The roles of amyloid precursor protein (APP) in neurogenesis, implications to pathogenesis and therapy of Alzheimer disease (AD)

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The amyloid-beta (Aβ) peptide is the derivative of amyloid precursor protein (APP) generated through sequential proteolytic processing by β- and γ-secretases. Excessive accumulation of Aβ, the main constituent of amyloid plaques, has been implicated in the etiology of Alzheimer disease (AD). It was found recently that the impairments of neurogenesis in brain were associated with the pathogenesis of AD. Furthermore recent findings implicated that APP could function to influence proliferation of neural progenitor cells (NPC) and might regulate transcriptional activity of various genes. Studies demonstrated that influence of neurogenesis by APP is conferred differently via its two separate domains, soluble secreted APPs (sAPPs, mainly sAPPα) and APP intracellular domain (AICD). The sAPPα was shown to be neuroprotective and important to neurogenesis, whereas AICD was found to negatively modulate neurogenesis. Furthermore, it was demonstrated recently that microRNA (miRNAs) could function to regulate APP expression, APP processing, Aβ accumulation and subsequently influence neurotoxicity and neurogenesis related to APP, which was implicated to AD pathogenesis, especially for sporadic AD. Based on data accumulated, secretase balances were proposed. These secretase balances could influence the downstream balance related to regulation of neurogenesis by AICD and sAPPα as well as balance related to influence of neuron viability by Aβ and sAPPα. Disruption of these secretase balances could be culprits to AD onset.

Neurodegenerative diseases such as Alzheimer disease (AD) are characterized by the progressive loss of neurons which are region-specific in the brain. Accumulative evidences support the amyloid hypothesis for AD pathogenesis that amyloid-beta (Aβ), derived from amyloid precursor protein (APP), plays a crucial initial role that triggers a complex pathological cascade which leads to the neurodegenerative conditions observed in the disorder.1 Recently, the presence of adult neurogenesis has been demonstrated, which impact our understanding of physiology and pathology of brain significantly. Furthermore, it was also demonstrated recently that APP could play a role in influencing neurogenesis via its two separate domains, the soluble secreted APPs (sAPPs, mainly sAPPα) and the APP intracellular domain (AICD). The sAPPα was shown to protect neuron cells and promote neurogenesis, whereas AICD was found to negatively modulate neurogenesis. Therefore, questions were raised on whether APP could contribute to AD pathogenesis via influence of adult neurogenesis by APP processing fragments, besides via Aβ-induced toxicity. Furthermore it was demonstrated recently that microRNA (miRNAs) could function to regulate APP expression, APP processing, Aβ accumulation and subsequently lead to altered Aβ toxicity or influence neurogenesis, which was implicated to AD pathogenesis, especially for sporadic AD. Therefore dysregulation of miRNAs could be the causes for alteration of APP expression and APP processing, leading to subsequent changes in neuron viability and neurogenesis, which could be implicated to AD. Based on data accumulated so far, secretase balances related to APP processing were proposed. These secretase balances could influence the downstream balances related to AICD-induced inhibition of neurogenesis, sAPPα-induced neuroprotection and promotion of neurogenesis as well as Aβ-induced neurotoxicity. Disruption of these secretase balances could disrupt downstream balances and finally contribute to AD. This review highlights and discusses recent new findings focusing on roles of APP in neurogenesis, which would be significant to pathogenesis and therapeutic applications of AD and even other neurodegenerative diseases.

Etiology of AD Related to APP

AD is the most common form of senile dementia that affects more than 30 million individuals worldwide. It is a degenerative neurological disorder characterized by gradual memory loss, cognitive impairments and deterioration of language skills.2 The disorder is characterized by neuropathological hallmarks which include the development of neuritic plaques constituting cores of aggregated Aβ derived from the APP and neurofibrillary tangles.
(NFT) composed of abnormally hyperphosphorylated tau (τ) proteins. Such features indicative of AD are further accompanied by gliosis, synaptic loss and neuronal death. Although age and environmental factors might increase the risk of the disorder, significant genetic background is implicated in AD. Based on symptomatology, the rare autosomal dominant inherited forms of early-onset AD has been linked with mutations in APP (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes. In contrast, the sporadic late-onset form accounting for the majority of all AD cases has been consistently associated with the presence of the apolipoprotein E (APOE) e4 allele. Other susceptibility genetic factors include α2-macroglobulin, the dihydrolipoyl succinyltransferase, which is a component of α-ketoglutarate dehydrogenase, the K-variant of butyryl-cholinesterase and multiple mitochondrial genes. Epidemiological studies also demonstrated several tentative associations which can be linked to a decreased reserve capacity of the brain, previous head injury and cardiovascular disease. To date, the cause of both forms of AD is not well established as a conclusive molecular mechanism remains obscure.

However, a major pathogenic mechanism widely accepted to be relevant for the etiology of AD is the “amyloid cascade hypothesis.” Previous studies had implicated that aggregated Aβ proteins could induce neurotoxicity via increased reactive oxygen species (ROS). The detailed mechanisms on APP induced ROS production and related to neurodegeneration in AD could be found in recent published review papers in references 14 and 15. On the other hand, dysregulation of intracellular calcium is significantly involved in the toxicity of APP related to pathogenesis of neurodegeneration in AD. It has been known that aggregated Aβ proteins could induce calcium influx into neurons and increase intracellular calcium concentration. Furthermore presenilins, γ-secretases responsible for APP cleavage, was found to be involved in the regulation of intracellular calcium stores. The detailed informations related to APP, presenilins, calcium and AD onset could be found in some well written recent reviews in reference 19. Therefore the aggregated Aβ proteins could contribute to neurodegeneration via increased ROS and dysregulated intracellular calcium as converging steps for “amyloid cascade hypothesis” related to pathogenesis of AD.

Furthermore, recent findings implicated that the APP induced neurotoxicity was tau-dependent. Tau protein is known for its role in the stabilization of microtubules, which is important for the generation and maintenance of neurite. In AD, tau loses its microtubule-binding and stabilizing function and form neurofibrillary tangles leading to the degeneration of neurons, which was implicated to AD pathogenesis. It was reported that tau inhibits transport of APP into axons and dendrites, causing its accumulation in the cell body. Furthermore recent new studies provided strong evidence for tau-dependent Aβ toxicity. They found that tau, which was known to be axonal protein, has a dendritic function in postsynaptic targeting of Fyn, the Src kinase. One of Fyn substrates is the NMDA receptor (NR). Missorting of tau in transgenic mice expressing truncated tau or absence of tau in tau knockout mice both disturb postsynaptic targeting of Fyn. Hereby alleviated NR-mediated excitotoxicity and abrogated Aβ toxicity. A model was proposed that Fyn localized to the postsynapse in a tau-dependent manner and phosphorylated the NR subunit NR2b at Y1472. This phosphorylation promotes the interaction of NRs with PSD-95, a scaffolding protein. The interaction enhances the stability of NRs within the postsynaptic density and facilitates NRs to excitotoxic downstream signaling, which could be the downstream pathway of Aβ induced toxicity. Hence, decrease of tau level or targeting of tau-dependent toxic mechanisms, such as the Fyn-mediated interaction of NRs and PSD-95, could be suitable strategies for therapy of AD and related disorders.

