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### Activity- and pharmacology-dependent modulation of adult neurogenesis in relation to Alzheimer's disease

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**Chapter 7: Neurogenesis and Alzheimer's disease: Biology and Pathophysiology in Mice and Men**

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### **Abstract**

The hippocampus is critical for learning and memory and heavily affected in dementia. The presence of stem cells in this structure has led to an increased interest in the phenomenon of adult neurogenesis and its role in hippocampal functioning. Not surprising, investigators of Alzheimer's disease have also evaluated adult neurogenesis due to its responsiveness to hippocampal damage. Although causal relationships have not been established, many factors known to impact neurogenesis in the hippocampus, are implicated in the pathogenesis of AD. Also, adult neurogenesis has been proposed to reflect a "neurogenic reserve" that may determine vulnerability to hippocampal dysfunction and neurodegeneration. Since neurogenesis is modifiable, stimulation of this process, or the potential use of stem cells, recruited endogenously or implanted by transplantation, has been speculated as a possible treatment of neurodegenerative disorders. As the structural and molecular mechanisms governing adult neurogenesis are important for evaluating therapeutic strategies, we will here review collective literature findings and speculate about the future of this field with a focus on findings from Alzheimer's mouse models. Continued research in this area and use of these models is critical for evaluating if neurogenesis based therapeutic strategies will indeed have the potential to aid those with degenerative conditions.

## **Introduction**

Our understanding of stem cell biology including adult neurogenesis is rapidly developing and currently approaching a crossroads with investigators seeking new methods to confront neurologic conditions such as AD. The discovery of stem cells within the human body had led to anticipation that these unique cells can be used therapeutically. Stem cells are restricted to specific micro-environments and have been identified through unique molecular markers that distinguish these cell populations.

Characterization of stem cell niches and of the dynamics of these unique microenvironments can provide a great deal of insight into stem cell regulation during physiological and pathological conditions. While experimental evidence illustrates that stem cells can be utilized for therapeutic uses during neurodegenerative conditions, a great deal of information has yet to be uncovered regarding the relationships between endogenous neurogenesis and its functional role. The functional significance of adult neurogenesis will have to be fully understood before potential regenerative capacities of these cells for the brain can be utilized for the treatment of Alzheimer disease.

Transgenic models allow investigators to identify how genes impact phenotype; in recent years, various mouse models have been produced that recapitulate pathological lesions and behavioral characteristics of Alzheimer's disease. Some models have been evaluated for changes in neurogenesis providing insight into gene interactions and adult neurogenesis during neurodegenerative conditions. Important translational studies have been conducted that identify differences between neurogenesis in humans and other mammals. Progress in these areas allows biologists to identify the critical signaling and structural elements needed to successfully stimulating neurogenesis. Evaluating the therapeutic potential of endogenous neurogenesis and grafted neurons is contingent on progress in these areas.

## **Adult Neurogenesis**

### **Introduction**

In the brains of adult mammals, new cell birth and neurogenesis has been characterized in two locations; the subventricular (SVZ) and subgranular zones (SGZ) located in the lateral ventricles and dentate gyrus, respectively. These specialized micro-environments support the

production of new cells in the brain and are representative, but structurally distinct, of stem cell niches found in other tissues. These zones are unique as they contain neural stem cells (NSCs) with the capacity to proliferate, migrate, and differentiate into adult, functional cell-types. Self-renewal and multipotency are exceptional properties distinguishing stem cells from other dividing cells, properties conferred by the microenvironments surrounding stem cells. The highly structured nature of SGZ and SVZ determines stem cell maintenance and effectively controls proliferation and maturation of nascent cells selectively. Due to complex experimental constraints, little definitive evidence regarding the factors that control maintenance of stem cells in these niches has been collected so far but identifying common and distinct mechanisms impacting stem cell maintenance in these zones is a critical area of discovery to fully appreciate the potential of endogenous stem cells for repair.

The SGZ is part of the dentate gyrus (DG), an integral portion of the hippocampal formation. The DG has a unique trilaminar anatomy and represents a trisynaptic circuit that corresponds with highly specific information processing (reviewed by Amaral)[1]. Interestingly, stem cells isolated from the same regions behave differently when transplanted to other brain regions, confirming the important role for the local environment or neurogenic niche that enables stem cell maturation into functional neurons in these zones only[2], (reviewed by Morrison). It is within this local context that neural stem cells are able to mature into granule neurons of the DG.

