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Neurogenesis and Alzheimer's disease: At the crossroads

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Abstract

While a massive and progressive neuronal loss in specific areas such as the hippocampus and cortex unequivocally underlies cognitive deterioration and memory loss in Alzheimer's disease, noteworthy alterations take place in the neurogenic microenvironments, namely, the subgranule layer of the dentate gyrus and the subventricular zone. Compromised neurogenesis presumably takes place earlier than onset of hallmark lesions or neuronal loss, and may play a role in the initiation and progression of neuropathology in Alzheimer's disease. Neurogenesis in the adult brain is thought to play a role in numerous forms and aspects of learning and memory and contribute to the plasticity of the hippocampus and olfactory system. Misregulated or impaired neurogenesis on the other hand, may compromise plasticity and neuronal function in these areas and exacerbate neuronal vulnerability. Interestingly, increasing evidence suggests that molecular players in Alzheimer's disease, including PS1, APP and its metabolites, play a role in adult neurogenesis. In addition, recent studies suggest that alterations in tau phosphorylation are pronounced in neurogenic areas, and may interfere with the potential central role of tau proteins in neuronal maturation and differentiation. On the other hand, numerous neurogenic players, such as Notch-1, ErbB4 and L1 are substrates of α - β - and γ -secretase that play a major role in Alzheimer's disease. This review will discuss current knowledge concerning alterations of neurogenesis in Alzheimer's disease with specific emphasis on the cross-talk between signaling molecules involved in both processes, and the ways by which familial Alzheimer's disease-linked dysfunction of these signaling molecules affect neurogenesis in the adult brain.

Keywords

Neurogenesis; Alzheimer's disease; tau; amyloid precursor protein; presenilin; stem cells; brain plasticity; LDL receptors

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Introduction

Alzheimer's disease (AD) is characterized by a progressive memory loss and cognitive decline [For review see (Caselli et al., 2006)]. Hippocampus-dependent memory (Rosen et al., 1984; Haxby et al., 1992; Jacobs et al., 1995) and olfaction-dependent memory (Warner et al., 1986; Albers et al., 2006; Serby, 1987; Kesslak et al., 1988; Bacon et al., 1998) are severely impaired in the disease. The vast majority of AD cases are the late onset sporadic form of the disease. While aging is the greatest environmental risk factor for the sporadic form, apolipoprotein E (apoE) genotype is the greatest known genetic risk factor [For review see (Ashford, 2004; Bu, 2009)]. Rare, familial, early-onset autosomal dominant forms of Alzheimer's disease (FAD) are caused by mutations in genes encoding amyloid precursor protein (APP), presenilin-1 (PS1) and presenilin-2 (PS2). PS play a central role in the function of the aspartyl protease γ -secretase complex that cleaves numerous membrane proteins intramembranously, including APP [(De Strooper, 2003) for review see (Selkoe and Wolfe, 2007)]. APP can undergo regulated intramembrane proteolysis (RIP) in at least two pathways known as the non-amyloidogenic and amyloidogenic pathways. In the former, APP first undergoes ectodomain shedding by an enzymatic activity termed α -secretase. While the identity of α -secretase is not fully known, members of the ADAM family and matrix metalloproteases ADAM10 and ADAM17, as well as the aspartyl protease BACE 2 exhibit α -secretase activity *in vivo*, cleaving APP in the A β region. Hampering A β formation, this cleavage results in the release of soluble fragment of APP (sAPP α) and the generation of a membrane-bound carboxyl-terminal fragment (CTF) that undergoes a second cleavage event within its transmembrane domain (via RIP) by γ -secretase (see figure 1). γ -secretase is a unique membrane multicomponent protease complex, in which PS are the catalytic core of the enzyme. In the amyloidogenic pathway, APP ectodomain shedding is carried out by the aspartyl protease β -site APP cleaving enzyme 1 [(BACE1; also known as memapsin and Asp2) (Hussain et al., 1999; Sinha et al., 1999; Vassar et al., 1999; Lin et al., 2000; Yan et al., 1999; Hong et al., 2000)]. Followed by γ -secretase cleavage, this RIP pathways yields the production of the beta-amyloid peptide (A β) and other APP metabolites involved in the progression of AD.

The hallmarks of AD are neurofibrillary tangles, intraneuronal lesions composed of aggregated hyperphosphorylated tau, and amyloid deposition, composed of aggregated A β [For review see (Goedert et al., 1991)]. These lesions are evident in and around vulnerable neurons in specific brain areas. The parahippocampal regions are the earliest to be affected [Braak stages I and II, (Braak and Braak, 1985; Braak and Braak, 1996)]. In particular, the entorhino-hippocampal circuit exhibits an early and significant neuropathology. Progressive neuropathology in this area correlates significantly with Braak stages, hippocampal content of abnormally phosphorylated tau (PHF- τ) and degree of dementia as defined by the clinical dementia rating (CDR) scale (Thal et al., 2000). The first morphological and cytoskeletal lesions are in pre- α cells (layer II) of the transentorhinal and entorhinal region that projects to the outer molecular layer of the dentate gyrus (Braak AD stage I). Abnormally phosphorylated tau protein is found in the neuropil of the CA1-subiculum region, followed by the stratum radiatum and stratum oriens, correlating with Braak stage II. In the Braak stages IV and V, the stratum radiatum is fully affected, and the stratum oriens is increasingly affected. Beginning in Braak stage III, tau pathology is prominent in the perforant pathway target zone of the outer molecular layer of the dentate gyrus. Parahippocampal regions and limbic structures, early involved in the course of the disease, have olfactory connections. The primary olfactory cortical targets of the olfactory bulb, the piriform cortex and lateral entorhinal cortex project to the DG, CA3 and CA1 of the hippocampal formation (Lynch et al., 1991). Tau pathology in the olfactory bulb correlates with stage of disease (Attems and Jellinger, 2006) and volume of olfactory bulb and tract inversely correlates with global cognitive performance as determined by the mini-mental state examination [MMSE, (Thomann et al., 2009a; Thomann et al., 2009b)]. Likewise, impaired odor identification correlates with tangles in the entorhinal cortex

and CA1/subiculum area of the hippocampus, but not for tangles in other cortical sites (Wilson et al., 2007).

While most of the self-renewal capacity characterizing its embryonic development ceases, the adult mammalian central nervous system retains at least two sites of continuous production of neurons and glial cells: the subventricular zone (SVZ) underneath the walls of the ventricles and the subgranule layer (SGL) of the dentate gyrus (DG) [For review (Alvarez-Buylla and Lim, 2004; Alvarez-Buylla et al., 2002; Lie et al., 2004)]. The SVZ is currently the most robust of the known neurogenic regions in the adult CNS, producing as many as 30,000 new neuroblasts each day in the young adult rats (Alvarez-Buylla et al., 2000). Neuroblasts migrate from the SVZ through the rostral migratory stream (RMS) and populate the olfactory bulb. Approximately 9000 neural stem cells (NSC) are produced daily (or 250,000 NSC per month) in the SGL of the DG of sexually mature, 9-10 weeks old rats, amounting to 0.1% of the population of the entire DG, with a survival rate of about 50% (Cameron and McKay, 2001). Neuroblasts born in these niches migrate out and are able to populate the olfactory bulb (OB) and the granule layer of the DG, respectively, where they differentiate into glial cells and neurons. Newly formed neurons in the GCL send axonal projections to the CA3 subfield of the hippocampus and dendrites to the molecular layer (Zhao et al., 2006). New neurons in the adult hippocampus receive a variety of inputs from existing mature neurons, and preferentially contact and form synapses with preexisting boutons (Toni et al., 2007). It is thought that during maturation, newly formed granule neurons transiently express the Na⁺-K⁺-2Cl⁻ transporter NKCC1 for the enhancement of synaptic integration as they form glutamatergic synapses around 2-3 weeks after birth (Ge et al., 2006). Newly generated dentate granule cells have decreased thresholds for activation, increased resting potentials and they undergo long term potentiation more rapidly (van Praag et al., 2002). While the precise physiological functions of neurogenesis, as well as the full spectrum of functional implications of this extent of plasticity in the adult brain are still under intense investigation, it becomes apparent that new neurons that integrate in the hippocampus and olfactory bulb, play important roles in aspects of learning and memory.

