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Molecular mechanisms of neurodegeneration in Alzheimer's disease

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Alzheimer's disease (AD) is characterized by cognitive impairment, progressive neurodegeneration and formation of amyloid-β (Aβ)-containing plaques and neurofibrillary tangles composed of hyperphosphorylated tau. The neurodegenerative process in AD is initially characterized by synaptic damage accompanied by neuronal loss. In addition, recent evidence suggests that alterations in adult neurogenesis in the hippocampus might play a role. Synaptic loss is one of the strongest correlates to the cognitive impairment in patients with AD. Several lines of investigation support the notion that the synaptic pathology and defective neurogenesis in AD are related to progressive accumulation of Aβ oligomers rather than fibrils. Abnormal accumulation of Aβ resulting in the formation of toxic oligomers is the result of an imbalance between the levels of Aβ production, aggregation and clearance. Aβ oligomers might lead to synaptic damage by forming pore-like structures with channel activity; alterations in glutamate receptors; circuitry hyper-excitability; mitochondrial dysfunction; lysosomal failure and alterations in signaling pathways related to synaptic plasticity, neuronal cell and neurogenesis. A number of signaling proteins, including fyn kinase; glycogen synthase kinase-3β (GSK3β) and cyclin-dependent kinase-5 (CDK5), are involved in the neurodegenerative progression of AD. Therapies for AD might require the development of anti-aggregation compounds, pro-clearance pathways and blockers of hyperactive signaling pathways.

INTRODUCTION

It is estimated that over 5 million people live with Alzheimer's disease (AD) in the USA, and it is predicted that by the year 2025 there will be an average 50% increase in patients with AD (1). AD is a leading cause of dementia in the aging population (2). Patients with AD experience symptoms including cognitive alterations, memory loss and behavioral changes (3,4). The dementia in AD is associated with neurodegeneration that is characterized initially by synaptic injury (5–7) followed by neuronal loss (8). This is accompanied by astrogliosis (9), microglial cell proliferation (10,11) and the presence of neurofibrillary tangles composed of dystrophic neurites and hyperphosphorylated tau (5,12–16). More recent studies have uncovered evidence, suggesting that another component to the neurodegenerative process in AD might include the possibility of interference with the process of adult neurogenesis in the hippocampus (17,18; Fig. 1). In transgenic (tg) animal models of AD, previous studies have shown significant alterations in the process of adult neurogenesis in the hippocampus (19–23).

Of the various neuropathological features of AD, cognitive impairment in patients with AD is closely associated with synaptic loss in the neocortex and limbic system (7,24,25). Several lines of investigation support the notion that the pathogenesis of AD is related to progressive accumulation of amyloid-β (Aβ) protein, which is derived from the proteolysis of Aβ precursor protein [APP (26–28)]. Abnormal accumulation of Aβ is the result of an imbalance between the levels of Aβ production, aggregation and clearance (Fig. 2). Aβ clearance is mediated by proteolytic enzymes such as neprilysin (29), chaperone molecules such as apoE (30), lysosomal [e.g. autophagy (31)] and non-lysosomal pathways [e.g. proteasome (32)]. While in familial forms of AD, mutations result in an increased Aβ production or aggregation, in sporadic AD, failure of the clearance mechanisms might play a central role (Fig. 2). Progressive accumulation of Aβ results in the formation of Aβ oligomers (33) and fibrils which are

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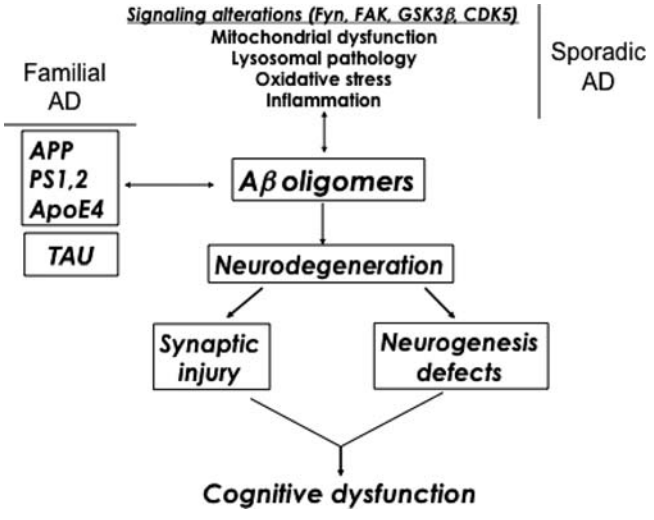