Granule neurons and their interconnections define operation and structure of the DG. The trisynaptic circuit starts with projections from the entorhinal cortex that connect to DG granule neurons. Mossy fibers from DG granule neurons then project to large pyramidal neurons in the Cornu Ammonis 3 (CA3) region of the hippocampus and these CA3 pyramidal neurons project to hippocampal CA1 neurons. Thus the hippocampal formation is a critical region of the brain responsible for executive functions such as spatial and working memory tasks. Importantly, AD progresses through structures of the brain in a well-defined, hierarchical spatial sequence that initially does not impact this area. AD is not often clinically diagnosable until pathology advances to include the hippocampus, amygdala, frontal, temporal, and/or parietal lobes when anterograde memory and executive functions are impacted.

For these reasons we will focus almost exclusively on neurogenesis in the DG impacting hippocampal structure and function.

NSCs proliferate and produce identical multipotent NSCs with the capacity to produce neurons, astrocytes, or oligodendrocytes[3]. Within the DG, astrocytes are the NSCs of the brain and generate new granule neurons through a series of immature cells[4, 5]. Wnt signaling has been previously demonstrated to be responsible for the neurogenic activity of these astrocytes[6]. Two types of NSCs have been identified by morphology and molecular markers (reviewed by Zhao)[7]. Recognizing adult NSCs *in vivo* is dependent on these criteria and typically labeled with molecular markers within the DG. NSC daughter cells are multipotent, having not been selected for a cell fate up to that point. A population of these daughter cells matures to become neural progenitor cells (NPCs) that further divide and/or mature as functional neurons.

### **Markers of Neurogenesis**

A prerequisite for discussing the published literature in this field is reviewing markers and methodologies used to identify neurogenesis. There are a number of techniques and this review only provides a brief discussion serving primarily to introduce these concepts.

Identification of NPCs is critically dependent on proper location, cell morphology, and selective protein expression. Type-1, radial astrocytes, and Type-2, non-radial astrocytes, co-express specific proteins that distinguish these cells within the SGZ of the DG e.g. NPCs express Nestin[8], Sox2, and glial fibrillary acidic protein (GFAP)[9-11] indicating their astrocytic nature. Astrocytes in the SGZ also express the unique structural marker GFAP- $\delta$  observed in stem cells of the SVZ and subpial zones[12]. Sox2 expression describes the pool of NPCs with capacity to generate all three neural lineages[11]. Sox2 is a member of the Sox (SRY-related HMG box) gene family; this transcription factor, known to be expressed during development and in adult brain NSCs, binds DNA at a single HMG DNA-binding domain[13, 14]. Interestingly, Sox genes further encode proteins that regulate transcription and determine cell fate during development e.g. the Sry (sex-determining region of Y chromosome) gene encodes mammalian testis-determining factor[15].

Many of the protein markers described above have been studied through the combined use of the birth date marker Bromodeoxyuridine

(BrdU), a synthetic thymidine analog typically injected *in vivo*. BrdU is incorporated into the DNA of dividing cells during genome replication and allows for later co-labeling with phenotypic molecular markers. Critically, the time between injection and euthanasia will determine the cell population identified. Typically observations are made: a) 24 hours after injection to label the population of proliferating cells, b) 3-6 weeks after injection to label and identify cells that have migrated and survived. By utilizing two cohorts of animals with these survival times it is possible to identify and stereologically count proliferating and mature cells. Co-labeling BrdU positive cells with additional markers can confirm that a cell in question is indeed a daughter cell from a neural stem cell that has differentiated into a specific adult glial or neuronal phenotype. Such dual label cell-fate analyses allow molecular markers to be appropriately identified with newly generated cells. Markers such as NeuN [18] and S100 $\beta$  are used quite frequently in the field to identify mature neurons and astrocytes respectively. The location of a BrdU positive cell also aids in confirming the phenotype of a mature cell.