Increasing evidence suggests that new neurons play a role in certain forms of brain function involving olfaction- and hippocampal- dependent learning and memory. Studies in mammals using different strains of mice (Kempermann and Gage, 2002), Environmental Enrichment (Kempermann et al., 1997; van Praag et al., 1999), Genetic manipulations (Shimazu et al., 2006; Zhao et al., 2003; Saxe et al., 2006; Zhang et al., 2008a), aged rats [For review see (Bizon and Gallagher, 2005)], stress paradigms (Lemaire et al., 2000), irradiation (Rola et al., 2004; Madsen et al., 2003; Raber et al., 2004) and the DNA methylating agent methylazoxymethanol acetate (MAM; (Shors et al., 2002)), have each shown direct correlations between neurogenesis and performance in spatial memory tasks. Recently, Trouche and colleagues (2009) show that newly integrated neurons in the granule layer of the DG are recruited in a context- and stimulus-specific manner, and contribute to strengthening of memory circuits related to the stimulus given (Trouche et al., 2009). Computational hypotheses have suggested that the turnover of neurons in the DG associated with neurogenesis may provide protection against memory interference when similar items are presented (Becker, 2005; Wiskott et al., 2006). An alternative theory suggests that due to the tendency of newly formed neurons to be easily excitable and more readily undergo long term potentiation, they may be a means by which memories are temporally organized (Aimone et al., 2006). Impairments in neurogenesis may compromise the extent of plasticity of the hippocampus, olfactory system and their associated neural circuits. This could lead to enhanced neuronal vulnerability in these brain areas and functional impairments, such as a reduced capacity for learning and memory. Recent evidence in support of this hypothesis suggests that neurogenesis is impaired in animal models of AD in both SVZ and SGL (Demars et al., 2009). Neurogenic impairments may underlie, at least in part, the progressive loss of memory and compromised

ability to learn and process new information characterizing the disease. Both olfactory and hippocampal dysfunction might be enhanced by compromised neurogenesis in the SVZ and SGL of the dentate gyrus, respectively. Most strikingly, molecules central to the pathology of FAD play a regulatory role in aspects of neurogenesis in the embryonic and adult brain, suggesting that dysfunction of these proteins may compromise neurogenic signaling. Here we summarize the recent knowledge on neurogenic roles of molecules that, in their mutated forms cause FAD, and on the dysfunction of neurogenic signaling pathways in AD with consequential alterations in neurogenesis in this disorder.

Converging Pathways Implicated in Neurogenesis and AD Pathology

The neurogenic niche (key pathways)

The neurogenic niche is thought to be a specialized microenvironment within the adult brain, which has the capacity to sustain self-renewal of multipotent NSC and promote their migration, as well as their differentiation into neurons and glia (Ninkovic and Gotz, 2007). Adult progenitor cells derived from nonneurogenic areas exhibit self renewal and multipotentiality once transplanted in a neurogenic brain area, and can differentiate in a region-specific context, suggesting that the microenvironment has a crucial role in providing and regulating fate-determining cues of in the adult brain (Shihabuddin et al., 2000). What makes the SVZ and SGL special in supporting the proliferation and differentiation of multipotent neural progenitors is an area of intensive investigation. It is postulated that endothelial cells and some special astrocytes provide a unique neurogenic niche and have the capability to promote proliferation and neuronal fate determination (Lie et al., 2004; Doetsch, 2003a; Doetsch, 2003b; Lim and Alvarez-Buylla, 1999; Song et al., 2002a). In contrast, astrocytes from nonneurogenic regions, e.g., the adult spinal cord, do not promote either proliferation or neuronal differentiation (Song et al., 2002a). *In vivo* hot spots of cell proliferation in the SGL are found to be in close proximity to capillaries and astrocytes (Palmer et al., 2000; Seri et al., 2001). It is thought that astrocytes in the neurogenic niche have a broad diversity of functions; some exhibit stem cell characteristics (Seri et al., 2001; Doetsch et al., 1999), some provide neurogenic signals (Lim and Alvarez-Buylla, 1999; Song et al., 2002a), and some provide synaptogenic factors (Song et al., 2002b). The neurogenic niche is believed to play a regulatory role in all steps of NSC maturation (Seidenfaden et al., 2006).

The neurogenic niche is comprised of soluble, membrane-tethered and extracellular matrix signaling molecules expressed by endothelial cells, astrocytes and progenitor cells, as well as ependymal cells in the SVZ niche (Lim et al., 2007). Progenitor cells actively interact with their microenvironment and have the capability to regulate it (Song et al., 2002a; Wurmser et al., 2004; Shen et al., 2004). Numerous signaling pathways, some of which are developmental signals, are implicated in regulation of adult neurogenesis, such as GABA receptors, E2F, Ephrins and Eph receptors, the sonic hedgehog signaling pathway, WNT signaling pathway, Notch 1, neural cell adhesion molecule (NCAM), bone morphogenetic protein (BMP), neurogenesis1 (NG1), noggin, reelin signaling pathway, and paired box 6 (PAX6) (Yoshikawa, 2000; Cooper-Kuhn et al., 2002; Conover et al., 2000; Machold et al., 2003; Machold et al., 2007; Lai et al., 2003; Lie et al., 2005; Amoureux et al., 2000; Grandbarbe et al., 2003; Kohwi et al., 2005; Heinrich et al., 2006; Won et al., 2006; Zhao et al., 2007).

Of particular interest, the Wnt family (Lie et al., 2005; Sato et al., 2004), β -catenin (Chenn and Walsh, 2003; Shimizu et al., 2008) and notch -1 were identified as critical regulators of neurogenesis in the adult brain [Figure 1, For review see (Shi et al., 2008)]. Wnts are made and secreted by astrocytes in the adult hippocampal niche and specifically increase proliferating neuronally-restricted precursor proliferation and differentiation (Lie et al., 2005). Wnt has also been implicated in neurogenesis originating from the SVZ during stroke repair (Morris et al., 2007; Lei et al., 2008). It was suggested that in the adult brain, notch signaling modulates cell

cycle time thus enabling self-renewal of NSC (Alexson et al., 2006). Interestingly, Shimizu and colleagues (2008) provide evidence suggesting that glycogen synthase kinase 3 (GSK3) inactivation and β -catenin stabilization by Wnts are essential for the self-renewal of neural stem cells. Noteworthy are the findings that β -catenin promotes neural precursor cell proliferation through the activation of LEF/TCF transcription factors. Interestingly, nuclear accumulated β -catenin also induces antineurogenic *hes1* gene expression through the enhancement of Notch1- and RBP-J –mediated transcription. β -catenin can associate with the Notch1 intracellular domain (NICD), and it is present in a nuclear protein-DNA complex containing the *hes1* gene promoter. The β -catenin–NICD complex is efficiently formed when transcriptional coactivators p300 and P/CAF both are present (Shimizu et al., 2008).

