the transcriptional regulators for TREM2 expression may therefore open a new avenue for AD therapy.

Conclusions

This present review summarizes the mechanisms of transcriptional regulation for several important AD genes and their misregulation that leads to AD susceptibility. Mounting evidence has emerged to support an important role of transcription regulation in the initiation and progression of AD. With a more thorough understanding of the changes for the gene expression profile, reciprocal drug targets can be developed to reverse the changes in transcription and alleviate AD symptoms. In addition, an alteration in gene expression presumably occurs in the early stage of the disease and accounts for the appearance of pathological hallmarks. Therefore, diagnostic techniques based on gene expression changes have the potential to detect the onset of AD before it is histologically obvious, thus allowing early treatment to prevent disease onset and provide long-lasting efficacy after discontinuation of the treatment [130].

AD therapy based upon the modulation of gene expression profiles relies heavily on a comprehensive understanding of the regulatory transcription factors and their responding elements on the promoter of AD genes. In recent years, important progress has been made in understanding the transcription regulation of BACE1, APOE, APP and PSEN promoters. The regulation of BACE1 promoter activity has been extensively studied and the derived knowledge has been guiding the identification of compounds to inhibit BACE1 expression through comprehensive drug screening. Regulation of APOE transcription is only partially investigated in the central nervous system and could be extremely complex. Human ApoE exists as three polymorphic alleles: ε2, ε3 and ε4, special attention needs to be drawn to mechanisms of differential expression of the different ApoE isoforms. Aβ peptide generation depends largely on the amount of APP substrate. Therefore, the regulation of APP transcription plays an important role in AD susceptibility. Several studies have observed an increase of APP mRNA levels in AD brains which exacerbates Aβ deposition [8,131]. The up-regulated levels of APP could be attributed to the altered binding of transcription factors to their specific positive and negative cis-elements. Because presenilins are the catalytic subunits of γ-secretase, drugs developed to inhibit the transcription of PSENs could potentially reduce Aβ generation. However, presenilins cleave a large number of trans-membrane targets (such as Notch), significant side effects could be induced by down-regulating PSEN transcription or enzymatic activity [132-134]. Better understanding of the transcriptional properties of PSENs in the future could provide a mechanistic target to potentially alleviate AD pathology; with minimal side effects. Intriguingly, a recent study demonstrated that PSEN2, but not PSEN1, plays an important role in mediating Notch cleavage [135]. PSEN2-sparing γ-secretase inhibition was suggested to a novel and efficacious γ-secretase targeting strategy for AD. Therefore, transcription factors that specifically inhibit the expression of PSEN1, but not PSEN2, would be an effective and novel drug target for AD therapy. At this present time, researchers have also focused on polymorphisms within the AD gene promoter, since single-nucleotide changes have been documented to affect transcriptional activity of AD genes. These polymorphisms may affect transcription factor binding either by directly altering a transcription factor binding site, or by changing the structure of DNA thereby affecting the access of transcription factor to the binding site.

Recently, genome-wide expression studies have been performed to investigate the complex pathogenesis of AD by using transgenic AD animals, patient-derived cell lines, and post-mortem brain tissues [136]. Changes in the transcription levels of a group of genes have been identified, although the results have been discordant, and may be possibly due to different experimental approaches used [136]. With the development of array technologies especially the RNA-seq technique, more comprehensive and accurate transcriptome analysis could be derived to interpret the pathogenesis of AD. With the increasing number of AD genes being discovered, further analysis of the transcriptional regulation of these AD genes and the variants in their regulatory regions will not only help to elucidate AD etiology, but also guide targeted drug development for AD therapy.