Molecular markers of neurogenesis have been identified during development and can be expressed in other brain regions. Previous rodent studies have established that e.g. the microtubule associated protein Doublecortin (DCX) is expressed in migrating, immature neurons that co-express neuron-specific class III  $\beta$ -tubulin (Tuj1). Its pattern of distribution overlaps with that of adult neurogenesis in e.g. the hippocampus. DCX is a well accepted molecular marker of neurogenesis in rodents; *In utero* electroporation during cortical development in E14 mice revealed the requirement of DCX for proper migration of immature neurons to the cortical plate[16]. Radial migration is disrupted when an RNAi against the 3'UTR of DCX is administered providing evidence for non-cell-autonomous components of DCX expression. However, in adult cortex, DCX is also observed in cortical astrocytes and in various neurodegenerative disorders. As there is no evidence that these cells have been generated from endogenous stem cells, this suggest that in neurodegenerative conditions, DCX may have additional functional roles, such as e.g. in glia-to-neuron communication[17].

In the next section we will review findings regarding the discrete function of neurogenesis in the SGZ niche and comment further on our

ability to characterize adult neurogenesis in detail and the potential of these unique cells.

### **Plasticity and Regulation**

While synaptic plasticity is thought to be the main structural change corresponding to rapid changes in cognitive function, the addition of new neurons to an existing circuit through adult neurogenesis represents a novel and unique form of structural plasticity for the longer term. In young rats, it has been estimated that approximately 9000 new cells per day are generated in the entire hippocampus, but a considerable proportion of these cells die within several days[19]. While the number of new neurons incorporated into the DG may be quite low, particularly during aging, investigators regard this ongoing phenomenon as potential for adaptation. The Neurogenic Reserve hypothesis states that ongoing adult neurogenesis is a special type of brain plasticity allowing for adaptation during activity that may influence vulnerability to accumulating deleterious events[20]. Through a global evaluation of neurogenesis it is arguable that the functional consequences of adult neurogenesis will only become apparent over long time scales.

The fact that neurogenesis occurs throughout the lifespan of many species indicates an important role that is conserved throughout evolution. Interestingly, the process is highly susceptible to environmental/experience-dependent modulation, i.e. voluntary exercise and environmental enrichment change *in vivo* fates of the newborn cells[21]. Various studies have further identified factors that can regulate production and survival of hippocampal neurons maturing during rodent adulthood. Some, like estrogen[22-24], environmental complexity[25-31], exercise[32-34] and NMDA-related excitatory input[35-37] positively regulate neurogenesis, while others such as stress[38-44], cholinergic denervation[45], and aging[26, 31, 46, 47] decrease the levels of neurogenesis (reviewed by Casadesus)[48]. Acute and chronic brain diseases, such as Alzheimer's disease, have acute and chronic responses from the endogenous NSC population. Head injury, epileptic seizures[49] and transient global and focal ischemia[50-53] increase hippocampal neurogenesis, but the effects on hippocampal circuit properties and Alzheimer's disease are poorly understood (reviewed by Castellani et al.)[54].

While the links between Alzheimer's disease and neurogenesis are controversial, connections have been established between neurogenesis and depression. Stress-induced reductions in neurogenesis have been implicated in depression and in antidepressant drug action[38-44]. Adult CA1 pyramidal neurons and DG granular neurons express both mineralocorticoid (MR) and glucocorticoid receptors (GR). Prolonged exposure to stress may induce alterations in HPA feedback that can subsequently lead to overexposure to glucocorticoids. Of interest, high circulating levels of stress hormones form a substantial risk factor for Alzheimer disease[55]. Whether neurogenesis that occurs during these pathological conditions contributes to functional recovery is still an enigma; distinguishing between the capacity for recovery and those factors responsible for functional recovery is not firmly established.

### **Behavior**

Importantly, the aforementioned factors not only effect neurogenesis but also correlate with changes in behavioral performance, including hippocampal learning and memory [56-62]. This suggests a direct relationship between neurogenesis and cognitive function. For example, housing rodents in an enriched housing environment [25-31] or allowing them access to a running wheel [32-34] increases the survival of progenitor cells and also leads to an enhanced performance in the water maze task; conversely, other factors such as stress, which are linked to a decrease in neurogenesis, impair behavioral performance on such tasks[38-44]. One of the most direct studies to address this question utilized an inducible transgenic model to ablate adult-born hippocampal neurons through expression of Bax in hippocampal neural precursors. These mice showed impairment of relational spatial memory while less complex forms of spatial memory were unaltered[63, 64]. Previous work established that spatial learning promotes newborn neuron death in the DG (63). Therefore, neurogenesis appears to be, at least in part, involved in modulating behavioral output and more specific aspects of hippocampal learning and memory.