EGF is a critical growth factor regulating neural progenitor cell proliferation in the SVZ [Figure 1; (Kuhn et al., 1997)]. The cellular response to EGF is initiated by rapid kinetics of receptor activation, followed by phosphorylation-dependent activation of signaling cascades. This is typically analyzed by observing activation of the ERK MAPKs and subsequent transcriptional activation of immediate-early genes [(IEGs), (Amit et al., 2007)]. EGFR is a receptor tyrosine kinase of the ErbB family, critical signaling molecules of cell proliferation and fate determination (Bubril and Yarden, 2007). The epidermal growth factor (EGF) ErbB system is one of the best studied signaling networks. Among all members of the large family of growth factor receptor tyrosine kinases (RTKs), the ErbB family (also called the type I RTKs) is considered the prototypic founder sub-group of the RTK super-family, which includes 18 other small sub-groups of related receptors. ErbB4 is autonomous; when bound by a ligand growth factor it undergoes dimerization and generates intracellular signals culminating in cell proliferation, migration or differentiation (Bubril and Yarden, 2007).

In the SVZ, the neuregulin receptor, ErbB4, is primarily expressed by immature neuroblasts but is also detected in a subset of astrocytes, ependymal cells, and *Dlx2*+ precursors. Of the neuregulin ligands, both neuregulin-1 and -2 are expressed by immature neuroblasts. ErbB4 activation is thought to be required for neuregulin-1 and -2-mediated regulation of cell proliferation and neuroblast migration in the SVZ (Ghashghaei et al., 2006). ErbB4 regulates neuroblast migration and organization in the RMS (Anton et al., 2004). In the DG, ErbB4 regulates formation of radial glial cells (Zheng and Feng, 2006). All of the above mentioned critical players in the neurogenic niche interact with known mediators of AD pathology, as described in detail in the following paragraphs, providing an intriguing mechanistic link between AD and neurogenesis (Fig. 1).

Alpha secretases in neurogenesis and AD

Members of the disintegrin-metalloproteinases (ADAMs) family and ADAM10 and ADAM17 (TACE) in particular, are thought to have α -secretase activity in vivo (Buxbaum et al., 1998; Asai et al., 2003). Perhaps α -secretase activity is best known for alpha site proteolysis of APP. This processing of APP prevents the production of A β and thus potential amyloid pathology, linking α -secretase activity to AD. Interestingly, ADAM10 KO mice die at E9.5 and exhibit multiple brain defects (Hartmann et al., 2002). These mice have a similar phenotype to EGF receptor (EGFR) KO mice or TGF α KO mice (Tropepe et al., 1997), suggesting an important role for ADAM10 in cleavage-dependent activation of these components of EGF signaling (Hinkle et al., 2004; Lee et al., 2003; Sunnarborg et al., 2002). Notch1 and EGF receptor ligands are substrates of ADAM10 (Hartmann et al., 2002; Cornell and Eisen, 2002). Both ADAM10 and 17 are implicated in development-regulated notch signaling by ectodomain shedding of Notch ligands Delta and Jagged (LaVoie and Selkoe, 2003). While localization and function of TACE and ADAM10 in the SVZ have been described (Katakowski et al., 2007; Yang et al., 2006; Yang et al., 2005) their expression by different cell types residing in this neurogenic area is yet to be determined. In that regard, Katakowski and colleagues report that TACE is

expressed in isolated and clustered cells in the SVZ, as well as in ependymal cells and cells in contact with the lateral ventricle. They further report that TACE is expressed by SVZ neuroblasts but not astrocytes (Katakowski et al., 2007). Yang and colleagues suggest that ADAM21 is a dominant ADAM family member expressed in the adult SVZ (Yang et al., 2006; Yang et al., 2005). Therefore, it appears that alterations in α -secretase activity would modulate aspects of both neurogenesis and AD.

Another recently identified enzyme exhibiting α -secretase activity is BACE2, a single transmembrane aspartyl protease of 518 amino acids. The coding sequences of *BACE2* and the β -secretase-encoding *BACE1* are about ~50% identical. Despite extensive studies about the function of BACE1, the function of BACE2 remains unknown. Studies show that BACE2 cleaves APP at the Phe 19 and Phe 20 sites, which are adjacent to the α -secretase cleavage site, suggesting that BACE2 functions as an alternative α -secretase and as an antagonist of BACE1 (Farzan et al., 2000).

α -secretase-like metalloprotease-dependent ectodomain shedding is an event common to numerous neurogenic signals, including insulin-like growth factor-1 (IGF-1) (McElroy et al., 2007), Notch1 (Brou et al., 2000), E-cadherin (Maretzky et al., 2005a), L1 (Maretzky et al., 2005b), ErbB4 (Rio et al., 2000), and EGFR ligands (Sahin et al., 2004). Both ADAM10 and 17 play major roles in the ectodomain shedding of EGFR ligands (Sahin et al., 2004). Soluble APP α (sAPP α), a cleavage product of α -secretase regulates proliferation of EGF-responsive NSC in the SVZ (Caille et al., 2004). Thus, FAD-linked reduction in sAPP levels may affect extent of neural progenitor cell proliferation and the amount of the NSC pool. Likewise, alterations in α -secretase activity may affect neurogenesis.

PS1 regulates embryonic and adult neurogenesis

PS1, a homologue of the *C. elegans* sel-12, a protein that plays a major role in cell fate decisions (Levitan and Greenwald, 1995; Hong and Koo, 1997), has increasingly been considered an appealing signal in fundamental neurogenic pathways. PS1, like sel-12 in *C. elegans*, mediates LIN-12/notch signaling. The *lin-12* gene mediates multiple cell–cell interactions during uterine–vulval development. In the vulva, *lin-12* is required first in the decision between the 1° and 2° vulval precursor cell fate (Sternberg, 1988; Sternberg and Horvitz, 1989), and then for proper vulval morphogenesis (Sundaram and Greenwald, 1993a; Sundaram and Greenwald, 1993b).

PS are thought to be the catalytic core of the aspartyl protease γ -secretase which is required for A β production linked to AD pathology. In mammals, PS1/ γ -secretase cleaves notch-1 receptor in response to ligand binding followed by an ectodomain shedding cleavage event (LaVoie and Selkoe, 2003; De Strooper et al., 1999; Wong et al., 1997). Notch intracellular domain (NICD) is then liberated, translocates to the nucleus and regulates gene expression. Interestingly, recent studies suggest that notch-1 functions in embryonic and adult neurogenesis are distinct (Alexson et al., 2006).

The first indication that PS1 may play a role in neurogenesis has been provided by experiments in mice with genomic deletions of *PSEN1* exhibiting severely abnormal somitogenic and neurogenic processes in the brain (Wong et al., 1997; Shen et al., 1997). The ventricular zone is substantially thinner in the brain of these mice after embryonic day 14.5, indicating a drastic reduction in the number of neural progenitor cells (Shen et al., 1997). In addition, expression of notch-1 and its ligand is dramatically reduced (Wong et al., 1997). The lethality of this mutation has hampered further studies of the role of PS1 in a natural brain setting in postnatal life. That led to the examination of neurogenesis in FAD-linked PS1 transgenic mice. Nevertheless, given the numerous cellular activities in which PS1 is implicated, most currently available transgenic mice offer little advantage when it comes to processes that take place

postnatally in restricted brain areas with a unique population of dividing progenitor cells, as transgenes are expressed in a ubiquitously, nonspecific manner. Lack or dysfunction of PS1 in mature neurons in the brain may induce processes that may alter neurogenesis indirectly (Chen et al., 2008).