References

1. Blennow K, de Leon MJ, Zetterberg H: **Alzheimer's disease.** *Lancet* 2006, **368**:387–403.
2. Hardy J, Selkoe DJ: **The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics.** *Science* 2002, **297**:353–356.
3. Cavallucci V, D'Amelio M, Cecconi F: **Abeta toxicity in Alzheimer's disease.** *Mol Neurobiol* 2012, **45**:366–378.
4. Koffie RM, Hyman BT, Spires-Jones TL: **Alzheimer's disease: synapses gone cold.** *Mol Neurodegener* 2011, **6**:63.
5. Jung CG, Uhm KO, Miura Y, Hosono T, Horike H, Khanna KK, Kim MJ, Michikawa M: **Beta-amyloid increases the expression level of ATBF1 responsible for death in cultured cortical neurons.** *Mol Neurodegener* 2011, **6**:47.
6. Zheng H, Koo EH: **Biology and pathophysiology of the amyloid precursor protein.** *Mol Neurodegener* 2011, **6**:27.
7. Ertekin-Taner N: **Gene expression endophenotypes: a novel approach for gene discovery in Alzheimer's disease.** *Mol Neurodegener* 2011, **6**:31.
8. Theuns J, Van Broeckhoven C: **Transcriptional regulation of Alzheimer's disease genes: implications for susceptibility.** *Hum Mol Genet* 2000, **9**:2383–2394.
9. Zhang H, Ma Q, Zhang YW, Xu H: **Proteolytic processing of Alzheimer's beta-amyloid precursor protein.** *J Neurochem* 2012, **120**(Suppl 1):9–21.
10. Chami L, Checler F: **BACE1 is at the crossroad of a toxic vicious cycle involving cellular stress and beta-amyloid production in Alzheimer's disease.** *Mol Neurodegener* 2012, **7**:52.
11. Cole SL, Vassar R: **The Alzheimer's disease beta-secretase enzyme, BACE1.** *Mol Neurodegener* 2007, **2**:22.
12. Holsinger RM, McLean CA, Beyreuther K, Masters CL, Evin G: **Increased expression of the amyloid precursor beta-secretase in Alzheimer's disease.** *Ann Neurol* 2002, **51**:783–786.
13. Yang LB, Lindholm K, Yan R, Citron M, Xia W, Yang XL, Beach T, Sue L, Wong P, Price D, *et al*: **Elevated beta-secretase expression and enzymatic activity detected in sporadic Alzheimer disease.** *Nat Med* 2003, **9**:3–4.
14. Rossner S, Sastre M, Bourne K, Lichtenthaler SF: **Transcriptional and translational regulation of BACE1 expression–implications for Alzheimer's disease.** *Prog Neurobiol* 2006, **79**:95–111.
15. Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, *et al*: **Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE.** *Science* 1999, **286**:735–741.
16. Luo Y, Bolon B, Kahn S, Bennett BD, Babu-Khan S, Denis P, Fan W, Kha H, Zhang J, Gong Y, *et al*: **Mice deficient in BACE1, the Alzheimer's beta-secretase, have normal phenotype and abolished beta-amyloid generation.** *Nat Neurosci* 2001, **4**:231–232.
17. Roberds SL, Anderson J, Basi G, Bienkowski MJ, Branstetter DG, Chen KS, Freedman SB, Frigon NL, Games D, Hu K, *et al*: **BACE knockout mice are healthy despite lacking the primary beta-secretase activity in brain: implications for Alzheimer's disease therapeutics.** *Hum Mol Genet* 2001, **10**:1317–1324.
18. Kobayashi D, Zeller M, Cole T, Buttini M, McConlogue L, Sinha S, Freedman S, Morris RG, Chen KS: **BACE1 gene deletion: impact on behavioral function in a model of Alzheimer's disease.** *Neurobiol Aging* 2008, **29**:861–873.
19. Laird FM, Cai H, Savonenko AV, Farah MH, He K, Melnikova T, Wen H, Chiang HC, Xu G, Koliatsos VE, *et al*: **BACE1, a major determinant of selective vulnerability of the brain to amyloid-beta amyloidogenesis, is essential for cognitive, emotional, and synaptic functions.** *J Neurosci* 2005, **25**:11693–11709.
20. Rajapaksha TW, Eimer WA, Bozza TC, Vassar R: **The Alzheimer's beta-secretase enzyme BACE1 is required for accurate axon guidance of olfactory sensory neurons and normal glomerulus formation in the olfactory bulb.** *Mol Neurodegener* 2011, **6**:88.
21. Lange-Dohna C, Zeitschel U, Gaunitz F, Perez-Polo JR, Bigl V, Rossner S: **Cloning and expression of the rat BACE1 promoter.** *J Neurosci Res* 2003, **73**:73–80.
22. Kwak YD, Wang R, Li JJ, Zhang YW, Xu H, Liao FF: **Differential regulation of BACE1 expression by oxidative and nitrosative signals.** *Mol Neurodegener* 2011, **6**:17.
23. Waby JS, Bingle CD, Corfe BM: **Post-translational control of sp-family transcription factors.** *Curr Genomics* 2008, **9**:301–311.