The role of neurogenesis has also been evaluated through more direct measurements of hippocampal-dependent tasks and changes in synaptic activity. In adult rats, investigators found that a substantial reduction in the number of newly generated neurons directly impaired

hippocampal-dependent trace conditioning, a task in which an animal must associate stimuli that are separated in time. This reduction in neurons had no effect on learning during hippocampal-independent tasks[58]. Also later studies indicated a role for adult neurogenesis in the encoding of time in new memories[65]. Therefore neurogenesis appears to be involved in modulating specific aspects of hippocampal-related cognitive output and as such, may prove important in degenerative diseases associated with selective impairments in this region such as AD.

Changes in synaptic number have important functional consequences on behavior, especially cognition. In neurodegenerative conditions, changes in synaptophysin are better correlated with disease progression than plaque load or cell death[66]. Alterations in synaptic density during normal aging have been revealed; an inverse correlation exists between age and presynaptic terminals[67]. Mechanisms of hippocampal synaptogenesis and its direct significance to learning and memory are presently being established [58, 68]. Decreased neurogenesis resulting from a loss of activity associated with synapse strength, could further impair hippocampal behavior. Ongoing adult neurogenesis implies a contribution to enrichment of synaptic density since new synapses are formed. Also, newly generated cells have lower long-term potentiation thresholds therefore changes in their numbers may affect functioning of the hippocampal circuit. Maintenance of adult neurogenesis could stabilize synaptic density, alleviating synapse loss and reducing age-associated changes. It has been shown that a loss of hematopoietic stem cells results in premature aging[69], however, currently no evidence has been collected regarding the relationship between loss of stem cells and specific neurologic dysfunction in humans.

### **Potential for Recovery**

Alzheimer's is the most prevalent form of dementia associated with aging. Interestingly, clear age-dependent reductions in NPC proliferation have been shown in rodents and old monkeys. Both physical and cognitive activities reduce this age-dependent decline in precursor cell proliferation. Maintenance of stem cell proliferation and the local microenvironment responsible for proper migration and connection, could prevent deterioration of the hippocampus. Investigators have established that neurons born in aged mammals are

just as functional as neurons that develop through neurogenesis in young mammals[70]. This phenomenon has been observed if the activity treatment is started in midlife, yielding improved learning performance[26].

Different models of pathology have shown robust and transient increases in adult cytogenesis that are nonspecific and likely involved in gliogenesis. This non-specific up regulation or proliferation will at least not result in acute functional recovery. Indeed, the main function of adult neurogenesis does not seem to lie in regeneration of neurons that have been lost during the course of disease. A more restricted view of adult neurogenesis implies that utilizing neurogenesis for healthy aging occurs over longer durations and may be perhaps most beneficial if activity is established in midlife to preserve adult neurogenesis prior to clinical presentation with dementia or Alzheimer's disease.

Astrocytes play a critical part in maintenance of neurogenesis; the effects of gliosis associated with pathology and aging have not been fully examined and could provide a more coherent understanding of age-related declines. Astrocytes provide trophic and metabolic support to neurons; astrocyte number and complexity distinguish the human brain from other mammals[71] and astrocytes are known to play an important role in SGZ neurogenesis[6] and factors secreted by activated astrocytes have been identified that modulate neural/progenitor cell differentiation but the significance of gliosis within the context of adult brain function and neurodegenerative diseases like AD has not been resolved.