**Molecular Structure of APP**

Human APP belongs to a highly conserved family of type 1 transmembrane glycoproteins which constitutes APP and the mammalian homologs APLP-1 and APLP-2, both homologs lacking the Aβ sequence. The evolutionary conservation of APP gene family also extends to invertebrate species with its orthologs APPL in Drosophila and APL-1 in Caenorhabditis elegans respectively. These proteins all share several conserved motifs within the large extracellular domain and a short cytoplasmic region which exhibits the highest sequence homology. The human APP gene contains 18 exons spanning more than 170 kbp. The region encoding the Aβ sequence comprises part of exons 16 and 17 and is composed of 40 to 43 amino acid residues that extend from the ectodomain into the transmembrane domain of this protein (Fig. 1). The presence of multiple distinct domains located within the extracellular portion includes a signal peptide (SP), a heparin-binding/growth-factor-like domain 1 (HPBD1), a copper-binding domain (CuBD), a zinc-binding domain (ZnBD), a Kunitz-type protease inhibitor domain (KPI), a second heparin-binding domain 2 (HPBD2), a random coil region (RC) and the Aβ sequence (Fig. 1). The remaining region consists of the cytoplasmic tail of APP, including AICD. Several isoforms of APP that arises from alternative splicing have been identified and the most common forms differ mainly by the absence (APP-695) or presence (alternatively spliced APP-751 and APP-770) of a KPI domain.

** Trafficking and Proteolytic Processing of APP**

APP can undergo amyloidogenic or non-amyloidogenic processing via cleavage by different secretases. The amyloidogenic processing of APP, cleaved initially by β-secretase, produces a long soluble secreted form of APP (sAPPβ) and a carboxy-terminal fragment (CTF99) containing the Aβ sequence and AICD. In the brain, β-site APP cleaving enzyme (BACE1) has been found to be the major β-secretase. In the alternative non-amyloidogenic pathway, APP could also be proteolytically processed by a presenilin-containing α-secretase complex, which cleaves at a site within Aβ sequence and consequently abrogates Aβ formation. The non-amyloidogenic cleavage releases a carboxy-terminal fragment (CTF83) and another soluble fragment (sAPPα) which, in contrast to Aβ, may be neuroprotective. Both CTF99 and CTF83 fragments are then sequentially cleaved within the
APP is also ubiquitously expressed in mammalian cells and was found to have complicated physiological roles in cell adhesion, neuronal differentiation, neuronal migration, neurite outgrowth and synapse formation.\(^{49-61}\) The immunoreactivity of APP was found to increase after brain injury of mice, which correlated well with traumatic brain injury.\(^{62}\) APP knockout mice showed reductions in weight, deficits in balance and strength, impairments in behavior and long-term potentiation.\(^{63-65}\) The evidence from other APP knockout in vivo animal model systems demonstrated potential roles of APP in neuron generation, differentiation as well as neural migration.\(^{66}\)

Taken together, these findings corroborate a potential crucial role for APP as part of a complex mechanism involved in a wide variety of neuronal functions, including normal neural development or response to traumatic brain injuries. Cumulative evidence suggests that the soluble sAPP\(^\alpha\) is neuroprotective and is associated with growth factor-like functions, while the interaction of AICD with a myriad of proteins links it with diverse processes such as axonal transport and transcriptional regulation. The different neuronal roles of various APP fragments will be further discussed in details below.

**Potential Neuronal Functions of APP**

While A\(^\beta\) is central to AD pathogenesis, the evolutionary conservation of APP and the presence of APP isoforms lacking A\(^\beta\) sequence indicates that amyloidogenesis is unlikely the main physiological function of this protein family.\(^{44}\) Recent cumulative evidence demonstrated that APP is important for neuron generation, neuron differentiation and neural migration. In nematode *Caenorhabditis elegans*, loss of APL-1 by genetic inactivation resulted in postnatal lethality due to abnormalities in multiple developmental processes such as molting defects. This phenotype could be successfully rescued by expressing the extracellular domain of APL-1 in neurons.\(^{45}\) Furthermore APP was found to be important in *Drosophila melanogaster*, as deletion of the APPL gene leads to behavioral defects in phototaxis that could be partially rescued by human APP.\(^{46}\) Interestingly, highly elevated APPL levels were observed in regenerating neurons of a *Drosophila* brain injury model.\(^{57}\) In contrast, lack of this stress response in APPL mutant flies increased mortality.\(^{38}\) As an upregulation of APPL correlated with an increase in neurite arborization, a potential role in axonal outgrowth after traumatic brain damage was attributed to APP.\(^{47}\) Another study showed that APPL overexpression promoted synapse differentiation, while APPL mutants resulted in decreased synaptic bouton numbers at the neuromuscular junction in *Drosophila*.\(^{48}\)

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**Role of sAPP\(^\alpha\) in the Positive Regulation of Neurogenesis**

The physiological functions of sAPP\(^\alpha\) have been implicated in the enhancement of synaptogenesis, neurite outgrowth, cell survival and cell adhesion.\(^{41,67}\) In separate reports, sAPP\(^\alpha\) has been observed to exert proliferative effects on NPC isolated from the embryonic brains.\(^{50,53}\) In 2005, Caille et al. first acquired evidence suggesting the in vivo role of sAPP\(^\alpha\) in adult neurogenesis.\(^{50}\) The authors found that sAPP\(^\alpha\) binds prominently to cells of the subventricular zone (SVZ), one of the two adult central nervous system sites harboring NPC that are capable of regeneration in the adult brain.\(^{50}\) Their findings suggested that