Figure 1. Mechanisms of neurodegeneration in AD. Defective cellular processes can lead to the accumulation of Aβ dimers, trimers and oligomers, which in turn contribute to neurogenesis defects and synaptic damage.

the principal components of the plaque. Most evidence supports the notion that the Aβ oligomers rather than the fibrils are responsible for the synapto-toxic effects of Aβ [(34,35) Fig. 2].

Sporadic forms of AD generally afflict patients later in life, with onset of sporadic AD occurring usually between the ages of 60 and 70 (36). Although patients with sporadic disease constitute the majority of the affected population, ∼10–15% of patients have a genetically-linked familial form of AD (FAD). These patients often have earlier onset of the disease, and it is associated with mutations in several genes, including APP, tau and presenilin-1 [PS1 (37–41), Fig. 1]. Animal models of AD have been developed based on these familial mutations, and a number of models that express high levels of mutant APP recapitulate several of the neuropathological, neurodegenerative and behavioral characteristics of the spectrum of disease in human patients (42–44).

Most efforts toward developing tg models have been focused on overexpression of mutant APP in combination with mutant PS1. A summary of the FAD mutations of APP reproduced in tg mouse models is presented in ref. (16). Previously developed tg animal models have shown that it is possible to reproduce certain aspects of AD pathology over a shorter period of time (42–44).

In one such model, lines of tg mice express hAPP751 cDNA containing the London (Lon, V717I) and Swedish (Swe, K670N/M671L) mutations under the regulatory control of the mThy1 gene [mThy1-hAPP751 (16,45)]. While expression of mutant hAPP under the PDGF-β promoter results in the production of diffuse (and some mature) plaques (46,47), tg expression of mutant hAPP under the mThy1 (48) and PrP (49,50) promoters favors the formation of mature plaques in the hippocampus and neocortex.

This suggests that the differential patterns of Aβ deposition might be dependent on the specific neuronal populations selected by the promoter, levels of expression and topographical distribution of the transgene and levels of $A\beta_{1-40}$ and $A\beta_{1-42}$. Extensive investigation of these animal models has led to better understanding of the neuropathological alterations and some of the pathways involved in AD pathogenesis; however, the molecular mechanisms are still not entirely clear, and other deficits may play a role in the cognitive alterations in AD.

Loss of synapses (7,51,52) and axonal pathology (53) are probably key neuropathological features leading to dementia in these neurodegenerative disorders; however, other factors may contribute. In addition to the alterations in synaptic plasticity and neuronal integrity in mature neuronal circuitries, the neurodegenerative process in AD has recently been shown to be accompanied by alterations in neurogenesis (17,18,22,23,54–56). This suggests that the pathogenesis of AD may represent a two-pronged attack on the brain, contributing to degeneration of mature neurons, and disruption of the neurogenic niches in the adult brain [(16) Fig. 1].

Defective neurogenesis and AD

In addition to the alterations in synaptic plasticity and neuronal integrity in mature neurononal circuitries, the neurodegenerative process in AD have recently been shown to be accompanied by alterations in neurogenesis (17,18,22,23,54–56). Although there are some controversies over whether neurogenesis is increased (54) or decreased (17,18) in the pathogenesis of AD, more recent studies suggest that apparent increases in markers of neurogenesis in the brains of AD patients may be related to glial and vasculature-associated changes (17).