## **Alzheimer's disease**

### **Introduction**

Alzheimer's disease is the most prevalent form of dementia in the elderly and is best characterized as an age-dependent neurodegenerative disease. Questions regarding the role of neurogenesis in neurodegenerative conditions are warranted due to the high amount of overlap between risk factors that seemingly link these two areas together. However, little evidence has been found to describe direct links between a loss of neurogenesis and the occurrence of neurodegenerative conditions<sup>124</sup>. Indeed, cognitive dysfunction observed during AD is largely attributed to cellular dysfunction resulting from atrophy and a selective loss of hippocampal neurons. Without a direct implication for neurogenesis in disease etiology,

models of AD have so far typically evaluated neuronal dysfunction occurring after AD lesion formation and occasionally in relation to responses in neurogenesis.

### **Alzheimer's pathology: APP and A $\beta$ peptide**

The main lesions in the AD brain consist of pathological accumulations of amyloid  $\beta$  peptide (A $\beta$ ) and hyperphosphorylated tau proteins. However, the relationship between these lesions and cognitive dysfunction is poorly correlated. Genetic identification of three genes associated with Alzheimer pathology has provided insight into the molecular and cellular mechanisms underlying AD. Mutations in these genes are fully penetrant and result in AD. They have been described as both genetically complex and heterogeneous[72]. These mutations can be found on genes encoding the amyloid  $\beta$  protein precursor (APP), presenilin-1 protein (PSEN1) and the presenilin-2 protein (PSEN2) and are fundamental to both familial and sporadically acquired forms [73]. The role of A $\beta$  as an initiator of disease pathogenesis in early-onset AD has led to the formulation of the amyloid cascade hypothesis[74] (reviewed by Walsh and Selkoe[75]). The biological activity of the peptide is unknown but under normal physiological conditions, A $\beta$  is constitutively secreted by mammalian cells and is found in plasma and cerebrospinal fluid (CSF) [76, 77].

Soluble A $\beta$  oligomers are regarded as pathogenic molecules having been implicated in the physical degeneration of synapses [78]. *In vivo* experiments have established that oligomers cause a failure in long-term potentiation (LTP) of neurons in the hippocampus[79], indicating that oligomers and intraneuronal accumulations are responsible for synaptic failure[80]. A $\beta$  peptide is additionally truncated and can be chemically modified. Most recently evidence has been collected regarding N- truncated pyroglutamate (pE) A $\beta$ . Glutamate at the N-terminus of A $\beta$  can be cyclized by glutaminyl cyclase to yield pyroglutamate (pE) which is resistant to proteolysis and seeds aggregation. Inhibition of glutaminyl cyclase attenuates production of pE-modified A $\beta$  and is being evaluated as a therapeutic target[81].

Recent evidence regarding A $\beta$  plaques have shown that microglia rapidly respond to accumulated A $\beta$ , migrating to the site of deposition and extending processes to the lesion[82]. This fast response however does not correspond to plaque clearance; plaques remain in the parenchymal space despite these microglial responses. Plaques

occur as four histologically distinguishable subtypes including remnant plaques described as ragged with intense astrocytic participation[83]. The relationship between astrocytes and plaque pathology is not well understood. It has been previously demonstrated that cultured astrocytes bind and degrade  $A\beta_{1-42}$ [84]; N-terminal truncation of  $A\beta$  in human astrocytes indicates active *in vivo* degradation[85, 86]. Diffuse remnant plaques are more common in non-demented subjects and are not well correlated with Alzheimer disease.

Mature astrocytes can degrade  $A\beta$  plaques but the mechanisms responsible for gliosis in the brain and the astrocyte responses to plaques, be it astrogenic or not, are not well delineated. Gliosis, characterized by GFAP expression in mature astrocytes increases with oxidative stress and aging in humans and rodents[87]. Although some astrocyte-secreted factors are known that can affect progenitor proliferation, it is not known whether gliosis *in vivo* has a detrimental effect on neurogenesis in the SGZ that has been shown to decrease significantly with age[47].

### **Alzheimer's pathology: Tau**

Tau accumulations are required for positive post mortem diagnosis of AD. In contrast to amyloid plaques, neurofibrillary tangles (NFTs) have a substantial correlation with disease severity. Tau promotes the assembly of tubulin, a function governed by protein phosphorylation, and maintains structure in most cell types including neurons. In AD brain, accumulations of abnormally hyper-phosphorylated tau is observed at serine and threonine epitopes. Hyper-phosphorylated tau is a subunit in paired helical filament (PHF) and NFTs [88]. Pathologically active phospho-tau does not bind tubulin but instead sequesters normal tau in addition to other MAPs which interrupts assembly and disassembly of normal microtubules [89, 90]. Tau is not only of interest for AD, but also for neurogenesis as it is involved in cellular plasticity during e.g. neuronal migration, cell division and growth[91, 92].