24. Christensen MA, Zhou W, Qing H, Lehman A, Philipsen S, Song W: **Transcriptional regulation of BACE1, the beta-amyloid precursor protein beta-secretase, by Sp1.** *Mol Cell Biol* 2004, **24**:865–874.
25. Letovsky J, Dynan WS: **Measurement of the binding of transcription factor Sp1 to a single GC box recognition sequence.** *Nucleic Acids Res* 1989, **17**:2639–2653.
26. Chu J, Zhuo JM, Pratico D: **Transcriptional regulation of beta-secretase-1 by 12/15-lipoxygenase results in enhanced amyloidogenesis and cognitive impairments.** *Ann Neurol* 2012, **71**:57–67.
27. Perkins ND, Edwards NL, Duckett CS, Agranoff AB, Schmid RM, Nabel GJ: **A cooperative interaction between NF-kappa B and Sp1 is required for HIV-1 enhancer activation.** *EMBO J* 1993, **12**:3551–3558.
28. Hirano F, Tanaka H, Hirano Y, Hiramoto M, Handa H, Makino I, Scheidereit C: **Functional interference of Sp1 and NF-kappaB through the same DNA binding site.** *Mol Cell Biol* 1998, **18**:1266–1274.
29. Bourne KZ, Ferrari DC, Lange-Dohna C, Rossner S, Wood TG, Perez-Polo JR: **Differential regulation of BACE1 promoter activity by nuclear factor-kappaB in neurons and glia upon exposure to beta-amyloid peptides.** *J Neurosci Res* 2007, **85**:1194–1204.
30. Chami L, Buggia-Prevot V, Duplan E, Delprete D, Chami M, Peyron JF, Checler F: **Nuclear factor-kappaB regulates betaAPP and beta- and gamma-secretases differently at physiological and supraphysiological Abeta concentrations.** *J Biol Chem* 2012, **287**:24573–24584.
31. Maxwell P, Salnikow K: **HIF-1: an oxygen and metal responsive transcription factor.** *Cancer Biol Ther* 2004, **3**:29–35.
32. Lando D, Peet DJ, Whelan DA, Gorman JJ, Whitelaw ML: **Asparagine hydroxylation of the HIF transactivation domain a hypoxic switch.** *Science* 2002, **295**:858–861.
33. Sun X, He G, Qing H, Zhou W, Dobie F, Cai F, Staufenbiel M, Huang LE, Song W: **Hypoxia facilitates Alzheimer's disease pathogenesis by up-regulating BACE1 gene expression.** *Proc Natl Acad Sci USA* 2006, **103**:18727–18732.
34. Zhang X, Zhou K, Wang R, Cui J, Lipton SA, Liao FF, Xu H, Zhang YW: **Hypoxia-inducible factor 1alpha (HIF-1alpha)-mediated hypoxia increases BACE1 expression and beta-amyloid generation.** *J Biol Chem* 2007, **282**:10873–10880.
35. Guglielmotto M, Aragno M, Autelli R, Giliberto L, Novo E, Colombatto S, Danni O, Parola M, Smith MA, Perry G, *et al*: **The up-regulation of BACE1 mediated by hypoxia and ischemic injury: role of oxidative stress and HIF1alpha.** *J Neurochem* 2009, **108**:1045–1056.
36. Li QY, Wang HM, Wang ZQ, Ma JF, Ding JQ, Chen SD: **Salidroside attenuates hypoxia-induced abnormal processing of amyloid precursor protein by decreasing BACE1 expression in SH-SY5Y cells.** *Neurosci Lett* 2010, **481**:154–158.
37. Kliewer SA, Forman BM, Blumberg B, Ong ES, Borgmeyer U, Mangelsdorf DJ, Umesono K, Evans RM: **Differential expression and activation of a family of murine peroxisome proliferator-activated receptors.** *Proc Natl Acad Sci USA* 1994, **91**:7355–7359.
38. Tontonoz P, Hu E, Spiegelman BM: **Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor.** *Cell* 1994, **79**:1147–1156.
39. Mandrekar-Colucci S, Landreth GE: **Nuclear receptors as therapeutic targets for Alzheimer's disease.** *Expert Opin Ther Targets* 2011, **15**:1085–1097.
40. Sastre M, Dewachter I, Rossner S, Bogdanovic N, Rosen E, Borghgraef P, Evert BO, Dumitrescu-Ozimek L, Thal DR, Landreth G, *et al*: **Nonsteroidal anti-inflammatory drugs repress beta-secretase gene promoter activity by the activation of PPARgamma.** *Proc Natl Acad Sci USA* 2006, **103**:443–448.
41. McGeer PL, McGeer EG: **Inflammation, autotoxicity and Alzheimer disease.** *Neurobiol Aging* 2001, **22**:799–809.
42. Mahley RW: **Apolipoprotein E: cholesterol transport protein with expanding role in cell biology.** *Science* 1988, **240**:622–630.
43. Liu CC, Kanekiyo T, Xu H, Bu G: **Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy.** *Nat Rev Neurol* 2013, **9**:106–118.
44. Herz J, Chen Y: **Reelin, lipoprotein receptors and synaptic plasticity.** *Nat Rev Neurosci* 2006, **7**:850–859.