Animal models of APP overexpression present a more complex picture; however, in support of the more recent studies in human AD patients, a number of animal models of FAD display significantly reduced neurogenesis compared with non-tg controls [(21,23,56,57), for a more comprehensive review of neurogenic alterations in FAD-linked mouse models, see ref. (58)]. Taken together, these studies suggest that the pathogenesis of AD may be characterized by not only a loss of mature neurons but also by alterations in neural progenitor cells (NPCs) in neurogenic niches such as the dentate gyrus (DG) of the hippocampus. However, the molecular mechanisms involved in defective neurogenesis in AD and in animal models of FAD remain to be fully elucidated.

Neurogenesis in the mature healthy central nervous system occurs throughout adult life (59) in the olfactory bulb, the subventricular zone (SVZ) and the DG of the hippocampus (60). Neurogenesis is a complex process characterized by several progressive steps, including NPC *proliferation*, *migration*, *differentiation* (cell fate commitment) and *maturation*, including growth and synaptogenesis (Fig. 3). Moreover, during any one of these stages, survival and apoptosis may play a role in the net outcome of neurogenesis and numbers of surviving neural progeny in the adult hippocampus. Furthermore, each of these phases may be regulated by distinct molecular mechanisms, and could be susceptible to changes induced by pathological conditions in disease states. For studies of neurogenesis in both the SVZ and DG, characterization of different markers is used to distinguish between stages of the neurogenic process (Fig. 3); however, there is much overlap in expression of the different markers and phases themselves. Markers of cell division (Sox2, PCNA, Ki67, or BrdU in BrdU-treated cells or animals) or NPC-specific markers (nestin) are often used to

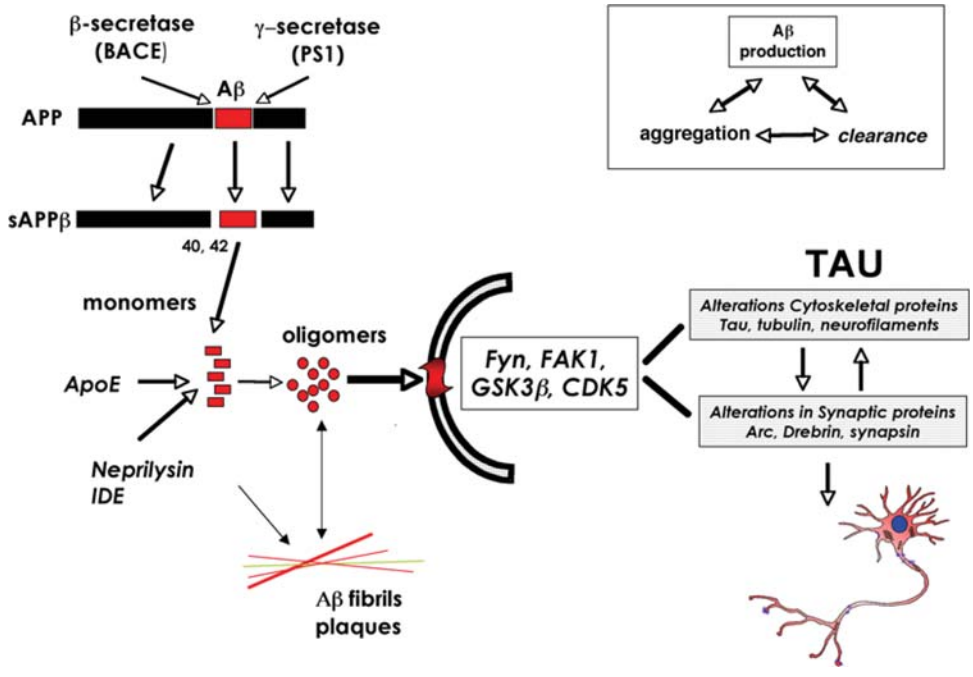

Figure 2. APP metabolism, Aβ oligomerization and signaling involvement in the mechanisms of synaptic damage in AD. Proteolytic cleavage of APP by β- and γ-secretase results in the generation of the $A\beta_{1-42}$ monomer, which under pathological conditions can assemble into potentially toxic oligomers. Enzymes such as Neprilysin and insulin-degrading enzyme (IDE) can degrade the Aβ monomer, whereas oligomers can be sequestered into fibrillar aggregates in plaques. Oligomers may be the toxic Aβ species that contribute to de-regulation of signaling pathways (Fyn, FAK, GSK3β, CDK5) and result in alterations to cytoskeletal and synaptic proteins and subsequent synaptic and neuronal damage. Aβ accumulation is mediated by factors including rates of peptide production, aggregation and clearance.