Tau protein is alternatively spliced to 6 different tau variants with either 3 (Tau-3R) or 4 (Tau-4R) microtubule binding repeats. Tau-4R has a higher binding affinity for microtubules and a developmental switch has been described for the change from Tau-3R to Tau-4R. Using a knockout-knockin approach, it was shown that expression of 4R reduces cell proliferation and increases differentiation and neuronal

maturation[92]. Additional work with models of Alzheimer's disease has provided some evidence that tau pathology follows accumulations of intraneuronal A $\beta$ . Evaluations with the triple transgenic model have shown that amyloid pathology precedes tau pathology[93]. However the neuropathological hallmarks of AD are generally insufficient markers of early pathological mechanisms and serve poorly as clinical correlates of cognitive function and outcome. Accumulated research indicates that multiple components are necessary to establish clinical manifestations of AD and dementia identifying AD as a multi-factorial disease.

### **Alzheimer pathology: cell cycle re-entry and apoptosis**

Outside identified neurogenic regions of the brain, aberrant expression of cell cycle proteins has been identified in neurons that are highly correlated with tau pathology. This is unusual as postmitotic neurons do not enter the cell-cycle and are arrested in G<sub>0</sub>; molecular regulation in post-mitotic mature neurons are unique from other tissue-specific cell types because they constantly regulate cell-cycle [94]. Nuclear localization of cyclin dependent kinase 5 (cdk5) has been identified in quiescent neurons where it is thought to act as a cell cycle repressor[95]. Interestingly, overexpression of p25 *in vivo* demonstrates that activation of cdk5 may be responsible for tau hyperphosphorylation and aggregation[96]. The dynamics of cell-cycle regulation are of specific interest because alterations in expression of cell-cycle proteins have been identified in the brains of AD patients (reviewed by Lee)[97]. It has been suggested that expression of cell cycle proteins in AD brain tissue may indicate the pathological changes not directly associated with A $\beta$ . Indeed a recent mouse model with aberrant inducible expression of MYC resulted in loss of CA1 neurons, providing evidence that induction of cell cycle proteins in mature neurons can result in apoptosis and cell loss [98].

Apoptosis was originally suspected to contribute to the volume loss in the AD hippocampus and other brain regions. Indeed, initial studies reported extensive presence of e.g. DNA fragmentation or apoptosis specific markers in neurons in the AD hippocampus and cortex[99-101]. More recent papers suggest than at least in animal models, apoptosis is a prominent mode of cell death in e.g. aging PS/APP mice[102, 103] however these results are difficult to compare to, or confirm in human brain.

Aside from the fact that additional and different modes of cell death have been identified more recently, apoptotic cell death remains a very fast process that can be completed within hours. As such, in terms of methodology, "trapping" a cell while undergoing apoptosis is extremely difficult to do in thin tissue sections from human postmortem brains that have experienced prolonged disease duration[104, 105].

### **Human postmortem tissue studies**

While seemingly conflicting reports have been published regarding neurogenesis in AD, each study provides a snapshot into the complexity encountered in identifying changes in neurogenesis in postmortem tissue. Conflicting reports, utilizing different patient cohorts used markers of immature neurons, including DCX, to identify neurogenesis in tissue from AD and control patients. A biochemical study of aged AD and control patients described higher expression of DCX and PSA-NCAM expression in the disease cohort [106]. However, histological examination in a younger cohort of pre-senile AD cases revealed that proliferative changes were increased in the hippocampus but were associated with glia and vasculature, and not with regions where neurogenesis was to be expected[107]. In the later study, expression of DCX could only be identified in approximately 20% of all cases evaluated and did not show any relevant connection with stage of disease. A third study has found dramatically decreased expression of MAP proteins in the DG indicating that increased neuroproliferation during AD does not produce new neurons, a finding providing some resolution of the prior conflicting reports[108].