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**Figure 1.** Schematic diagram of APP consisting of a large extracellular domain, a hydrophobic transmembrane domain and a short cytoplasmic carboxyl terminus. The protein is proteolytically processed by different secretases via amyloidogenic and non-amyloidogenic proceeding pathways which either releases the A\(^\beta\) peptide (cleaved by \(\beta\)- and \(\gamma\)-secretase) or precludes A\(^\beta\) formation (cleaved by \(\alpha\)-secretase).
It was reported that these growth-promoting properties of sAPP\(\alpha\) are possibly mediated by the ability of sAPP\(\alpha\) to downregulate CDK5 and inhibit tau hyperphosphorylation. Early in vitro studies have also demonstrated that sAPP\(\alpha\) protects cultured neurons against hypoglycemia damage and glutamate neurotoxicity through the activation of potassium channels, which in turn mediates the ability of sAPP\(\alpha\) to inhibit calcium influx and thus modulates neuronal excitability. Intriguingly, sAPP\(\alpha\) levels were shown to decrease in the cerebrospinal fluid (CSF) of sAPP\(\alpha\) were likely to participate in the EGF-induced proliferation of type A cells, although sAPP\(\alpha\) alone fails to induce proliferation of these cells. The authors also observed that infusion of sAPP\(\alpha\) into the lateral ventricle of mice led to an increase in number of progenitor cells. Conversely, blocking sAPP\(\alpha\) secretion by \(\alpha\)-secretase inhibitor or downregulating APP synthesis by antisense oligonucleotide against APP decreases the proliferation of EGF responsive cells, which leads to a reduction of the pool of progenitors. Their results also showed that sAPP\(\alpha\) activity may be delivered in an autocrine/paracrine manner. The crystal structure analysis at 1.8 Å resolution of APP further demonstrated that its cysteine-rich N-terminal heparin-binding domain is similar to other cysteine-rich growth factors, which is conceived to be responsible for its function to stimulate neurite outgrowth. These growth-promoting properties of sAPPs and its structural similarities with cysteine-rich growth factors suggest that sAPPs may function as a growth factor in vivo.

The APP processing procedure and cleavage products. The non-amyloidogenic APP processing pathway (right) involves proteolytic cleavages by \(\alpha\)- and \(\gamma\)-secretases resulting in the generation of sAPP\(\alpha\) and carboxyl terminal fragments including P3, CTF83 and AICD. The alternative amyloidogenic APP processing pathway (left) involves proteolytic cleavages by \(\beta\)- and \(\gamma\)-secretases resulting in the generation of sAPP\(\beta\) and carboxyl terminal fragments including A\(\beta\), CTF99 and and AICD. A\(\beta\) peptides could oligomerize and fibrillize leading to AD pathology. sAPP\(\alpha\) could function to promote neurogenesis and survival, while AICD could have effects to inhibit neurogenesis possibly via forming complex with Fe65 and leading to transcriptional regulation.

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Taken together, these results suggest that sAPP\(\alpha\) might function as specific growth factors or as a mediator for adult NPC proliferation. However, to date, no sAPP\(\alpha\) receptors have been identified yet and the signaling pathways triggered have not been thoroughly investigated. To this extent, it is of interest to note that two in vitro studies have reported a stimulation of MAP kinase activity by sAPP\(\alpha\) and it would thus be of importance to dissect this signaling pathway triggered by sAPP\(\alpha\) in detail. Intriguingly, sAPP\(\alpha\) levels were shown to decrease in the cerebrospinal fluid (CSF) of...
AD individuals, while infusion of sAPPα into the brain increased synaptic density and improved memory retention. Therefore, these findings raised the possibility that sAPPα may contribute to neurogenesis in adult brain and sAPPα might be used for AD patients clinically, while decrease of sAPPα levels in brain may be an indispensable precondition for AD pathogenesis.

**Role of AICD in the Negative Modulation of Neurogenesis**

AICD was termed by analogy to NICD (Notch intracellular domain) formed by the regulated intramembrane proteolysis (RIP) of another type I transmembrane glycoprotein Notch. Both AICD and NICD were produced via cleavage of APP or Notch by the same γ-secretase complex respectively. Extracellular binding of Notch to its ligand is one of the mechanisms responsible for this regulation of cleavage, stimulating release of NICD in cells. The NICD translocates into the nucleus and leads to a series of downstream signaling cascades. Although multiple proteins have been reported to interact with AICD including Fe65 that may be necessary for AICD-dependent signaling, no functional ligands for APP have been characterized so far. Recently Ma et al. discovered that transient axonal glycoprotein 1 (TAG1), a neural cell adhesion molecule of the F3 family, acts as an...
extracellular binding partner for APP through the immunoglobulin (Ig) and fibronectin repeat (FNIII) domains of TAG1. It was also found that the extracellular interaction between APP and TAG1 was essential for initiating the release of AICD, which could be abrogated by the presence of specific γ-secretase inhibitors. It was further confirmed in knockout in vivo studies that the interaction between TAG1 and APP negatively modulates neurogenesis through release of AICD and triggers a Fe65-dependent molecular event. These findings provided valuable insights that APP could function as a transmembrane receptor protein which negatively mediates neurogenesis through recognition of its specific cell surface-associated ligands.

However, the detailed mechanism by which AICD suppresses neurogenesis still remains to be elucidated. Several questions regarding TAG1-APP signaling pathway including its potential contributory roles in adult brain development and AD pathogenesis also remain unanswered. What physiological functions does this signaling pathway eventually mediate? As yet, few immediate downstream target genes have been identified for AICD and Fe65. Based on the resemblance of molecular structure and processing procedure between Notch and APP as well as known knowledge of the Notch cascade, it would be tempting to speculate that the AICD generated by γ-secretase cleavage may be capable of inducing an intracellular signaling pathway via modulation of gene expression after interaction with its adaptor protein Fe65. The interaction between AICD and Fe65 may promote the translocation of AICD directly to the nucleus or may initiate a Fe65-mediated nuclear signal independently of AICD translocation. However, the hypothesis that AICD could function to modulate transcriptional activity in cells appears highly controversial so far. Although numerous studies have suggested that AICD can regulate expression of various endogenous genes including KAI1, GSK-3b, APP and neprilysin, other groups were unable to replicate these findings. Therefore it would thus be necessary to delineate the downstream components of the TAG1-APP signaling cascade to clarify the precise mechanisms of negatively modulating the expression of various endogenous genes.

miRNAs, APP, Neurogenesis and AD

miRNAs are small non-coding RNA molecules that regulate gene expression by binding to the 3'UTR of their target mRNAs for repression of target gene expression by translation inhibition or mRNA degradation. It was known that miRNAs are abundantly expressed in the central nervous system and they have essential functional roles in brain development and neuronal specification. However dysfunctions or aberrant signaling of the miRNA pathway was demonstrated to result in neurodegenerative diseases. Recent accumulating evidence implicated the dysregulation of miRNAs expression in AD. It was reported that there was an upregulation of miR-9, miR-125b and miR-128 in hippocampus of AD affected post-mortem brain samples. Their findings also implicated that ROS might contribute to AD via pathways mediated by miRNAs. The alterations of miRNA expression profiles between AD and control brain samples have also been reported by other research groups. Importantly, all reports consistently demonstrated the consecutive upregulation of miR-125b and downregulation of miR-9 and miR-210 in AD brains. This is suggestive of important roles of these miRNAs, as miR-125b and miR-9 have also been implicated in neurodegenerative diseases such as Down Syndrome and Huntington disease. Furthermore miRNA dysregulation has also been observed in CSF of AD patients, suggesting that specific miRNAs may be used as putative biomarkers for neurodegenerative diseases.