identify cells in the progenitor cell (proliferative) phase of neurogenesis [(59,61) Fig. 3]. For later stages in the process, markers such as doublecortin (DCX) or β-III Tubulin are utilized to detect progeny in the early neuroblast phase (newly born neurons, often migratory) or immature new neurons, respectively [(62) Fig. 3]. For cells that are committed to a neuronal fate, eventually these progeny will be immunopositive with markers such as NeuN, MAP2 or synaptic markers (Fig. 3). Neurogenesis in the DG is an active process in the mature brain and plays a key role in synaptic plasticity, memory and learning (63). Environmental enrichment has been shown to stimulate neurogenesis and improve the performance in memory tasks in mice (64–66). Mechanisms of neurogenesis in the fetal brain have been extensively studied, and pathways such as the wnt (67) and Notch (68,69) signaling cascades play an important role in this process. However, less is known about the factors regulating neurogenesis in the adult nervous system and their role in neurodegenerative disorders.

Neurodegeneration in AD: the role of Aβ oligomers

During aging and in the progression of AD, synaptic plasticity and neuronal integrity are disturbed (5–8,55). Although the precise mechanisms leading to neurodegeneration in AD are not completely clear, most studies have focused on the role of APP and its products in AD pathogenesis (26,33,70). Recent studies suggest that alterations in the processing of APP, resulting in the accumulation of Aβ and APP C-terminal products, might play a key role in the pathogenesis of AD [(71,72) Fig. 2]. In this context, previous studies have shown that $A\beta_{1-42}$, a proteolytic product of APP metabolism (Fig. 2), accumulates in the neuronal endoplasmic reticulum (73) and extracellularly (12,74,75). Several products are derived from APP through alternative proteolytic cleavage pathways, and enormous progress has recently been made in identifying the enzymes involved [(33,76–79) Fig. 2].

The primary pathogenic event triggering synaptic loss and selective neuronal cell death in these disorders is the subject of debate (51,80); however, recent studies suggest that nerve damage might result from the conversion of normally non-toxic monomers to toxic oligomers [(34,81–83) Fig. 2], whereas larger polymers and fibers that often constitute the plaques might not be as toxic (84,85). Various lines of evidence suggest that the direct abnormal accumulation of Aβ oligomers in the nerve terminals might lead to the synaptic damage and ultimately to neurodegeneration in AD (33). A number of recent studies have begun to investigate the possibility that Aβ oligomers might interfere with synaptic function by altering synaptic proteins such as post-synaptic density-95 [PSD95 (86–89)], scaffold proteins such as Shank (90) and glutamate receptors (91).

In summary, the potential role of neurotoxic Aβ oligomers has emerged as a topic of considerable interest in recent years (34,35,83,92).

Molecular pathways of neurodegeneration in AD

The mechanisms through which of Aβ monomers, oligomers and other APP metabolites might lead to synaptic damage