45. Chen J, Li Q, Wang J: **Topology of human apolipoprotein E3 uniquely regulates its diverse biological functions.** *Proc Natl Acad Sci USA* 2011, **108**:14813–14818.
46. Frieden C, Garai K: **Structural differences between apoE3 and apoE4 may be useful in developing therapeutic agents for Alzheimer's disease.** *Proc Natl Acad Sci U S A* 2012, **109**:8913–8918.
47. Zhong N, Weisgraber KH: **Understanding the association of apolipoprotein E4 with Alzheimer disease: clues from its structure.** *J Biol Chem* 2009, **284**:6027–6031.
48. Bu G: **Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy.** *Nat Rev Neurosci* 2009, **10**:333–344.
49. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA: **Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families.** *Science* 1993, **261**:921–923.
50. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM: **Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer disease meta analysis consortium.** *JAMA* 1997, **278**:1349–1356.
51. Laws SM, Hone E, Gandy S, Martins RN: **Expanding the association between the APOE gene and the risk of Alzheimer's disease: possible roles for APOE promoter polymorphisms and alterations in APOE transcription.** *J Neurochem* 2003, **84**:1215–1236.
52. Taddei K, Clarnette R, Gandy SE, Martins RN: **Increased plasma apolipoprotein E (apoE) levels in Alzheimer's disease.** *Neurosci Lett* 1997, **223**:29–32.
53. Lindh M, Blomberg M, Jensen M, Basun H, Lannfelt L, Engvall B, Scharnagel H, Marz W, Wahlund LO, Cowburn RF: **Cerebrospinal fluid apolipoprotein E (apoE) levels in Alzheimer's disease patients are increased at follow up and show a correlation with levels of tau protein.** *Neurosci Lett* 1997, **229**:85–88.
54. Laws SM, Hone E, Taddei K, Harper C, Dean B, McClean C, Masters C, Lautenschlager N, Gandy SE, Martins RN: **Variation at the APOE −491 promoter locus is associated with altered brain levels of apolipoprotein E.** *Mol Psychiatry* 2002, **7**:886–890.
55. Pirttila T, Soininen H, Heinonen O, Lehtimaki T, Bogdanovic N, Paljarvi L, Kosunen O, Winblad B, Riekkinen P Sr, Wisniewski HM, Mehta PD: **Apolipoprotein E (apoE) levels in brains from Alzheimer disease patients and controls.** *Brain Res* 1996, **722**:71–77.
56. Harr SD, Uint L, Hollister R, Hyman BT, Mendez AJ: **Brain expression of apolipoproteins E, J, and A-I in Alzheimer's disease.** *J Neurochem* 1996, **66**:2429–2435.
57. Beffert U, Cohn JS, Petit-Turcotte C, Tremblay M, Aumont N, Ramassamy C, Davignon J, Poirier J: **Apolipoprotein E and beta-amyloid levels in the hippocampus and frontal cortex of Alzheimer's disease subjects are disease-related and apolipoprotein E genotype dependent.** *Brain Res* 1999, **843**:87–94.
58. Hesse C, Larsson H, Fredman P, Minthon L, Andreasen N, Davidsson P, Blennow K: **Measurement of apolipoprotein E (apoE) in cerebrospinal fluid.** *Neurochem Res* 2000, **25**:511–517.
59. Bien-Ly N, Gillespie AK, Walker D, Yoon SY, Huang Y: **Reducing human apolipoprotein E levels attenuates age-dependent Abeta accumulation in mutant human amyloid precursor protein transgenic mice.** *J Neurosci* 2012, **32**:4803–4811.
60. Kim J, Jiang H, Park S, Eltorai AE, Stewart FR, Yoon H, Basak JM, Finn MB, Holtzman DM: **Haploinsufficiency of human APOE reduces amyloid deposition in a mouse model of amyloid-beta amyloidosis.** *J Neurosci* 2011, **31**:18007–18012.
61. Lin-Lee YC, Tanaka Y, Lin CT, Chan L: **Effects of an atherogenic diet on apolipoprotein E biosynthesis in the rat.** *Biochemistry* 1981, **20**:6474–6480.
62. Smith JD, Melian A, Leff T, Breslow JL: **Expression of the human apolipoprotein E gene is regulated by multiple positive and negative elements.** *J Biol Chem* 1988, **263**:8300–8308.
63. Surguchov AP: **The apolipoprotein gene family: organization of upstream elements and regulation of gene expression.** *Biomed Sci* 1990, **1**:344–353.
64. Paik YK, Chang DJ, Reardon CA, Davies GE, Mahley RW, Taylor JM: **Nucleotide sequence and structure of the human apolipoprotein E gene.** *Proc Natl Acad Sci USA* 1985, **82**:3445–3449.
65. Garcia MA, Vazquez J, Gimenez C, Valdivieso F, Zafra F: **Transcription factor AP-2 regulates human apolipoprotein E gene expression in astrocytoma cells.** *J Neurosci* 1996, **16**:7550–7556.