Studies also demonstrated that miRNAs can regulate APP expression, APP processing and Aβ accumulations. It was found that miRNAs hsa-mir-106a and hsa-mir-520c could bind to their predicted target sequences in the APP 3'UTR and negatively regulate APP expression. Another recent study showed that miR-101 is a negative regulator of APP expression and could affect the accumulation of Aβ, suggesting a possible role for miR-101 in neuropathological conditions. Furthermore miRNAs belonging to the miR-20a family (miR-20a, miR-17-5p and miR-106b) was found to regulate APP expression in vitro and at the endogenous level in neuronal cell lines. In this study a tight correlation between these miRNAs and APP was found during brain development and in differentiating neurons. Such possibility is further corroborated by the observation that a significant decrease...
Alteration of Neurogenesis in AD

Several studies have suggested that the rate of neurogenesis in both SVZ and dentate gyrus (DG) declines with age, raising the possibility that reduced or misregulated neurogenesis may account, to a certain extent, for the cognitive deterioration in the elderly or contribute to learning and memory deficits in individuals with AD. Indeed, in vitro experiments have shown that excessive accumulation of Aβ affected the function of cultured human cortical NPC by suppressing their proliferation and neuronal differentiation and ultimately inducing apoptosis. The deteriorative effect of Aβ on neurogenesis has also been demonstrated in in vivo AD mouse models that have either been genetically mutated or intra-ventricularly infused with Aβ to cause neuritic plaque accumulation. These mice displayed impairments in neuronal generation from NPC in DG as well as reduced capacity of differentiation and survival of newly generated neurons. In support of these observations, it was revealed that a significant decrease in proliferation of progenitor cells was found in aged

in miR-106b expression was found in sporadic AD patients. On the other hand, two miRNAs (miR-298 and miR-328) was found to regulate BACE mRNA translation, while BACE was responsible for APP processing and Aβ production. These findings implicated the interesting internal link among miRNA, neurogenesis, APP and AD, which deserve extensive studies in the future.
mice (expressing human mutant APP plus a deletion of exon 9 of presenilin 1) at ages 6 and 9 months. This finding was supported by another similar study from Taniuchi et al. that the number of proliferating and newly differentiating neurons in SGL decreased significantly in 9-month-old FAD-linked APP<sup>swe</sup>/PS<sup>1ΔE9</sup> mice but not in 5-month-old mice. However, a recent study by Demars et al. examined the fate of NPC in both SGL and SVZ of young APP<sup>swe</sup>/PS<sup>1ΔE9</sup> transgenic mice. They showed that proliferation and differentiation of NPC were severely impaired early in mice at 2 months age, preceding onset of amyloid deposition and memory impairments.

Figure 5. Flow chart summarization of potential pathogenesis of AD related to APP. The altered APP processing could contribute to Aβ accumulation, increased AICD and decreased sAPP. The increased AICD and decreased sAPP could finally lead to decreased neurogenesis, while decreased sAPP could also facilitate neurodegeneration. The Aβ accumulation could lead to Aβ senile plaques and induce calcium flux via a tau protein-dependent manner. The dysregulated intracellular calcium and increased ROS level finally contribute to neurodegeneration. Hereby the decreased neurogenesis and increased neuron degeneration contribute to AD.
neurogenic niches was shown. Therefore, these results suggest that NPC are affected early in AD in both neurogenic areas of adult brain and may contribute to deficits in hippocampus- and olfaction-dependent memory in AD.

On the contrary other reports demonstrated increased neurogenesis in the context of AD. A recent report showed that transgenic mice expressing three or more FAD-linked APP mutations showed an upregulation of cell proliferation and neuronal differentiation in hippocampus and SVZ. In a different study, Jin et al. found an increase in numbers of newly proliferating cells in the SGL and SVZ in FAD-linked transgenic mice expressing human APP isoforms APP695, APP751 and APP770 with (V717F, K670N, M671L) mutations. Lopez-Toledana et al. also demonstrated an increase in proliferation of hippocampal cells and their neuronal differentiation in APP mice models similar to Jin. Furthermore one report on postmortem study of senile AD brain showed increased levels of cells with proliferative and immature neuron markers. On the contrary, another study on presenile AD brains demonstrated that the increased proliferation of cells in DG were non-neuronal, which could not reflect an increase in neurogenesis in AD brains.

In summary, conflicting results were observed in seemingly similar AD mice models. However, as APP metabolites, including sAPPα, CTF, AICD and Aβ, may have unique roles that modulate neurogenesis differently, the complexities may result from the numerous FAD-linked variables that could influence APP metabolism in cells. Although it still remains to be firmly established whether impairments of neurogenesis contribute to the pathogenesis of AD, findings on molecular links between neurogenesis and AD so far implicates the disorders of neurogenesis to be an integral part of AD pathology.

**Neurogenesis as a Therapeutic Strategy for AD**

Currently, ongoing clinical trials are directed towards evaluating therapeutic approaches to stall the progression of AD by preventing neurons from further degeneration and providing symptom relief. Unfortunately, strategies aimed to arrest the degenerative process may fall short of cognitive recovery as they still leave the brain marred with defective neural synapses and neuronal loss. The understanding of stem cell biology and discovery of neurogenesis in adult brain thus hold the promise on the regeneration of damaged neural tissue and restoration of neuronal circuits essential for cerebral function. In the developing brain, most stem cells and microenvironments are spatially shifting and are temporally transient, as the cellular and molecular programs of neurogenesis and morphogenesis are "assembled and disassembled." In contrast, the adult brain restricts such proliferative potential of NPC to special selective microenvironments. These specialized domains are restricted to the SVZ of the lateral ventricle and the DG subgranular zone of the hippocampus, retaining developmental potential throughout life span. Therefore the adult CNS may be amenable to repair and this provide the basis for new strategies for AD therapy: to stimulate endogenous NPC or stem cells of the adult brain and to transplant adult-derived NPC or stem cells into brains of AD patients. While the potential of stem cell regeneration in the adult brain is vast, its delivery to target areas of the brain poses a challenge. Systemic injection provides a non-invasive strategy but direct delivery of NPC to the brain faces the challenge of how to distribute cells throughout the brain as AD is characterized by a diffuse pattern of degeneration. Furthermore, as the progression of AD is not uniformly distributed, the affected regions of degenerating and degenerated neural circuits present challenges for integration of injected NPC.