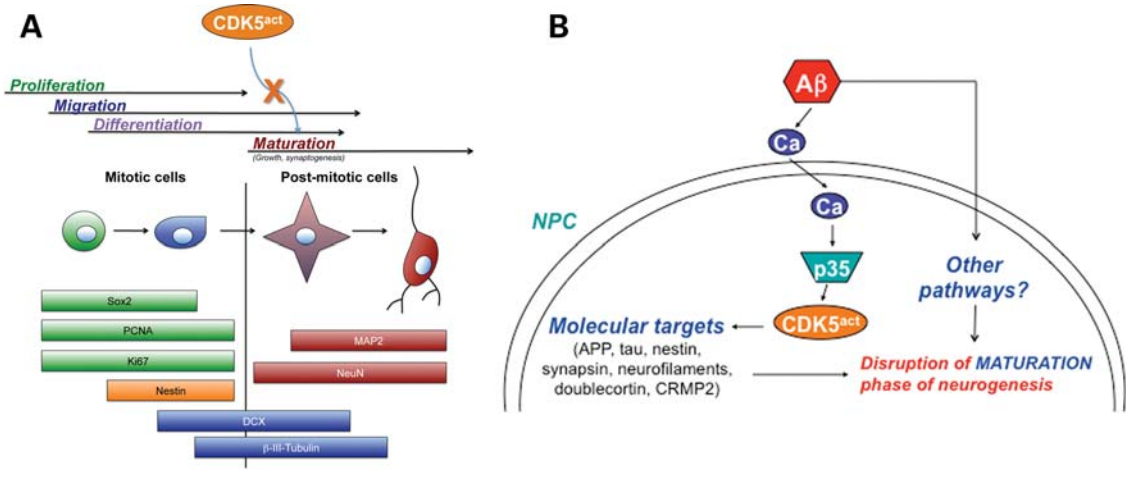

Figure 3. Aberrant activation of signaling molecules such as CDK5 (CDK5^{act}) might impair adult neurogenesis during the cell maturation stage. (**A**) Schematic model of the stages that comprise the neurogenic process of NPC development in the adult brain, and representative markers that can be utilized to identify cells in various phases of development. (**B**) Aberrant signaling through CDK5 and other pathways might disrupt the maturation stage of adult neurogenesis in the pathogenesis of AD.

and neurodegeneration is not completely clear. A number of possibilities are under investigation, including the formation of pore-like structures with channel activity (93–96); alterations in glutamate receptors and excitotoxicity (97–101); circuitry hyper-excitability (102); mitochondrial dysfunction (103,104); lysosomal failure (105) and alterations in signaling pathways related to synaptic plasticity, neuronal cell death and neurogenesis.

Previous studies have shown that a number of signaling proteins, including fyn kinase (106–109), glycogen synthase kinase-3β [GSK3β (110–113)] and cyclin-dependent kinase-5 [CDK5 (114–116)], are involved in the neurodegenerative progression of AD (Fig. 1). Other signaling pathways that have been investigated include members of the MAPK family such as ERK (117–121) and JNK (122–124) as well as other pathways such as p21-activated kinase (125).

Abnormal activation of signaling pathways might lead to synaptic failure and altered neurogenesis by promoting abnormal Tau phosphorylation and aggregation (126–128), cytoskeletal abnormalities (129), activating caspase pro-apototic pathways (130–132) and activating calcium and calpain dependent proteolysis [(133,134) Fig. 2].

Contribution of the CDK5 pathway to neurodegeneration in AD, and potential role for this pathway in the mechanisms of defective neurogenesis

In AD, the neurodegenerative process has been linked with hyperactivation of CDK5 and its activators p35 and p25 (115,116,135). Furthermore, levels of CDK5 are increased in the brains of AD patients (136). CDK5 is the predominant CDK found in the brain, is highly expressed in neurons and plays an important role in synaptic plasticity and neuronal development (137). CDK5 is a Ser-Thr protein kinase with postmitotic activity that phosphorylates KSP motifs on cytoskeletal (MAP1b, tau, NF, nestin, DCX, CRMP2), synaptic proteins (PSD95, synapsin, cadherin) and transcription factors [MEF2 (138–140)]. While in dividing neurons CDKs are activated by cyclins, in the nervous system CDK5 is activated by forming a complex with p35 or p39 (139,141). The primary activator of CDK5 is p35 (142), which under high calcium conditions is cleaved by calpain into p25 (134). While CDK5 activation via complex formation with p35 is associated with physiological activation of CDK5, the truncated p25 form hyperactivates CDK5 and leads to abnormal phosphorylation of substrates such as tau (143). Through these effects, CDK5 and p35/p25 may play a critical role in neuroplasticity in the pathogenesis of AD.