In addition to notch-1 and APP, RIP of the membrane-anchored carboxyl terminal fragments of the neurogenic signals receptor tyrosine kinases ErbB4 (Ni et al., 2001; Sardi et al., 2006), IGF-1R (McElroy et al., 2007), insulin receptor (Kasuga et al., 2007), L1 (Maretzky et al., 2005b) and E-cadherin (Marambaud et al., 2002) are catalyzed by PS1/ γ -secretase. Neuregulin 1 (NRG1)-induced presenilin-dependent ErbB4 nuclear signaling regulates the timing of astrogenesis in the developing brain (Sardi et al., 2006). Upon activation and presenilin-dependent cleavage of ErbB4 juxtamembrane-a (JMa), its intracellular domain (E4ICD) forms a complex with the signaling protein TAB2 and the corepressor N-CoR. This complex translocates to the nucleus of undifferentiated neural precursors and inhibits their differentiation into astrocytes by repressing the transcription of glial genes (Sardi et al., 2006).

Interesting new information is provided by a recent study suggesting that during embryonic development TAG1 binds APP. As a result, levels of the C-terminal intracellular domain of APP, namely, AICD, are upregulated in a γ -secretase-dependent manner, leading to modulation of neurogenesis (Ma et al., 2008). However, information concerning the role of AICD in regulation of adult neurogenesis is largely unknown. Recent studies also suggest that PS1/ γ -secretase processing of APP regulates EGFR (Zhang et al., 2007; Li et al., 2007; Repetto et al., 2007). PS1/ γ -secretase cleavage of APP results in the generation of AICD, which directly binds to *EGFR* promoter and regulates *EGFR* gene expression (Zhang et al., 2007). Therefore, FAD alterations in APP and PS1 processing and/or function may affect EGFR expression and function. Reduced PS1/ γ -secretase activity is inversely correlated with EGFR levels in fibroblasts and induces skin tumors (Li et al., 2007). These studies suggest that PS1/ γ -secretase plays a role of tumor suppressor in fibroblasts. In that regard, PS1 is implicated as a negative regulator of the Wnt/ β -catenin signaling pathway (Xia et al., 2001). Following its cleavage, PS1CTF/NTF forms a complex with GSK3 and β -catenin (Tesco and Tanzi, 2000). Kang and colleagues suggest that PS1 functions as a scaffold that rapidly couples β -catenin phosphorylation through sequential kinase activities independent of the Wnt-regulated Axin/CK1 α complex (Kang et al., 2002).

The role of PS1 in neurogenesis may be γ -secretase-dependent, at least in part. Treatment with γ -secretase inhibitor enhances neuronal differentiation of embryonic stem cells (Ma et al., 2008). In addition, treatment with a γ -secretase inhibitor reduces the extent of proliferation of mesenchymal stem cells and alters their differentiation (Vujovic et al., 2007).

APP metabolites in neurogenesis and AD

APP belongs to a family of evolutionary conserved type I membrane proteins, that includes amyloid precursor-like protein 1 and 2 (APLP1 and APLP2) [For review see (Selkoe, 2001)]. The lethality of APP/APLP2 and of APLP1/APLP2 knockout mice revealed that these proteins have crucial developmental and postnatal functions, and suggested functional redundancy between APP and APLP2 (von Koch et al., 1997; Herms et al., 2004). In the central nervous system, increase in APP expression during development overlaps with neuronal differentiation (Hung et al., 1992). Nevertheless, the physiological role(s) of APP and APP metabolites remains largely unknown. Interestingly, soluble APP (sAPP), a cleavage product released following cleavage of APP by α -secretase, has been implicated in regulation of cell proliferation (Saitoh et al., 1989; Slack et al., 1997; Schmitz et al., 2002; Meng et al., 2001; Pietrzik et al., 1998). Recent intriguing information is provided by studies suggesting that the SVZ is a major sAPP binding site, where sAPP regulates proliferation of transit amplifying

(type C cells) EGF-responsive cells (Caille et al., 2004; Ohsawa et al., 1999). These cells self-renew in the presence of EGF, and differentiate into neurons and glia upon EGF removal (Morshead et al., 1994). Caille and colleagues show that EGF-induced proliferation of NSC is partly dependent on the EGF-induced release of sAPP into the medium. However, sAPP is necessary but not sufficient, as it does not induce cell division in EGF-free medium (Caille et al., 2004). Taken together with the resemblance between notch and APP processing, it would be tempting to speculate that other metabolites of APP, such as the carboxyl-terminus of APP (APP-CTFs) may play a regulatory role in different aspects of neurogenesis in the adult brain. AICD production has also been linked to AD through the discovery that this transcription factor binds to the neprilysin promoter and induces expression of this A β degrading enzyme (Belyaev et al., 2009; Pardossi-Piquard et al., 2005). Recent studies have revealed that A β ₄₂ enhances the survival and differentiation of progenitor cells (Lopez-Toledano and Shelanski, 2004) or compromise these processes (Haughey et al., 2002a; Calafiore et al., 2006; Mazur-Kolecka et al., 2006; Millet et al., 2005). This controversy may be the result of the use of variable A β preparations *in vitro*, exhibiting differential conformations.

Wnt, reelin and the low-density lipoprotein receptor family in neurogenesis and AD

Polymorphisms in the apolipoprotein E (apoE) gene show the most significant effects on relative genetic risk of sporadic AD. The ϵ 4 isoform (Cys112-Arg) of apoE is associated with increased risk of developing AD, while ϵ 2 (Arg158-Cys) is associated with protection from the disease compared to the normal ϵ 3 allele (Bu, 2009). This has been reproduced in gene modified mouse models of AD (Bales et al., 1999; Holtzman et al., 2000; Fagan et al., 2002). Furthermore, intrahippocampal lentiviral gene transfer of ϵ 4 and ϵ 2 can respectively promote and prevent AD-like pathology in APP transgenic mice (Dodart et al., 2005). ApoE binds to every member of a class of receptors known as the low-density lipoprotein receptors (LDLR) [reviewed in (Herz, 2001)]. There are upwards of 10 members to this family of receptors. Classically they have been shown to function in cholesterol and lipid transport. However, this large receptor family has also been shown to function as signal transducers (Hoe et al., 2005a). Blocking the LDLR family results in embryonic lethality as a result of the inability to form mesoderm (Herz and Marschang, 2003; Hsieh et al., 2003).