### **Measuring AD and neurogenesis *in vivo***

Ultimately, temporal associations between disease states and neurogenesis may provide insight regarding the contribution or risk associated with reduced or depleted neurogenesis. Data directly obtained in human subjects is ideal since postmortem human and non-human primate studies have identified distinct differences in neurogenesis. In parallel, a concerted effort is also underway to identify biomarkers and imaging techniques to identify those at risk of developing Alzheimer's disease. These facts highlight the utility of direct *in vivo* measurements in humans[109]. Recent experimental evidence describes the use of a novel imaging technique for identifying human NPCs in live human subjects. Although some discussion exists

concerning the methodology[110], proton nuclear magnetic resonance spectroscopy ( $^1\text{H}$ -MRS) was reported to identify the 1.28-ppm biomarker as being selective for newborn and proliferating precursors *in vitro* and rodent brain preparations[111]. Subsequent analysis of this MRS biomarker in live human subjects revealed substantial numbers of newborn cells in the live human hippocampus but not the cortex, as had been found before in postmortem tissue samples[112], while confirming a clear reduction with age, similar to published rodent literature[47, 113]. Determining the relationship between deposition of  $\text{A}\beta$  and disease has been greatly aided by advances in imaging and biomarkers. Identification of Pittsburgh Compound B[114] and ongoing investigations into surrogate biomarkers are of relevance for early identification of AD and in parallel will provide improved correlations between pathology and dementia. The relevance of plaques in disease continues to evolve as more information is collected, including cellular responses to their accumulations.

## **Mouse models of Alzheimer's disease**

### **Introduction**

Mouse models of AD serve a critical function in our understanding of genotype-phenotype interactions and also allow therapeutic strategies to be tested. Transgenic AD models have primarily focused on measures of efficacy associated with disease markers or behavior modification. Neurogenesis has so far been evaluated only to a limited extent in mouse models of AD; further characterization of these models and more importantly, new model development, is needed.

In the following paragraphs we will review work conducted with Alzheimer's mouse models and the special circumstances of each one. As promoter, transgene, and age at which the mice are evaluated are critical to interpretation of the results, a brief description of each study is followed by critical information relevant to the results. For an overview of the studies conducted on neurogenesis in AD mouse models the table presented offers a quick reference for testing already completed.

### **Presenilin 1 transgenics**

Interest in  $\gamma$ -secretase and the generation of highly fibrillogenic  $\text{A}\beta_{42}$  has led to the development of presenilin-1 (PS1) transgenic mice

expressing mutant PS1. PS1 is part of the  $\gamma$ -secretase complex but this pleiotropic gene also participates in mechanisms regulating cellular proliferation. Although PS1 is a key regulator in Notch and Wnt signaling mechanisms, there is no direct evidence demonstrating that familial PS1 can influence proliferation or survival of NPCs in humans. PS1 signaling is responsible for developmental maturation of glia and neurons (reviewed by Gaiano and Fishell)[115]. In Wnt signaling PS1 is directly involved with  $\beta$ -catenin turnover, a mechanism responsible for proliferation of progenitor cells in the developing brain[116]. Normal PS1 facilitates phosphorylation of  $\beta$ -catenin leading to proteosomal degradation; mutant PS1 cells have increased stability of  $\beta$ -catenin leading to downstream nuclear signaling events. It is therefore not surprising that neuronal expression of mutant PS1 with a Thy1 promoter increased proliferation in the DG of 4-month old transgenic mice[117]. Increased cell proliferation did not result in increased neuron survival in the hippocampus of these mice.

Table 1 provides a direct comparison of the studies that have utilized PS1 models. PS1/PS2 KO mice were evaluated at two ages and found to have increased proliferation and survival[118]. A study of PS1 expressed under the NSE promoter found that proliferation was reduced by both wild-type and mutant PS1. Interestingly, the wild-type PS1 mice had increased survival of immature neurons while the mutants did not[119]. A follow-up to this study incorporated groups with environmental enrichment - expression of the wild-type protein was sufficient to increase survival of immature neurons expressing Tuj1. Enrichment in these mice increased proliferation and survival compared to the non-enriched group. This normal physiology was not preserved in mice expressing mutant PS1; enrichment increased proliferation however there were no changes in Tuj1 expression and less surviving BrdU+ cells[120]. A more sensitive experiment was produced by crossing mutant PS1 knock-in mutants with PS1 knockouts. Investigators generated mice with one mutant copy of PS1. Expression of mutant PS1 resulted in impaired learning in a contextual fear conditioning test. This impaired associative learning was positively correlated with impaired neurogenesis[121]. The investigators, through comparison with the parental knock-in line, concluded that expression of wild-type PS1 can override the mutant PS1 gene.