Although the hyperactivation of CDK5/p35/p25 has been associated with the pathogenesis of neurodegenerative diseases such as AD (Figs 1 and 3), its physiological function has been implicated in critical functions such as neuroblast migration (144–146) and synaptic plasticity (147,148). Furthermore, the Cdk5/p35 complex localizes to the leading edge of axonal growth cones (149) where it regulates neurite outgrowth in mature cortical neurons (150). More recently, CDK5 has been shown to be essential for adult neurogenesis (151,152). In this context, it is possible that the neurogenesis deficits in AD might be related to alterations in CDK5 activity in NPCs.

Recent evidence in support of this possibility suggests that the neurodegenerative process in patients with AD might not only target mature neurons, but also interfere with the process of neurogenesis (22,23,56). Studies demonstrating that in mice deficient in this kinase and its activator (p35) neuronal development and migration is arrested (137,144,153) support the notion that CDK5 plays an important role in neurogenesis in the developing brain. In the adult nervous system the role of the p35-CDK5 signaling pathway in neurogenesis is less well understood. The mechanisms through which AD-related molecular changes interfere with neurogenesis in the adult brain might involve signaling alterations (e.g. CDK5/p35/p25) analogous to those involved in the neurodegenerative process (Fig. 3).

In this context, in models of AD, Aβ has been shown to impair neurogenesis via calpain activation and p35 deregulation (154); however, the downstream effectors involved and

the consequences of CDK5 and p35/p25 manipulation remain to be revealed. CDK5 may mediate alterations in neurogenesis in AD via aberrant phosphorylation of CDK5 substrates, which include cytoskeletal (neurofilaments, nestin) (155), synaptic proteins [e.g. synapsin (156)], among others (Fig. 3). Previous studies have shown that the Aβ/CDK5 neurotoxic pathway may involve the destabilization of microtubules (157) since CDK5 can associate with microtubules indirectly (158) and its substrates include microtubule-associated proteins (MAPs). Since CDK5 plays a role both in synaptic function and neuronal integrity, then abnormal activation of this molecule by Aβ might impair the functioning of mature neurons and also contribute to alterations in neurogenesis by impairing cell *maturation* (Fig. 3). Elucidating the signaling pathways and *downstream molecular targets* involved in the deregulation of neurogenesis is important to fully understand the mechanisms of neuroplasticity in AD (Fig. 3).

Therapeutical strategies for AD

The focus in past years for AD therapies has been to improve memory by activating cholinergic neurotransmission (159) and, more recently, anti-oxidants (160) and blockers of calcium channels (161) have been utilized. In recent years, the focus has been on reducing Aβ or Tau deposition. The alternative approach is to protect selective neuronal populations and promote synaptic formation and neurogenesis.

Several possibilities are currently being tested to reduce Aβ accumulation, including (i) anti-aggregation molecules that block oligomers and fibrils, (ii) regulators of APP proteolysis by blocking the β- or γ-secretase pathways or increasing α-secretase activity, (iii) regulation of APP processing by modulating cholesterol and lipid metabolism, (iv) reducing APP production (e.g. siRNA), (v) increasing Aβ clearance with antibodies, ApoE and other chaperones (e.g. HSP70), (vi) increasing clearance via lysosomal and proteasomal pathways, (vii) increasing Aβ clearance by increasing degradation (e.g. NEP and IDE delivery) and (viii) blocking signaling pathways and receptors activated by neurotoxic Aβ oligomers (e.g. Fyn kinase, GSK3β and CDK5 inhibitors and glutamate receptor blockers).

Neuroprotective strategies include the use of neurotrophic factors (e.g. brain-derived neurotrophic factor, nerve growth factor), neuroprotective peptides [e.g. cerebrolysin (162)], anti-oxidants [e.g. curcumin, vitamin E (163)] and calcium channel blockers [e.g. memantine (164)]. Tau is also an important target, and in this context recent studies have shown that in a Tau-deficient background APP transgenic mice are protected from the toxic effects of Aβ (165). Tau has been targeted by reducing Tau synthesis or decreasing Tau phosphorylation with compounds such as lithium (166,167). In addition to the traditional delivery methods and strategies with oral small molecules, new approaches are currently been tested, including gene therapy, vaccination, changes in lifestyle that enhance neurogenesis, intra-thecal drug delivery and use of compounds bound to lipids.

Conflict of Interest statement. None declared.

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