On the other hand, although the appropriate delivery of exogenous NPC to restricted regions of the affected brain remains a challenge, ongoing neurogenesis by endogenous NPC provides an exciting avenue that has the potential to resolve cognitive deficits in individuals with AD. Endogenous stem cells exist in low abundance in the adult brain, but could be stimulated to induce proliferation under appropriate conditions. To this aim, a potential therapeutic approach is the delivery of growth factors to brain to promote neurogenesis. Basic scientific analyses and human trials indicated that constituents of microenvironments within the brain determine the potential of neurogenesis, differentiation of NPC and magnitude of the NPC pool. Multiple analyses have been documented that AD neurogenesis is regulated by FGF-2, IGF-1 and VEGF. For example, FGF-2 enhanced DG neurogenesis in both neonatal and adult brain and intra-cerebroventricular (ICV) infusions of FGF-2 increased DG neurogenesis in aged brain. Likewise, IGF-1 increased DG neurogenesis in adult and aged brain following ICV administration of IGF-1. VEGF can promote DG neurogenesis in both intact and injured adult brain following ICV administration. Recently, a report has also demonstrated that fetal NPC transplantation reduced memory deficits and amyloid plaque deposition in a mouse AD model, transgenic overexpression of K670N or M671L APP mutation. In addition, the mice model showed significant improvement in cognition after NPC transplantation.

While NPC are currently being investigated as potential therapies for neurodegenerative diseases like AD, concerns have also been raised over the safety of this experimental therapeutic approach. This includes the possibility of tumor formation from transplanted NPC in human brain. A report on a human brain tumor from NPC complicating NPC therapy suggests that NPC may also be involved in gliomagenesis and this finding provides an example of a donor-derived human brain tumor. Therefore, further researches are urgently required to assess the safety of these therapies.

**Potential Secretase Balances and Implications to AD**

It was known that sAPPα could protect neurons and promote neurogenesis, while sAPPβ could be produced via α-secretase cleavage. Furthermore the α-secretase cleavage of APP could abrogate Aβ proteins production. On the other hand, β-secretase and γ-secretase cleavage of APP could lead to Aβ proteins formation, which should be deleterious and could contribute to neurodegeneration in AD. Furthermore the γ-secretase cleavage of
Based on above-mentioned analysis, it can also be concluded that the activity of α-secretase was a key factor related to AD onset. Therefore factors to downregulate α-secretase activity should be paid more attentions, as they might be the original underlying cause for AD, especially sporadic AD. On the other hand, factors to control β-secretase and γ-secretase, such as miRNAs, should also be paid attention. As dysfunction of these controlling factors might lead to enhancement of activities of β-secretase and γ-secretase, which will overwhelm the activity of α-secretase and contribute to AD.

**Future Prospects and Directions**

The secreted sAPPα has been demonstrated to promote neurogenesis, which could be a factor to prohibit AD onset. Therefore factors to downregulation of α-secretase activity should be paid more attentions, as they might be the original underlying cause for AD, especially sporadic AD. On the other hand, factors to control β-secretase and γ-secretase, such as miRNAs, should also be paid attention. As dysfunction of these controlling factors might lead to enhancement of activities of β-secretase and γ-secretase, which will overwhelm the activity of α-secretase and contribute to AD.
another signal pathway, which is crucial to neurogenesis and neuron cell survival. In this context, sAPPα might function as a modulator to influence the binding affinity between ligands and receptors. However the third possibility that sAPPα could penetrate through cell membrane and confer its effects in the cytoplasmia still cannot be completely excluded. One practical way to solve these questions is to utilize LC-MS-MS to identify sAPPα interacting proteomics. Progresses within this aspect in the future should help to further understand the detailed mechanisms of sAPPα induced neurogenesis and anti-apoptosis effects. This will also help to develop better therapeutic strategies for AD.

On the other spectrum, further studies on the detailed molecular events of TAG1-APP signaling pathway in cells should also be vital to understanding the influence of neurogenesis by APP. Currently, it is of great interest urgent to decipher how AICD functions to negatively regulate neurogenesis following the activation of the TAG1-APP pathway. It can be hypothesized that the AICD-F65 complex might act as transcription factors, transcription co-activators or transcription co-repressors to regulate various gene expressions. Another possibility could be that AICD might inhibit neurogenesis via interaction with key players of other signal pathways, which are vital to neurogenesis. The LC-MS-MS analysis to search for AICD interacting partners in cells should also help to provide interesting answers for the questions to these.

Recently, it has been demonstrated that the dysregulation of miRNAs was linked to AD pathogenesis. The dysregulation of miRNAs could also influence APP expression level, APP processing and even Aβ accumulations in cells. Therefore, identifying miRNAs that could function to regulate the expression of APP as well as miRNAs which could regulate expressions of BACE (B-secretase) and presenilins (γ-secretase), should be significant to AD pathogenesis in the near future especially for sporadic AD. Future progress on miRNAs to control the expressions of APP, secrete AD and factors related to TAG1-APP signaling pathway should be significant to AD pathogenesis and therapy.

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References

1. Golde TE, Dickson D, Hurtont M. Filling the gaps in the abeta cascade hypothesis of Alzheimer's disease. Curr Alzheimer Res 2006; 3:423-30.
2. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006; 368:387-403.
3. Chohan MO, Haque N, Alonso A, El-Akkad E, Grundleigh I, Gerner A, et al. Hyperphosphorylation, induced self assembly of murine tau: a comparison with human tau. J Neuro Transm 2005; 112:1035-47.
4. Hardy J, Allshop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci 1991; 12:383-8.
5. Lenes S, Koh MT, Kottlik S, Kayed R, Glabe CG, Yang A, et al. A specific amyloid-beta protein assembly in the brain impairs memory. Nature 2006; 440:352-7.
6. Glenner GG, Wong CW. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. Biochem Biophys Res Commun 1984; 122:1131-15.
7. Sherrington R, Rogaei E, Liang Y, Rogaes A, Vevesque G, Ikeda M, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995; 375:574-60.
8. Levy-Lahad E, Waco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 1995; 269:973-7.
9. Poitier J, Miniich A, Davignon J. Apo lipoprotein E, synaptic plasticity and Alzheimer's disease. Ann Med 1995; 27:663-70.
10. Ali G, Waco W, Cai X, Stobo P, Sheu KF, Cooper AJ, et al. Isolation, characterization and mapping of gene encoding dihydrodipicolinic succinimydolase (EZK) of human alpha-ketoglutarate dehydrogenase complex. Somat Cell Mol Genet 1994; 20:99-105.
11. Blacker D, Wilcos MA, Laird NM, Rodes L, Horvath SM, Go RC, et al. Alpha-2 macroglobulin is genetically associated with Alzheimer disease. Nat Genet 1998; 19:379-60.
12. Law A, Garnier S, Quirion R. Say NO to Alzheimer's disease: the putative links between nitric oxide and dementia of the Alzheimer's type. Brain Res Brain Res Rev 2001; 35:73-96.
13. Mayeux R. Epidemiology of neurodegeneration. Annu Rev Neurosci 2003; 26:81-104.