66. Jiang Q, Lee CY, Mandrekar S, Wilkinson B, Cramer P, Zelcer N, Mann K, Lamb B, Willson TM, Collins JL, *et al*: **ApoE promotes the proteolytic degradation of Abeta.** *Neuron* 2008, **58**:681–693.
67. Terwel D, Steffensen KR, Verghese PB, Kummer MP, Gustafsson JA, Holtzman DM, Heneka MT: **Critical role of astroglial apolipoprotein E and liver X receptor-alpha expression for microglial Abeta phagocytosis.** *J Neurosci* 2011, **31**:7049–7059.
68. Yue L, Rasouli N, Ranganathan G, Kern PA, Mazzone T: **Divergent effects of peroxisome proliferator-activated receptor gamma agonists and tumor necrosis factor alpha on adipocyte ApoE expression.** *J Biol Chem* 2004, **279**:47626–47632.
69. Philipp J, Mitchell PJ, Malipiero U, Fontana A: **Cell type-specific regulation of expression of transcription factor AP-2 in neuroectodermal cells.** *Dev Biol* 1994, **165**:602–614.
70. Luscher B, Mitchell PJ, Williams T, Tjian R: **Regulation of transcription factor AP-2 by the morphogen retinoic acid and by second messengers.** *Genes Dev* 1989, **3**:1507–1517.
71. Eckert D, Buhl S, Weber S, Jager R, Schorle H: **The AP-2 family of transcription factors.** *Genome Biol* 2005, **6**:246.
72. Damberg M: **Transcription factor AP-2 and monoaminergic functions in the central nervous system.** *J Neural Transm* 2005, **112**:1281–1296.
73. Rossello XS, Igbavboa U, Weisman GA, Sun GY, Wood WG: **AP-2beta regulates amyloid beta-protein stimulation of apolipoprotein E transcription in astrocytes.** *Brain Res* 2012, **1444**:87–95.
74. Cramer PE, Cirrito JR, Wesson DW, Lee CY, Karlo JC, Zinn AE, Casali BT, Restivo JL, Goebel WD, James MJ, *et al*: **ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models.** *Science* 2012, **335**:1503–1506.
75. Liang Y, Lin S, Beyer TP, Zhang Y, Wu X, Bales KR, DeMattos RB, May PC, Li SD, Jiang XC, *et al*: **A liver X receptor and retinoid X receptor heterodimer mediates apolipoprotein E expression, secretion and cholesterol homeostasis in astrocytes.** *J Neurochem* 2004, **88**:623–634.
76. Bullido MJ, Valdivieso F: **Apolipoprotein E gene promoter polymorphisms in Alzheimer's disease.** *Microsc Res Tech* 2000, **50**:261–267.
77. Artiga MJ, Bullido MJ, Frank A, Sastre I, Recuero M, Garcia MA, Lendon CL, Han SW, Morris JC, Vazquez J, *et al*: **Risk for Alzheimer's disease correlates with transcriptional activity of the APOE gene.** *Hum Mol Genet* 1998, **7**:1887–1892.
78. Bullido MJ, Artiga MJ, Recuero M, Sastre I, Garcia MA, Aldudo J, Lendon C, Han SW, Morris JC, Frank A, *et al*: **A polymorphism in the regulatory region of APOE associated with risk for Alzheimer's dementia.** *Nat Genet* 1998, **18**:69–71.
79. Lambert JC, Pasquier F, Cottel D, Frigard B, Amouyel P, Chartier-Harlin MC: **A new polymorphism in the APOE promoter associated with risk of developing Alzheimer's disease.** *Hum Mol Genet* 1998, **7**:533–540.
80. Mui S, Briggs M, Chung H, Wallace RB, Gomez-Isla T, Rebeck GW, Hyman BT: **A newly identified polymorphism in the apolipoprotein E enhancer gene region is associated with Alzheimer's disease and strongly with the epsilon 4 allele.** *Neurology* 1996, **47**:196–201.
81. Artiga MJ, Bullido MJ, Sastre I, Recuero M, Garcia MA, Aldudo J, Vazquez J, Valdivieso F: **Allelic polymorphisms in the transcriptional regulatory region of apolipoprotein E gene.** *FEBS Lett* 1998, **421**:105–108.
82. Lambert JC, Berr C, Pasquier F, Delacourte A, Frigard B, Cottel D, Perez-Tur J, Mouroux V, Mohr M, Cecyre D, *et al*: **Pronounced impact of Th1/E47cs mutation compared with −491 AT mutation on neural APOE gene expression and risk of developing Alzheimer's disease.** *Hum Mol Genet* 1998, **7**:1511–1516.
83. Yoshikai S, Sasaki H, Doh-ura K, Furuya H, Sakaki Y: **Genomic organization of the human amyloid beta-protein precursor gene.** *Gene* 1990, **87**:257–263.
84. Goedert M: **Neuronal localization of amyloid beta protein precursor mRNA in normal human brain and in Alzheimer's disease.** *EMBO J* 1987, **6**:3627–3632.
85. Chernak JM: **Structural features of the 5' upstream regulatory region of the gene encoding rat amyloid precursor protein.** *Gene* 1993, **133**:255–260.
86. Izumi R, Yamada T, Yoshikai S, Sasaki H, Hattori M, Sakaki Y: **Positive and negative regulatory elements for the expression of the**