Numerous studies during the last 10 years established that LDLR linked cellular signaling pathways modulate AD pathology [For review see (Qiu et al., 2006)]. Reelin and its homolog F-spondin are recognized by the very-low density lipoprotein receptor (VLDLR) and apolipoprotein E receptor-2 (apoE-R2), two members of the LDLR family. Mice lacking Reelin, double-knockouts lacking VLDLR and ApoER2, and mice lacking disabled-1 (Dab1) display increased levels of phosphorylated tau. It was suggested that the reelin-ApoE receptor complex initiates a signaling cascade that regulates phosphorylation of *tau* by GSK3 (Ohkubo et al., 2003). F-spondin and recently reelin have been shown to regulate APP processing through their interaction with APP and ApoER-2 (Hoe and Rebeck, 2008; Hoe et al., 2009; Hoe et al., 2005b). ApoER-2 has also been shown to be neuroprotective during aging (Beffert et al., 2006), and F-spondin was reported to protect against A β toxicity (Cheng et al., 2009). Finally, reelin expression has recently been shown to be downregulated in APP transgenic mice and in AD (Chin et al., 2007). Other LDLR family members including LRP1, LRP1B, and LR11/sorLA have also been shown to modulate APP processing [For review see (Marzolo and Bu, 2009)]. LRP5 and LRP6 are LDLR family members that function as co-receptors required for Wnt signaling. As discussed above, wnt functions to inhibit GSK3 and so plays a role in modulation of *tau* phosphorylation in AD. However the effects of wnt on AD pathology are not limited to potential modulation of *tau* phosphorylation. Lithium, a potent inhibitor of GSK3 activity, was shown to substantially reduce levels of A β , *in vitro* and *in vivo* (Phiel et al., 2003). RNA interference experiments showed that the α and β isoforms of GSK3 produced opposite effects on A β levels indicating a more complex relationship to APP processing (Phiel

et al., 2003). Furthermore, it has also been shown that lithium could ameliorate neurodegeneration induced by A β fibrils and improve memory performance in rats (De Ferrari et al., 2003). However, the potential effects of lithium on A β pathology remain controversial as a more recent publication has contradicted the effect of lithium on A β production and memory but confirmed a role in blocking *tau* pathology in 3 $\times$ Tg (APP/PS1/*tau* transgenic) mice (Caccamo et al., 2007). A β has been shown to antagonize wnt signaling through the induction of the Dickkopf-1 (Dkk1) Wnt inhibitor producing a potential negative feedback loop promoting AD (Caricasole et al., 2004). Also, recently Dickkopf-1 down regulation by estrogen was found to reduce tau phosphorylation during cerebral ischemia (Zhang et al., 2008b). Lastly, genetic linkage analysis has found an association between the Wnt co-receptor LRP6 and risk of developing AD (De Ferrari et al., 2007).

A more recent study showed that in transgenic mice carrying human ϵ 4 (apoE4) apoptosis of neural progenitor cells takes place after exposure of these mice to environmental enrichment (Levi and Michaelson, 2007) suggesting that at least part of the mechanism by which apoE4 induces susceptibility to AD is by compromising neurogenesis. In addition to apoE there are a variety of LDLR ligands which have been implicated in neurogenesis. Reelin is perhaps the best characterized of these neurogenic factors. Reelin is highly regulated during embryogenesis and functions to guide neuroblasts towards their destinations during lamination of the cortex [For review see (Herz and Chen, 2006)]. During adulthood reelin continues to be expressed from interneurons of the brain and particularly from pyramidal neurons of the entorhinal cortex, which send major projections to the DG, as well as receive projections from CA1 and CA3 regions of the hippocampus (Pesold et al., 1998; Ramos-Moreno et al., 2006). Reelin expression has been shown to mediate the migration of neuroblasts and direct cell fate determination of adult NSC (Heinrich et al., 2006; Won et al., 2006; Zhao et al., 2007; Gong et al., 2007). F-spondin has also been implicated in neuroblast chain formation in the rostral-migratory-stream (Andrade et al., 2007). In summary, increasing evidence points towards a role for numerous LDL receptor ligands and pathways in neurogenesis, most of which are associated with AD, providing further support for a mechanistic link between these processes.

Tau phosphorylation and Kinase activity in neurogenesis and AD

Hyperphosphorylation of *tau* is one of the earlier events in the formation of neurofibrillary tangles. Recent studies provide interesting information concerning the course of tau pathology in relation to amyloid pathology in the 3 $\times$ Tg-AD mice (Oddo et al., 2003) and shed new light on the pathological effects of *tau* hyperphosphorylation and aggregation (Santacruz et al., 2005; Binder et al., 2005). Functional implications of hyperphosphorylation of tau may be far-reaching when it comes to developing neural progenitor cells, affecting mitosis, axonal transport, process elongation and neuronal maturation [For review see (Johnson and Stoothoff, 2004)].

Recent studies suggest that in young APP^{swe}/PS1 Δ E9 mice, neural progenitor cell proliferation and early differentiation is impaired in the SVZ, a neurogenic area exhibiting low steady state levels of A β but a dramatic increase in tau phosphorylation. Importantly, increase in PHF-1-immunoreactive phosphorylated tau is detected as early as 2 months of age (Demars et al., 2009). The known function-associated phosphorylation sites of tau are reportedly on serine and threonine, suggesting a role for serine and threonine kinases and phosphatases in AD. There are more than ten serine/threonine protein kinases that have been shown to phosphorylate tau *in vitro*. According to the motif-specificity, these kinases can be divided into two major groups, i.e., the proline-directed protein kinases (PDPKs) and nonproline-directed protein kinases (NPDPKs). Among these kinases, GSK-3 β is among the most implicated in the abnormal hyperphosphorylation of tau in AD brains. As discussed above, glycogen synthase kinase 3 (GSK3) is a component of the Wnt signaling pathway, that plays a major

role in adult neurogenesis (Lie et al., 2005), microtubule dynamics and fast axonal transport (Frame et al., 2001; Morfini et al., 2002). GSK3 is inactivated by phosphorylation at serine 9 (Ser9) in its N'-terminus. Among GSK3's numerous substrates are PS1, β -catenin, tau, and kinesin-I light chains (KLC) [(Tesco and Tanzi, 2000; Morfini et al., 2002; Takashima et al., 1998) For review see (Frame and Cohen, 2001)]. Previous studies suggest that FAD-linked PS1 mutations affect GSK3 kinase activity in transfected cell lines (Takashima et al., 1998; Weihl et al., 1999a; Weihl et al., 1999b). Significantly, phosphorylation of KLC by GSK3 promotes the release of kinesin-I from membrane-bound organelles, leading to a reduction in fast anterograde axonal transport (Morfini et al., 2002). GSK3 has been recently suggested to play a role in the induction of mammalian neurogenesis in embryonic stem cells and in regulation of neurogenesis in the adult SVZ (Maurer et al., 2007), raising the possibility that alterations in GSK3 kinase activity in the SVZ and SGL microenvironments underlie alterations in tau phosphorylation in these neurogenic niches of adult mice. Wen and colleagues show an interplay between cyclin-dependent kinase 5 (cdk5), previously shown to be central for tau phosphorylation (Noble et al., 2003) and GSK3 β in mice overexpressing p25. While cdk5 activity increases APP processing, GSK3 β activity induces tau phosphorylation. Interestingly, inhibition of cdk5 activates GSK3 β activity (Wen et al., 2008a). Finally, transcriptional regulation of β -secretase by cdk5 was also shown to lead to enhanced amyloidogenic processing of APP (Wen et al., 2008b). Therefore, these kinases may function as a critical focal point for processes that mediate both neurogenesis and AD.

Evidence for Altered Neurogenesis in Alzheimer's disease

Numerous studies have suggested that the rate of neurogenesis in both SVZ and DG declines with age, raising the possibility that reduced neurogenesis may account, to some degree, for the impaired learning and memory and cognitive deterioration in the elderly (Tropepe et al., 1997; Seki and Arai, 1995; Kuhn et al., 1996; Kempermann et al., 1998; Kempermann et al., 2002). Examination of neurogenesis in brain tissue of AD patients revealed increased expression of immature neuronal marker proteins (Jin et al., 2004a). However, these observations have been challenged recently (Boekhoorn et al., 2006). Other reports suggest that in the aged and AD brain, there is a significant decline in extent of proliferation of progenitor cells and their numbers [For review see (Brinton and Wang, 2006)]. A recent study suggests that levels of stem cell factor (SCF), a hematopoietic growth factor that supports neurogenesis in the brain, are reduced in the plasma and cerebrospinal fluid of individuals affected with AD (Laske et al., 2008).