14. Butterfield DA. Amyloid beta-peptide (1-42)-induced oxidative stress and neurotoxicity: implications for neurodegeneration in Alzheimer's disease brain. A review. Free Radic Biol Med 2002; 33:1307-13.
15. Varadharajan S, Vain T, Akesonova M, Butterfield DA. Review: Alzheimer's amyloid-beta protein-associate free radical oxidative stress and neurotoxicity. J Struct Biol 2000; 130:184-208.
16. Kluckman SJ. Hypothesis on the regulation of cytoplasmatic calcium concentration and the aging brain. Neurobiol Aging 1987; 8:345-6.
17. Mattson MP, Cheng B, Davis D, Bryant K, Lieberman I, Rydel RE. Beta-Amyloid peptides destabilize calcium homeostasis and regulate human cortical neurons vulnerable to excitotoxicity. J Neurosci 1992; 12:376-89.
18. Zhang H, Sun S, Herremans A, De Strooper B, Berzovzanny I. Role of presenilins in neuronal calcium homeostasis. J Neurosci 2000; 30:8656-60.
19. Mattson MP ER calcium and Alzheimer's disease: in a state of flux. Sci Signal 2007; 7:310.
20. Binder LJ, Frankfurtter A, Brehm H. The distribution of tau in the mammalian central nervous system. J Cell Biol 1985; 101:1371-38.
21. Caceres A, Kosik KS. Inhibition of neurite polarity by tau antisense oligonucleotides in primary cerebellar neurons. Nature 1990; 343:661-3.
22. Cleveland DW, Hsue SY, Kirkner MW. Physical and chemical properties of purified tau factor and the role of tau in microtubule assembly. J Mol Biol 1977; 116:227-47.
23. Drubin DG, Kirchmer MW. Tau protein function in living cells. J Cell Biol 1986; 103:2739-46.
24. Garcia ML, Cleveland DW. Going new places using an old MAP: tau, microtubules and human neurodegenerative disease. Curr Opin Cell Biol 2001; 13:41-8.
25. Itner LM, Ke YD, Delerue E, Bi M, Gladbach A, van Eersel J, et al. Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. Cell 2010; 142:887-97.
26. Stamer K, Vogel R, Thies E, Mandelkow EM, Mandelkow E. Tau blocks traffic of organelles, neurotransmissions and APP vesicles in neurons and enhances oxidative stress. J Cell Biol 2002; 156:1561-63.
27. Goldaber D, Lerman MI, McBride WO, Saffourt I, Gajdusek DC. Isolation, characterization and chromosomal localization of human brain cDNA clones coding for the precursor of the amyloid of brain in Alzheimer's disease, Down's syndrome, and aging. J Neural Transm Suppl 1987; 24:23-8.
28. Karg J, Lemaire HG, Unterbeck A, Salbaum JM, Masters CL, Grzeschik KH, et al. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature 1987; 325:733-6.
29. Waco W, Bupp K, Maegandz M, Guella JF, Tanzi RE, Solomon F. Identification of a mouse brain cDNA that encodes a protein related to the Alzheimer disease-associated amyloid beta protein precursor. Proc Natl Acad Sci USA 1992; 89:10758-62.
30. Waco W, Gurubachavanil, Paradis MD, Romano DM, Sindoa SS, Hyman BT, et al. Isolation and characterization of APP2 encoding a homologue of the Alzheimer's associated amyloid beta protein precursor. Nat Genet 1993; 5:99-100.
31. Diage I, Li C, apl-1, a Caenorhabditis elegans gene encoding a protein related to the human beta-amyloid protein precursor. Proc Natl Acad Sci USA 1993; 90:12045-9.
32. Rosen DR, Martin-Morris L, Luo LQ, White K. A Drosophila gene encoding a protein resembling the human beta-amyloid protein precursor. Proc Natl Acad Sci USA 1989; 86:2478-82.
33. Galle M, Ferrera ST. Structure and functions of the human amyloid precursor protein: the whole is more than the sum of its parts. Prog Neurobiol 2007; 82:11-32.
34. Yoshikai S, Sada H, Doh-ura K, Furuya H, Sakaki Y. Genomic organization of the human amyloid beta-protein precursor gene. Gene 1990; 87:257-63.
35. Koriguchi N, Takahaishi Y, Tokuhashi Y, Shiojiri S, Ito H. Novel precursor of Alzheimer's disease amyloid protein shows protease inhibitory activity. Nature 1988; 331:530-2.
36. Konig G, Monning U, Czech C, Prior R, Banati R, Schreitter-Gasser U, et al. Identification and differential expression of a novel alternative splice isoform of the beta A4 amyloid precursor protein (APP) mRNA in leukocytes and brain microglial cells. J Biol Chem 1992; 267:10804-9.
37. Ling Y, Morgan K, Kalishker N. Amyloid precursor protein (APP) and the biology of proteolytic processing: relevance to Alzheimer's disease. J Biol Chem 2003; 278:15055-35.
Amino-terminal region of secreted form of human type 2 lissencephaly in mice lacking all three micro RNA-146a-mediated inflammatory circuit in micro RNA expression in the developing mammalian cortex. BMC Genomics 2011; 12:160.

Pillai RS, MicroRNA family: multiple mechanisms for a tiny mRNA 2005; 11:1753-61.

Barad O, Meiri E, Avniel A, Aharonov R, Barzilai A, Bentwich I, et al. MicroRNA expression detected by oligonucleotide microarrays: system establishment and expression profiling in human tissues. Genome Res 2004; 14:2486-94.

Misra EA, Alvarez-Saavedra E, Townsend M, Yohssi A, Sestan N, Rakic P, et al. Microarray analysis of microRNA expression in the developing mammalian brain. Genome Biol 2004; 5:68.

Sminovska I, Gura A, Seier A, Schumacher S, Nitsch R, Walczyn FG. Regulation of miRNA expression during neural cell specification. Eur J Neurosci 2005; 21:1469-77.

Cogswell JR, Ward J, Taylor IA, Waters M, Shi Y, Cannon B, et al. Identification of mRNA changes in Alzheimer's disease brain and CSF yields putative biomarkers and insights into disease pathways. J Alzheimers Dis 2008; 12:271-212.