Alzheimer's disease amyloid precursor-encoding gene in mouse. *Gene* 1992, **112**:189–195.

87. Salbaum JM, Weidemann A, Lemaire HG, Masters CL, Beyreuther K: The promoter of Alzheimer's disease amyloid A4 precursor gene. *EMBO J* 1988, **7**:2807–2813.

88. La Fauci G, Lahiri DK, Salton SR, Robakis NK: Characterization of the 5'-end region and the first two exons of the beta-protein precursor gene. *Biochem Biophys Res Commun* 1989, **159**:297–304.

89. Quitschke WW, Matthews JP, Kraus RJ, Vostrov AA: The initiator element and proximal upstream sequences affect transcriptional activity and start site selection in the amyloid beta-protein precursor promoter. *J Biol Chem* 1996, **271**:22231–22239.

90. Quitschke WW, Goldgaber D: The amyloid beta-protein precursor promoter. A region essential for transcriptional activity contains a nuclear factor binding domain. *J Biol Chem* 1992, **267**:17362–17368.

91. Song W, Lahiri DK: Functional identification of the promoter of the gene encoding the Rhesus monkey beta-amyloid precursor protein. *Gene* 1998, **217**:165–176.

92. Pollwein P, Masters CL, Beyreuther K: The expression of the amyloid precursor protein (APP) is regulated by two GC-elements in the promoter. *Nucleic Acids Res* 1992, **20**:63–68.

93. Quitschke WW: Two nuclear factor binding domains activate expression from the human amyloid beta-protein precursor promoter. *J Biol Chem* 1994, **269**:21229–21233.

94. Vostrov AA, Quitschke WW: The zinc finger protein CTCF binds to the APBbeta domain of the amyloid beta-protein precursor promoter. Evidence for a role in transcriptional activation. *J Biol Chem* 1997, **272**:33353–33359.

95. Vostrov AA, Quitschke WW, Vidal F, Schwarzman AL, Goldgaber D: USF binds to the APB alpha sequence in the promoter of the amyloid beta-protein precursor gene. *Nucleic Acids Res* 1995, **23**:2734–2741.

96. Pollwein P: Overlapping binding sites of two different transcription factors in the promoter of the human gene for the Alzheimer amyloid precursor protein. *Biochem Biophys Res Commun* 1993, **190**:637–647.

97. Dewji NN, Do C: Heat shock factor-1 mediates the transcriptional activation of Alzheimer's beta-amyloid precursor protein gene in response to stress. *Brain Res Mol Brain Res* 1996, **35**:325–328.

98. Grilli M, Goffi F, Memo M, Spano P: Interleukin-1beta and glutamate activate the NF-kappaB/Rel binding site from the regulatory region of the amyloid precursor protein gene in primary neuronal cultures. *J Biol Chem* 1996, **271**:15002–15007.