Information from studies using FAD transgenic animal models seems to be more complex (Table 1). This complexity may result from the numerous FAD-linked variables that affect neurogenesis, as revealed above. In an attempt to better understand the effect of FAD aspects on neurogenesis as they are reflected in the animal models we categorized studies by type of transgene(s) and number of mutation(s) expressed, and then analyzed the experimental settings used in individual studies (Table 1). Most studies which examined hippocampal or SVZ neurogenesis in transgenic mice expressing one or two APP mutation show impaired proliferation of progenitor cells and/or impaired neuronal differentiation in these mice. Thus, for example, using PDAPP mice expressing human V717F mutant APP under control of the PDGF promoter, Donovan and colleagues report a decrease in number of BrdU+ newly-formed cells and in the number of surviving cells in the SGL of the hippocampus. These impairments were evident at one year of age, post-onset of deposition, but not at 2 months of age. Examination of newly-formed BrdU+DCX+ neuroblasts revealed their decrease in the SGL concomitantly with an increase in their number in the granule layer (Donovan et al., 2006), emphasize the necessity for a subregion-specific analysis for the assessment of the numbers of newly-formed cells in the hippocampal microenvironment, as well as the need for cell-lineage specific markers in addition to BrdU for a thorough analysis of neurogenesis. Similar

observations were obtained in mice harboring FAD-linked mutant APP^{sw}e (double mutation). These studies revealed reduced extent of proliferation of newly formed cells and neuronal differentiation in the SGL of the dentate gyrus (Haughey et al., 2002a) and in the SVZ (Haughey et al., 2002b) in these mice. The APP^{sw}e transgene is ~2.5 fold overexpressed compared to endogenous levels, and mice exhibit increased β -secretase activity, resulting in increased levels of β -CTF, A β and sAPP β , concomitantly with lower levels of sAPP α (Thinakaran et al., 1996; Borchelt et al., 1996). All of these APP metabolites are thought to modulate variable aspects of neurogenesis, and thus the results of these studies suggest that alterations in ratios and amounts of these metabolites caused by the Swedish mutation may not be favorable when it comes to neurogenesis. In addition, infusion of 5 μ l of 1mM A β 1-42 or A β 25-35 into the lateral ventricle decreased cell proliferation in the SVZ over the next five days (Haughey et al., 2002b). While the conformation of the A β used in this study was not determined, these results suggest that A β levels and/or conformation may affect neurogenesis *in vivo*. In a different study, oligomeric A β ₄₂ was shown to enhance neuronal differentiation of embryonic and postnatal NSC *in vitro* (Lopez-Toledano and Shelanski, 2004). Mirochnic and colleagues examined hippocampal neurogenesis in APP23. They observed an increase in cell proliferation, but ultimately a decrease in the number of newly-differentiated neurons (Mirochnic et al., 2009). Interestingly, examination of neurogenesis in transgenic mice expressing three or more mutations in APP observed enhanced cell proliferation and neuronal differentiation in the hippocampus and/or SVZ. This may suggest that increased fibrillogenic properties or expression level of A β to the extent exhibited by triple mutation in APP, and APP^{sw},Ind in particular, enhances proliferation and neuronal differentiation. Thus, for example, Jin and colleagues (2004) used FAD-linked mutant platelet-derived growth factor- (PDGF)-APP^{sw},Ind transgenic mice, which express human APP isoforms APP695, APP751, and APP770 with both the Indiana (V717F) and Swedish (K670N M671L) mutations, driven by a PDGF promoter. These mice exhibit increased numbers of newly-proliferating cells in the SGL and SVZ pre- and post-onset of amyloid deposition (Jin et al., 2004b). It should be noted that the APP^{sw},Ind mice exhibit extracellular amyloid deposits beginning at 6–9 months of age, as well as synaptic loss, astrogliosis and microgliosis, all of which do not occur in the APP^{sw}e mice, at least not until very late in life (Borchelt et al., 1996). Caution should be taken as for the interpretation of the observations presented in these studies. Thus for example, some of the studies depend on BrdU alone for the assessment of newly formed cells in the SGL and/or SVZ. Such proliferating cells may include glia and/or peripheral immune cells that do not belong to the neural progenitor cell population. In order to determine the fate of neural progenitor cell proliferation in these mice, further examination of neural progenitor cell marker, such as nestin or cell lineage-specific markers should be used.

In a different study, Lopez-Toledano and colleagues (2007) used PDGF-APP^{sw},Ind mice, similar to Jin and colleagues (2004). In support of the latter Lopez-Toledano et al. observed an increase in proliferation of hippocampal cells, as well as an increase in their neuronal differentiation. This increase was attributed to detectable levels of oligomeric A β (Lopez-Toledano and Shelanski, 2007). In contrast, increased proliferation at later time points, close to onset of deposition or post deposition could not be observed (Lopez-Toledano and Shelanski, 2007). The different regimen of BrdU injection (single injection in Lopez-Toledano and colleagues and repetitive dose for consecutive days in the Jin and colleagues and Haughey and colleague studies) makes the comparison between the different observations challenging, particularly if a change in cell cycle takes place in one of the animal models. Similar observations to Jin and colleagues and Toledano-Lopez and colleagues were observed in a separate study using pPDGF-APP^{sw},Ind (Gan et al., 2008), suggesting an increase in proliferation and differentiation of hippocampal progenitors in these mice at 2 months of age. Interestingly, in contrast to Jin et al. (2004) and Lopez-Toledano et al. (2007), Gan and colleagues observed a decrease in cell proliferation concomitantly with an increase in neuronal differentiation in transgenic mice at 12 months of age (Gan et al., 2008). Examination of BrdU

+ cells in Tg9291 mice expressing three FAD linked mutations: APP₍₆₉₅₎swe,dutch,Lnd and aged-matched controls revealed amyloid deposition-dependent increase in the number of proliferating cells in the hippocampus (Kolecki et al., 2008). However, the nature of these cells and their cellular lineage is not clear. Ermini and colleagues observed an increase in the number of new neurons in aged but not in adult (pre-onset of amyloid deposition) in APP23 mice expressing KM670/671NL mutated human APP_{swe} under a murine Thy-1 promoter element. However, a decrease in proliferation of hippocampal neural progenitor cells was found in APP_{KM670/671NL}/PS1_{L166P} mice post onset of deposition (Ermini et al., 2008). Several additional studies examined hippocampal neurogenesis in transgenic mice coexpressing FAD-linked APP and PS1 mutant variants. Thus, for example, in APP_{swe}/PS1 Δ E9 mice, a decrease in long-term survival of hippocampal progenitors was detected post onset of deposition (Verret et al., 2007). Long-lasting impairments in hippocampal neurogenesis were detected in APP/PS1 KI mice post onset of deposition (Zhang et al., 2006). Taniuchi and colleagues report a decrease in the number of proliferating cells and of newly-formed neuronal (DCX+) cells in the hippocampus of APP_{swe}/PS1 Δ E9 mice at age of 9 months, post amyloid deposition, but not at onset of deposition (5 months) (Taniuchi et al., 2007). In 3 $\times$ Tg-AD, an age- and gender-dependent reduction in proliferation of hippocampal progenitor cells correlates with number of hippocampal neurons accumulating intracellular A β (Rodriguez et al., 2008).