Qiu WQ, Ferreira A, Miller C, Koo EH, Selkoe DJ. Cell-surface beta-amyloid precursor protein stimulates neurite outgrowth of hippocampal neurons in an isoform-dependent manner. J Neurosci 1995; 15:2577-67.

Schubert D, Jin LW, Saitoh T, Cole G. The regulation of amyloid beta precursor protein secretion and its modulatory role in cell adhesion. Neuron 1989; 3:689-94.

57. Siemes C, Quan T, Kummer C, Wehner S, Kröfel H, Muller U, et al. Keratinocytes from APP/APLP2- deficient mice are impaired in proliferation, adhesion and migration in vitro. Exp Cell Res 2006; 312:1939-49.

58. Wang B, Yang L, Wang Z, Zheng H. Amyloid precursor protein mediates presynaptic localization and activity of the high-affinity choline transporter. Proc Natl Acad Sci USA 2007; 104:14140-5.

59. Wang P, Yang G, Mosier DR, Chang P, Zaidi T, Gong YD, et al. Defective synaptic vesicle density and active zone size in mice lacking amyloid precursor protein (APP) and APP-like protein 2. J Neurosci 2005; 25:1219-25.

60. Yang G, Gong YD, Kong G, Jiang WL, Kwon E, Wang P, et al. Reduced synaptic vesicle density and active zone size in mice lacking amyloid precursor protein (APP) and APP-like protein 2. Neurosci Lett 2005; 386:62-71.

61. Young-Perel TE, Bai J, Chang R, Zheng JB, LoTurco JJ, Selkoe DJ. A critical function for beta-amyloid precursor protein in neuronal migration revealed by an urchin RNA interference. J Neurosci 2007; 27:14459-69.

62. Johnson VE, Stewart W, Smith DH. Traumatic brain injury and amyloid-beta pathology: a link to Alzheimer's disease? Nat Rev Neurosci 2004; 5:473-84.

63. Dawson GR, Seabrook GR, Zheng H, Smith DW, Graham S, O'Dowd G, et al. Age-related cognitive deficits, impaired long-term potentiation and reduction in synaptic marker density in mice lacking the beta-amyloid precursor protein. Neuroscience 1999; 90:1-13.

64. Seabrook GR, Smith DW, Bowery BJ, Easter A, Reynolds T, Fitzjohn SM, et al. Mechanisms contributing to the deficits in hippocampal synaptic plasticity in mice lacking amyloid precursor protein. Neuropharmacology 1999; 38:349-59.

65. Zheng FJ, Jiang M, Trumblauer ML, Sinrat/anghingh Dj, Hopkins R, Smith DW, et al. beta-Amyloid precursor protein-deficient mice show reactive glia and decreased locomotor activity. Cell 1995; 81:525-31.

66. Bergmans BA, Sariati SA, Habets RL, Veenekolk R, Schoonjes J, Muller U, et al. Neurons generated from APP/APPL1/APPL2 triple knockout embryonic stem cells behave normally in vitro and in vivo: lack of evidence for a cell autonomous role of the amyloid precursor protein in neuronal differentiation. Stem Cells 2008; 26:399-406.

67. Gakhar-Koppole N, Hundeshagen P, Mandl C, Weyer SW, Allinquant B, Muller U, et al. Activity requires the amyloid precursor protein family members in the adult subventricular zone. Development 2004; 131:2173-81.

68. Herms J, Andeker B, Heber S, Ring S, Fuhrmann M, Kreutzer S, et al. Cortical dysplasia resembling human type 2 lissencephaly in mice lacking all three APP family members. EMBO J 2004; 23:4106-15.

69. Milward EA, Papadopoulos Fuller SJ, Moor RD, Small D, Beyreuther K, et al. The amyloid precursor protein of Alzheimer's disease is a mediator of the effects of nerve growth factor on neurite outgrowth. Neuron 1992; 9:129-37.

70. Ohawa I, Takamura G, Morimoto T, Ishiguro M, Kohsaka S. Amino-terminal region of secreted form of amyloid precursor protein stimulates proliferation of progenitors in the adult subventricular zone. Development 2004; 131:2173-81.

71. Caille I, Allinquant B, Dupont E, Bouillot C, Langer A, Muller U, et al. Soluble form of amyloid precursor protein mediates presynaptic growth in the adult subventricular zone. Development 2004; 131:2173-81.