99. Grilli M, Ribola M, Alberici A, Valerio A, Memo M, Spano P: Identification and characterization of a kappa B/Rel binding site in the regulatory region of the amyloid precursor protein gene. *J Biol Chem* 1995, **270**:26774–26777.

100. Wang PL, Niidome T, Akaike A, Kihara T, Sugimoto H: Rac1 inhibition negatively regulates transcriptional activity of the amyloid precursor protein gene. *J Neurosci Res* 2009, **87**:2105–2114.

101. Ge YW, Ghosh C, Song W, Maloney B, Lahiri DK: Mechanism of promoter activity of the beta-amyloid precursor protein gene in different cell lines: identification of a specific 30 bp fragment in the proximal promoter region. *J Neurochem* 2004, **90**:1432–1444.

102. Bellingham SA, Lahiri DK, Maloney B, La Fontaine S, Multhaup G, Camakaris J: Copper depletion down-regulates expression of the Alzheimer's disease amyloid-beta precursor protein gene. *J Biol Chem* 2004, **279**:20378–20386.

103. Lv H, Jia L, Jia J: Promoter polymorphisms which modulate APP expression may increase susceptibility to Alzheimer's disease. *Neurobiol Aging* 2008, **29**:194–202.

104. Tomita T: Secretase inhibitors and modulators for Alzheimer's disease treatment. *Expert Rev Neurother* 2009, **9**:661–679.

105. Edbauer D, Winkler E, Regula JT, Pesold B, Steiner H, Haass C: Reconstitution of gamma-secretase activity. *Nat Cell Biol* 2003, **5**:486–488.

106. De Strooper B, Saftig P, Craessaerts K, Vanderstichele H, Guhde G, Annaert W, Von Figura K, Van Leuven F: Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein. *Nature* 1998, **391**:387–390.

107. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, et al: Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 1995, **375**:754–760.

108. Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Yu CE, Jondro PD, Schmidt SD, Wang K, et al: Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* 1995, **269**:973–977.

109. Uemura K, Farner KC, Nasser-Ghodsi N, Jones P, Berezovska O: Reciprocal relationship between APP positioning relative to the membrane and PS1 conformation. *Mol Neurodegen* 2011, **6**:15.

110. Kovacs DM, Fausett HJ, Page KJ, Kim TW, Moir RD, Merriam DE, Hollister RD, Hallmark OG, Mancini R, Felsenstein KM, et al: Alzheimer-associated presenilins 1 and 2: neuronal expression in brain and localization to intracellular membranes in mammalian cells. *Nat Med* 1996, **2**:224–229.

111. Lee MK, Slunt HH, Martin LJ, Thinakaran G, Kim G, Gandy SE, Seeger M, Koo E, Price DL, Sisodia SS: Expression of presenilin 1 and 2 (PS1 and PS2) in human and murine tissues. *J Neurosci* 1996, **16**:7513–7525.

112. Mitsuda N, Roses AD, Vitek MP: Transcriptional regulation of the mouse presenilin-1 gene. *J Biol Chem* 1997, **272**:23489–23497.

113. Prihar G, Fuldner RA, Perez-Tur J, Lincoln S, Duff K, Crook R, Hardy J, Philips CA, Venter C, Talbot C, et al: Structure and alternative splicing of the presenilin-2 gene. *Neuroreport* 1996, **7**:1680–1684.

114. Pastorcic M, Das HK: An upstream element containing an ETS binding site is crucial for transcription of the human presenilin-1 gene. *J Biol Chem* 1999, **274**:24297–24307.

115. Pastorcic M, Das HK: Regulation of transcription of the human presenilin-1 gene by ets transcription factors and the p53 protooncogene. *J Biol Chem* 2000, **275**:34938–34945.

116. Pastorcic M, Das HK: Analysis of transcriptional modulation of the presenilin 1 gene promoter by ZNF237, a candidate binding partner of the Ets transcription factor ERM. *Brain Res* 2007, **1128**:21–32.

117. Pastorcic M, Das HK: The C-terminal region of CHD3/ZFH interacts with the CIDD region of the Ets transcription factor ERM and represses transcription of the human presenilin 1 gene. *FEBS J* 2007, **274**:1434–1448.

118. Das HK: Transcriptional regulation of the presenilin-1 gene: implication in Alzheimer's disease. *Front Biosci* 2008, **13**:822–832.

119. Mitsuda N, Ohkubo N, Tamatani M, Lee YD, Taniguchi M, Namikawa K, Kiyama H, Yamaguchi A, Sato N, Sakata K, et al: Activated cAMP-response element-binding protein regulates neuronal expression of presenilin-1. *J Biol Chem* 2001, **276**:9688–9698.