Observations obtained in several transgenic mice expressing FAD-linked mutant PS1 suggest that alterations in neurogenesis in these mice are apparent only following introduction of an external neurogenic stimulus, such as enriched environment. Thus, Choi and colleagues (2008) as well as Feng and colleagues (2001) report impairments in enriched environment-induced neurogenesis, but no impairment without stimulus (Feng et al., 2001; Choi et al., 2008). While Feng and colleagues used a conditional PS1 KO, Choi and colleagues used transgenic mice harboring mutant PS1. These results may suggest that either PS1 plays a role in regulation of the neurogenic response to enriched environment or that without stimulus, the effect of the mutation on neurogenesis is milder. Transgenic mice expressing FAD-linked PS1 P117L that were maintained in either standard housing or environmentally enriched conditions exhibit compromised survival of new neurons. In PS1 P117L mice maintained in standard housing conditions, survival of new astrocytes is compromised as well (Wen et al., 2004). Using PS1M146V knockin mice Wang and colleagues show that the number of newly formed cells and neurons in the hippocampus of these mice is decreased compared to wild type mice and that impaired neurogenesis correlates with deficient associative learning (Wang et al., 2004). In contrast, PS1KO mice rescued with PS1A246 exhibit increased proliferation of newly born cells in the dentate gyrus compared to mice rescued with PS1HWT, but no difference in extent of differentiation (Chevallier et al., 2005).

As described above, the different roles that APP metabolites, PS1 and other critical molecules play in neurogenesis, may account, at least in part, for some of the observed variations in the fate of neurogenesis in the different animal models used in these studies. Importantly, the high responsiveness and sensitivity of neurogenesis to internal and external stimuli may require a careful examination of the data as a function of age, neurodegeneration, extent and onset of amyloidosis, and, other experimental conditions, such as regimen of BrdU injection. Furthermore, differences in behavioral manipulations (e.g. training, and enriched environment) may also account for the observed heterogeneity in observed effects on neurogenesis. For example, notably, two recent studies suggest that induced reduction of amyloidosis enhances neurogenesis. Becker and colleagues show that anti- EFRH immunotherapy (i.e. antibodies raised against the EFRH sequence, encompassing amino acids 3-6 of the 42 residues of the A β) reduces amyloid deposition and enhances neurogenesis in PDAPP mice (Becker et al., 2007). Mirochnic and colleagues shows that experience of APP23 in enriched environment enhances neurogenesis, while reducing the ratio of A β ₄₂/A β ₄₀ (Mirochnic et al., 2009). While the majority of studies suggest that expression of FAD linked mutations compromise

neurogenesis in the adult brain, the reaction of neurogenesis to alterations in the neuronal environment may induce temporally differential extent of neurogenesis. This is demonstrated well in a study of Chen and colleagues, which showed that conditional ablation of PS1 in the forebrain and knock out of PS2 in adult mice (PS1/PS2 KO mice) induces massive neurodegeneration in the cortex and hippocampus. This neurodegeneration is accompanied by induced cell proliferation in the SGL. However, most of these newly formed cells do not survive. In late stages of neurodegeneration the survival of newly generated neurons was severely impaired so that the enhanced neurogenesis could not be detected any more (Chen et al., 2008). This study shows that alterations in neurogenesis are neurodegenerative stage-dependent.

It appears that in the majority of murine studies (12 of 18) neurogenesis is primarily impaired (excluding the conditional knockout studies which are not directly associated with FAD) (Table I). It is interesting to note that studies in which only one naturally occurring mutation of APP and or PS1 are used, a greater majority found impaired neurogenesis (12 of 14). Also, in both cases where only knockin technology was used, an impairment of neurogenesis was found (Wang et al., 2004; Zhang et al., 2006). Conversely, in all cases where mutations in APP were combined (triple or quadruple mutations) increased neurogenesis was found.

Based on the evidence presented above demonstrating that molecular players of FAD, i.e. APP and metabolites, PS1, γ -, α - and potentially β -secretase play a role in neurogenesis, it is reasonable to assume that mutations in these players and/or their dysfunction would compromise neurogenesis in both cell-autonomous and non-cell-autonomous manner. Indeed, recent studies demonstrate that microglia-secreted soluble factors may play a role in regulation of hippocampal neurogenesis, and that microglia derived from the brains of FAD-linked mutant PS1 variants secrete altered levels of soluble signaling factors, suggesting a non-cell-autonomous effect of FAD on hippocampal neurogenesis (Choi et al., 2008). This discussion underscores the need to perform studies in which select metabolites are exclusively expressed within, or exclusively secreted from specific cell populations.

In summary, often, seemingly contradicting results were observed in apparently similar animal models. However, as this review reveals, there are numerous players in FAD that may modulate neurogenesis. Neurogenic roles have been attributed to both PS1 and APP. Each APP metabolite alone (e.g., sAPP α , APP-CTFs, p3, A β), as well as different conformation and aggregation levels of a given metabolite, such as A β , may have unique or specialized role and effect on aspects of neurogenesis. As a consequence, whether a mutation affects β - or γ -secretase activity may modulate neurogenesis differently. In addition, both α - and γ - and possibly β -secretase have numerous neurogenic substrates. Fibrillogenic A β levels and concentrations have been shown to have variable effects on neurogenesis. Extent of amyloid deposition and specific pattern of accumulation in the hippocampus may affect neurogenesis differently, as well as astrogliosis, microgliosis, synaptic degeneration and neuronal cell death. Furthermore, the method of neurogenic analysis must be comprehensive and consistent (e.g. BrdU regimen, cell markers, age, etc.) Thus, a thorough understanding of the molecular mechanism underlying AD is required for the analysis of neurogenesis in FAD mouse models. This must be done first before a definite conclusion can be made regarding what is implied for the human disease. Interestingly, it becomes increasingly evident that alterations in neurogenesis take place early in life and may be a contributing factor rather than a result of neural dysfunction. A recent study suggests that in APP^{swe}/PS1 Δ E9 transgenic mice, impairments in neurogenesis take place long before amyloid deposition (Demars et al., 2009). Impairments in neurogenesis early in life, prior to processes that secondarily affect neurogenesis, such as neuronal loss, A β accumulation, and inflammation, may suggest that expression of FAD-linked proteins directly compromises neurogenesis in the adult brain and contribute to the disease. As AD pathology is progressive, it remains to be determined under

what conditions impairment in neurogenesis is causative, at least in part, and under what conditions alterations are a downstream effect of AD pathology. Our summary of the molecular links between neurogenic and AD pathways suggest that neurogenesis is an integral part of AD pathology.

Summary

We have presented evidence that multiple factors known to be intimately involved in AD pathogenesis are now being shown to modulate adult neurogenesis. Most notably PS1 and APP are emerging as a critical player in these processes. Conversely, multiple factors known to be involved in neurogenesis are emerging as critical players in AD pathogenesis. These include Wnt/Notch and reelin signaling. This convergence of signaling should be taken into account in the development of potential therapies.