72. Herms J, Andler B, Heber S, Ring S, Fuhrmann M, Kreutzer S, et al. Cortical dysplasia resembling human type 2 lissencephaly in mice lacking all three APP family members. EMBO J 2004; 23:4106-15.
92. Krichhevsky AM, King KS, Donahue CP, Khorapko K, Kosik KS. A microRNA array reveals extensive regulation of microRNAs during brain development. RNA 2003; 9:1274-81.
93. Maes OC, Chertkow HM, Wang E, Schipper HM. MicroRNA: Implications for Alzheimer Disease and other Human CNS Disorders. Curr Genomics 2009; 10:154-68.
94. Patel N, Hoang D, Miller N, Ansaloni S, Huang Q, Rogers JT, et al. MicroRNAs can regulate human APP levels. Mol Neurodegener 2008; 3:10.
95. Vilarde O, Barbas C, Ciotii M, Cognoni C, Ruberti E. MicroRNA-101 regulates amyloid precursor protein expression in hippocampal neurons. J Biol Chem 285:18344-51.
96. Provost P. Interpretation and applicability of microRNA data to the context of Alzheimer’s and age-related diseases. Aging (Albany NY) 2:166-9.
97. Kempermann G, Gage FH. Genetic determinants of adult hippocampal neurogenesis correlate with acquisition, but not probe trial performance, in the water maze task. Eur J Neurosci 2002; 16:129-36.
98. Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci 1996; 16:2027-33.
99. Seki T, Arai Y. Age-related production of new granule cells in the adult dentate gyrus. Neuroreport 1995; 6:2479-82.
100. Tropepe V, Craig CG, Morshead CM, van der Kooy D. Transforming growth factor-alpha null and senecent mice show decreased neural progenitor cell proliferation in the forebrain subependyma. J Neurosci 1997; 17:7850-9.
101. Haughey NJ, Liu D, Nath A, Broghard AC, Martin MP. Disruption of neurogenesis in the subventricular zone of adult mice, and in human cortical neuronal precursor cells in culture, by amyloid beta-peptide: implications for the pathogenesis of Alzheimer’s disease. Neuromolecular Med 2002; 1:125-35.
102. Klassen HJ, Infeld KL, Kirov II, Tai L, Gage FH, Young MJ, et al. Expression of cytokines by multipotent neural progenitor cells. Cyrcoxin 2003; 22:101-6.
103. Lindvall O, Bjorklund A. Cell replacement therapy: helping the brain to repair itself. NeuroRx 2004; 1:379-81.
104. Poddar K, Tai YT, Cole CE, Hideshima T, Sartler M, Hamblin A, et al. Essential role of caveolae in interleukin-6- and insulin-like growth factor-1-triggered Akt-1-mediated survival of multiple myeloma cells. J Biol Chem 2003; 278:5794-801.
105. Wen PH, Hof PR, Chen X, Gluck K, Austin G, Younkin SG, et al. The presenilin-1 familial Alzheimer disease mutant P117L impairs neurogenesis in the hippocampus of adult mice. Exp Neurol 2004; 188:224-37.
106. Donovan MH, Yazdani U, Norris RD, Games D, German DC, Esch AJ. Decreased adult hippocampal neurogenesis in the PDAPP mouse model of Alzheimer’s disease. J Comp Neurol 2006; 495:70-83.
107. Brintrup RD, Wang JM. Therapeutic potential of neurogenesis for prevention and recovery from Alzheimer’s disease: allopregnanolone as a proof of concept neurogenic agent. Curr Alzheimer Res 2006; 3:185-90.
108. Laske C, Steffis K, Stramsky E, Seizier P, Akoyy O, Schiewer GW, et al. Decreased plasma and cerebrospinal fluid levels of stem cell factor in patients with early Alzheimer’s disease. J Alzheimers Dis 2008; 15:451-60.
109. Haughey NJ, Nath A, Chan SL, Borchard AG, Rao MS, Martin MN. Disruption of neurogenesis by amyloid beta-peptide and perturbated neural progenitor cell homeostasis, in models of Alzheimer’s disease. J Neurochem 2002; 83:1509-24.
110. Thinakaran G, Teplow DB, Siman R, Greenberg, B, Sooudia SS. Metabolism of the “Swedish” amyloid precursor protein variant in neuron2a (N2a) cells. Evidence that cleavage at the “beta-secretase” site occurs in the Golgi apparatus. J Biol Chem 1996; 271:9390-7.
111. Borchelt DR, Davis J, Fischer M, Lee MK, Shunt HH, Ratovitsky T, et al. A vector for expressing foreign genes in the dentate gyrus of adult mice. Neuron 1996; 16:2027-33.
112. Li D, Tang J, Xu H, Fan X, Bai Y, Yang L. Decreased hippocampal cell proliferation correlates with increased expression of BMP4 in the APPsw/PS1DE9 mouse model of Alzheimer’s disease. Hippocampus 2008; 18:692-8.
113. Tanouchi N, Nidome T, Goto Y, Akaie K, Kihara T, Sugimoto H. Decreased proliferation of hippocampal progenitor cells in APPsw/PS1DE9 transgenic mice. Neuroreport 2007; 18:1801-5.
114. Domats M, Hu YS, Gadadhar A, Lazaro O. Impaired neurogenesis is an early event in the etiology of familial Alzheimer’s disease in transgenic mice. J Neurosci Res 88:2103-17.
115. Lopez-Toledano MA, Shalanski ML. Neurogenic effect of beta-amylloid peptide in the development of neural stem cells. J Neurosci 2004; 24:5439-44.
116. Jin K, Mao XO, Costello B, Schilling B, Xie L, Row RH, et al. Proreicin and -amino acidome characteristic of a role for stathmin in adult neurogenesis. FASEB J 2004; 18:287-99.
117. Jin K, Galvan V, Xie L, Mao XO, Gorostiza OF, Bridesen DE, et al. Enhanced neurogenesis in Alzheimer’s disease transgenic (PDGF-APPSw,Ind) mice. Proc Natl Acad Sci USA 2004; 101:13363-7.
118. Lopez-Toledano MA, Shalanski ML. Increased neurogenesis in young transgenic mice overexpressing human APP(sw,Ind). J Alzheimers Dis 2007; 12:229-40.
119. Jin K, Piel AL, Mao XO, Xie L, Costello BA, Henshall DC, et al. Increased hippocampal neurogenesis in Alzheimer’s disease. Proc Natl Acad Sci USA 2004; 101:343-7.
120. Boekhoff K, Joels M, Lucassen PJ. Increased proliferation reflects glial and vascular-associated changes, but not neurogenesis in the pristine Alzheimer hippocampus. Neurobiol Dis 2006; 24:1-14.
121. Taupin P. The therapeutic potential of adult neural stem cells. Curr Opin Mol Ther 2006; 8:225-31.
122. Martino G, Pluchino S. The therapeutic potential of neural stem cells. Nat Rev Neurosci 2006; 7:395-406.
123. Alvarez-Buylla A, Lim DA. For the long run: maintaining germinal niches in the adult brain. Neuro 2004; 41:683-6.
124. Lindvall O, Kokaia Z. Stem cells for the treatment of neurological disorders. Nature 2006; 441:1094-9.
125. Horner PJ, Gage FH. Regeneration in the adult and aging brain. Arch Neurol 2002; 59:1717-20.
126. Vallieres L, Campbell IL, Gage FH, Savchenko PE. Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. J Neurosci 2002; 22:486-92.
127. Kempermann G, Gast D, Gage FH. Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. Ann Neurol 2002; 52:135-43.
128. Anderson MF, Aberg MA, Nilsson M, Eriksson PS. Insulin-like growth factor-1 and neurogenesis in the adult mammalian brain. Brain Res Dev Brain Res 2002; 134:115-22.
129. Kuhn HG, Winkler J, Kempermann G, Thal LJ, Gage FH. Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. J Neurosci 1997; 17:5820-9.
130. Palmer TD, Markakis EA, Willhoite AR, Salafar J, Gage FH. Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. J Neurosci 1999; 19:8487-97.
131. Shetty AK, Hartiagady B, Shetty GA. Stem/progeni- tor cell proliferation factors FGF-2, IGF-1 and VEGF exhibit early, delayed during the course of aging in the hippocampus, role of astrocytes. Glia 2005; 51:173-86.
132. Sun LY. Bartke A. Adult neurogenesis in the hippocampus of long-lived mice during aging. J Gerontol A Biol Sci Med Sci 2007; 62:117-25.
133. Sun LY. Hippocampal IGF-1 expression, neurogenesis and slowed aging: clues to longevity from mutant mice. Age (Dordt) 2006; 28:181-9.
134. Parent JM. Injury-induced neurogenesis in the adult mammalian brain. Neuroscientist 2003; 9:261-72.
135. Marutle A, Ohmimus M, Nilbratt M, Greig NH, Nordinx A, Sugaya K. Modulation of human neural stem cell differentiation in Alzheimer (APP23) transgenic mice by phenserine. Proc Natl Acad Sci USA 2007; 104:12506-11.
136. Amarioglo N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Trakhtenbrot L, et al. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. PLoS Med 2009; 6:1000029.