120. Theuns J, Remacle J, Killick R, Corsmit E, Vennekens K, Huylebroeck D, Cruts M, Van Broeckhoven C: Alzheimer-associated C allele of the promoter polymorphism -22C > T causes a critical neuron-specific decrease of presenilin 1 expression. *Hum Mol Genet* 2003, **12**:869–877.

121. Lambert JC, Mann DM, Harris JM, Chartier-Harlin MC, Cumming A, Coates J, Lemmon H, StClair D, Iwatsubo T, Lendon C: The −48 C/T polymorphism in the presenilin 1 promoter is associated with an increased risk of developing Alzheimer's disease and an increased Abeta load in brain. *J Med Genet* 2001, **38**:353–355.

122. Pennypacker KR, Fuldner R, Xu R, Hernandez H, Dawbarn D, Mehta N, Perez-Tur J, Baker M, Hutton M: Cloning and characterization of the presenilin-2 gene promoter. *Brain Res Mol Brain Res* 1998, **56**:57–65.

123. Renbaum P, Beeri R, Gabai E, Amiel M, Gal M, Ehrengruber MU, Levy-Lahad E: Egr-1 upregulates the Alzheimer's disease presenilin-2 gene in neuronal cells. *Gene* 2003, **318**:113–124.

124. Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JS, Younkin S, et al: TREM2 variants in Alzheimer's disease. *N Engl J Med* 2013, **368**:117–127.

125. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, Bjornsson S, Huttenlocher J, Levey AI, Lah JJ, et al: Variant of TREM2 associated with the risk of Alzheimer's disease. *N Engl J Med* 2013, **368**:107–116.

126. Klesney-Tait J, Turnbull IR, Colonna M: The TREM receptor family and signal integration. *Nat Immunol* 2006, **7**:1266–1273.

127. Takahashi K, Rochford CD, Neumann H: Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. *J Exp Med* 2005, **201**:647–657.

128. Turnbull IR, Gilfillan S, Cella M, Aoshi T, Miller M, Piccio L, Hernandez M, Colonna M: Cutting edge: TREM-2 attenuates macrophage activation. *J Immunol* 2006, **177**:3520–3524.

129. Walker DG, Link J, Lue LF, Dalsing-Hernandez JE, Boyes BE: Gene expression changes by amyloid beta peptide-stimulated human postmortem brain

microglia identify activation of multiple inflammatory processes. *J Leukoc Biol* 2006, **79**:596–610.

130. Das P, Verbeeck C, Minter L, Chakrabarty P, Felsenstein K, Kukar T, Maharvi G, Fauq A, Osborne BA, Golde TE: Transient pharmacologic lowering of Abeta production prior to deposition results in sustained reduction of amyloid plaque pathology. *Mol Neurodegener* 2012, **7**:39.

131. Theuns J, Brouwers N, Engelborghs S, Sleegers K, Bogaerts V, Corsmit E, De Pooter T, van Duijn CM, De Deyn PP, Van Broeckhoven C: Promoter mutations that increase amyloid precursor-protein expression are associated with Alzheimer disease. *Am J Hum Genet* 2006, **78**:936–946.

132. Haapasalo A, Kovacs DM: The many substrates of presenilin/gamma-secretase. *J Alzheimers Dis* 2011, **25**:3–28.

133. Milano J, McKay J, Dagenais C, Foster-Brown L, Pognan F, Gadient R, Jacobs RT, Zacco A, Greenberg B, Ciaccio PJ: Modulation of notch processing by gamma-secretase inhibitors causes intestinal goblet cell metaplasia and induction of genes known to specify gut secretory lineage differentiation. *Toxicol Sci* 2004, **82**:341–358.

134. Tamayev R, D'Adamio L: Inhibition of gamma-secretase worsens memory deficits in a genetically congruous mouse model of Danish dementia. *Mol Neurodegener* 2012, **7**:19.

135. Borgegard T, Gustavsson S, Nilsson C, Parpal S, Klintenberg R, Berg AL, Rosqvist S, Serneels L, Svensson S, Olsson F, et al: Alzheimer's disease: presenilin 2-sparing gamma-secretase inhibition is a tolerable Abeta peptide-lowering strategy. *J Neurosci* 2012, **32**:17297–17305.

136. Courtney E, Kornfeld S, Janitz K, Janitz M: Transcriptome profiling in neurodegenerative disease. *J Neurosci Methods* 2010, **193**:189–202.