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Figure 1. The cross-talk between Alzheimer's disease-linked signals and neurogenic signals

A summary of suggested function of signals in Alzheimer's neuropathology and in neurogenesis in the adult brain [Abbreviations: ADAM= a disintegrin and metalloproteinase, BACE= beta amyloid cleaving enzyme, PS1=presenilin 1, PEN= presenilin enhancer, sAPPα= soluble amyloid precursor protein alpha, Aβ= beta amyloid, AICD= APP intracellular domain, NICD= notch intracellular domain, APOE=apolipoprotein E, LRP= low-density lipoprotein receptor-related protein, EGFR= epidermal growth factor receptor].

Figure 2. Adult neural progenitor cells in culture

Neural progenitor cells derived from the SVZ or SGL can be cultured. They form neurospheres and proliferate in the presence of FGF2 and EGF. The image shows neurospheres labeled with antibodies raised against beta-tubulin (red), GFAP (green) and counterstained with DAPI (blue).

Table 1
Summary of studies examining alterations in neurogenesis in FAD-linked mouse models

Genetic manipulation	Reference	Genotype	Promoter	Age (months)	Pre, post, no deposition	Other neurogenic stimuli	BrdU regimen	SVZ	SGL
APP Transgene Single mutation	(Donovan et al., 2006)	APPInd (PDAPP)	PDGF	2	Pre	N/A	Single dose.	N/A	No impairments
				12	Post		Sacrificed 2 hours or 4 weeks after.		Impaired proliferation and survival of progenitors. Increased neuroblasts in the GCL
Double mutation	(Haughey et al., 2002a)	APP ⁽⁶⁹⁵⁾ swe	Prion Protein (PrP)	12-14	Pre	N/A	Daily dose for 5 days. Sacrificed either 24 h or 12 d after last dose	N/A	Impaired Proliferation, survival and differentiation
	(Haughey et al., 2002b)	APP ⁽⁶⁹⁵⁾ swe	PrP	11-12	Pre	N/A	Daily dose for 5 days. Sacrificed 24h after last dose	Impaired Proliferation, and differentiation	N/A
	(Mirochnic et al., 2009)	APP ⁽⁷⁵¹⁾ swe (APP23)	Thy-1.2	6	Post	No treatment	Daily dose for 3 days and sacrifice 4 weeks later.	N/A	Increased proliferation and decreased neuronal differentiation
				18		Enriched Environment Running			Increased proliferation and neuronal differentiation following enrichment
Triple mutation	(Jin et al., 2004)	APPswe,Ind	Platelet-derived growth factor (PDGF)	3	Pre and post	N/A	Twice daily for 3 consecutive days. Sacrificed one week later.	Enhanced proliferation and differentiation	Enhanced proliferation and differentiation
				12					
	(Lopez-Toledano and Shelanski, 2007)	APPswe,Ind (J20)	PDGF	3, 5, 9, 11	Pre and post	N/A	4 and 2 hours before sacrifice or daily dose for 5 days for 5 days sacrifice	N/A	Increased proliferation and differentiation at 3 months of age

Genetic manipulation	Reference	Genotype	Promoter	Age (months)	Pre, post, no deposition	Other neurogenic stimuli	BrdU regimen	SVZ	SGL
							one month later.		
	(Gan et al., 2008)	APP ^{sw} , Ind	PDGF pNes-LacZ	2 8 12	Pre Onset Post	N/A	Twice daily at 8 hour interval for 3 days and sacrificed 3d after last dose.	N/A	Increased proliferation and differentiation Increased proliferation and differentiation Decreased proliferation and increased differentiation
Quadruple mutation	(Kolecki et al., 2008)	APP ₍₆₉₅₎ ^{swe,dutch,Lnd} (Tg9291)	PtP	2-4 9-12	Pre Post	N/A	Daily dose for 4 days before sacrifice.	N/A	No change Increased proliferation
APP+ PS1 Transgenes	(Ermini et al., 2008)	APP23 APP23 APPKM670/671NL/PS1L166P	Thy-1.2	Adult aged	Pre Post Post	N/A	Daily dose for 7 consecutive days. Sacrificed 3 weeks after the last dose.	N/A	Decreased neuronal differentiation Increased proliferation and differentiation Decreased proliferation and differentiation
	(Verret et al., 2007)	APP ^{swe} APP ^{swe} /PS1 ^{ΔE9}	PtP	6	Pre Post	N/A	Daily dose for 12 consecutive days. Sacrificed either one day or 30 days post last injection.	N/A	Impaired long-term survival of progenitors
	(Taniuchi et al., 2007)	APP ^{swe} /PS1 ^{ΔE9}	PtP	5 9	Onset Post	N/A	Twice daily at 6-h intervals for 3 consecutive days, and were killed 24 h after the last BrdU injection.	N/A	No impairments Decreased proliferation and neuronal differentiation

Genetic manipulation	Reference	Genotype	Promoter	Age (months)	Pre, post, no deposition	Other neurogenic stimuli	BrdU regimen	SVZ	SGL
APP+tau Transgene+ PS1	(Nidome et al., 2008)	APP ^{swe} /PS1 ^{ΔE9}	PtP	9	Post	N/A	Double dose 6 hour interval for 3 consecutive days. Sacrificed 24 h after the last dose.	No change	Impaired proliferation
	(Zhang et al., 2006)	APP/PS1 KI	N/A	8-9 18-21	post	N/A	N/A	N/A	Impaired proliferation and differentiation
	(Rodriguez et al., 2008)	APP ^{swe} /tauP301L/PS1M146VKI (3×Tg-AD)	Thy-1,2	Females>4 Males>9	Correlation with Amyloid deposition and Intracellular Aβ	N/A	N/A	N/A	Impaired proliferation of progenitor cells
PS1 Transgene	(Chevallier et al., 2005)	PS1 ^{-/-} A246E	Thy-1	3	N/A	N/A	Double dose four hour apart. Sacrificed 24 h or 4 weeks later.	N/A	Increased proliferation
	(Wang et al., 2004)	PS1M146V/-KI	N/A	3	N/A	Fear conditioning tests	Twice daily 2 hour apart for 4 consecutive days. Sacrificed 12 hours after last dose.	N/A	Impaired proliferation and differentiation
	(Wen et al., 2004)	PS1 P117L	Neuron-specific enolase (NSE)	3-4	N/A	No treatment	Daily dose for 12 consecutive days.	N/A	Impaired survival of proliferating cells
	(Choi et al., 2008)	PS1ΔE9 and PS1M146L	PtP	3	N/	No treatment	Single dose. Sacrificed	N/A	No impairments

Genetic manipulation	Reference	Genotype	Promoter	Age (months)	Pre, post, no deposition	Other neurogenic stimuli	BrdU regimen	SVZ	SGL
Conditional knockout	(Feng et al., 2001)	Conditional PS1KO	Cre/loxP system	11-17		Enriched Environment	24 hours or 2 weeks later.		Impaired proliferation and differentiation
					N/A	No treatment Enriched Environment	Double dose in a 2 hour interval daily for 4 consecutive days. Sacrificed 12 hours later.	N/A	No Impairments Impaired proliferation and differentiation
Knockout+ conditional knockout	(Chen et al., 2008)	Conditional PS1/PS2KO	Cre/loxP system	7-9 18-20	N/A	Neurodegeneration	Single dose. Sacrificed 24 hours, 2 weeks or 4 weeks later.	N/A	Increased proliferation impaired survival

- orange

APP transgene
- pink

APP and PS1 transgene
- Light green

APP and tau transgene and mutant PS1KI
- Yellow

PS transgene/knockout
- purple

Special conditions/stimulus
- red

Decreased neurogenesis
- green

Increased neurogenesis