Continued research with PS1 mutants is justified since the expression of human transgenes does impact neurogenesis. It is difficult

however to assess whether behavioral changes are due to increased neurogenesis or expression of the transgene making direct cause-effect relationship between neurogenesis and learning difficult. Electrophysiological analysis can eliminate the possibility of changes in synapse function. Evaluating the collective nature of Alzheimer's mutation can also be done through double knock-in experiments that utilize PS1 and APP[122].

### **Amyloid Precursor Protein transgenics**

Transgenic models of Alzheimer's further include mice expressing mutant APP; typically bigenic mice are generated expressing mutant PS1 and human APP as murine APP does not generate fibrillogenic peptides. As reviewed recently, most APP and APP/PS1 mouse models show reductions in cell proliferation[123]. Limited information is present concerning the subsequent survival of the newborn cells. Table 2 provides a list of studies completed with APP models but does not provide a comprehensive inventory of all studies completed to date. While the data is quite variable, some consensus has been achieved. A study evaluating APP and APP-PS1 mice showed that APP mice had no difference in hippocampal neurogenesis when evaluated by BrdU incorporation. At this age the mice do not have amyloid deposits, however, when the mice were evaluated at 25-months of age, APP mice exhibited significant increases in the number of BrdU and DCX positive cells[124]. A separate study utilizing different APP-PS1 mice at 8-months of age showed increased BrdU and NeuN positive cells compared to controls despite finding that APP-PS1x NestinGFP mice exhibited decreases in nonproliferative Nestin positive NPCs[125]. From these results it is arguable that endogenous neurogenesis is elevated in response to pathology, however the molecular mechanisms establishing this response have yet to be elucidated. Furthermore the functionality of these new neurons has not been assessed; however these models certainly provide the framework for such experimentation.

The relationship between  $A\beta$  and neurogenesis has also been combined in interventional studies: environmental enrichment or running was expected to lead to improvements in behavior associated with reductions in  $A\beta$  plaque load and possibly increases in neurogenesis. As expected, mice provided with environmental enrichment had increases in newborn cell proliferation and survival.

These changes also corresponded to improved performance in a spatial memory task, but surprisingly, there was no change in plaque load. The results indicate that despite plaque burden, the neurogenetic environment is preserved allowing for functional recovery[126]. Curiously this recovery dissociates structural from functional pathology.

### **Tau transgenics**

So far, a few mouse models of tauopathy have also been evaluated. Here we see again that different models result in different, sometimes surprising, albeit not completely conflicting data sets<sup>84, 87, 106, 108, 109</sup>. A model utilizing human tau with two mutations, describes induction of hyperphosphorylation and NFTs in 3 to 6 month-old animals in the hippocampus. Cell bodies of the DG are spared at this young age but neuritis in these areas are immunopositive for AT8, indicating aberrant phosphorylation of tau, similar to what is found in AD. Compared to non-Tg mice, transgenic tau mice had two-fold higher DCX levels and significantly higher expression of TUC-4 in the DG through 6 months[127]. Mice with non-mutant human tau also show signs of proliferation, however this proliferation was identified outside the SGZ and SVZ[128]. Using a knockout-knockin approach, it was further shown that expression of 4R tau reduces cell proliferation and increases differentiation and neuronal maturation, confirming an important role for tau in neuronal plasticity and differentiation[92]. Also, in young mice carrying the tau-P301L mutation that is associated with frontotemporal lobe dementia, increased long-term potentiation in the dentate gyrus (LTP) was observed parallel to improved cognitive performance. As neither tau phosphorylation, motor deficits or neurogenesis could account for these changes, this demonstrated that protein tau plays an important role in hippocampal memory, and that it is not the tau mutations per se, but rather the ensuing hyperphosphorylation that must be critical for cognitive decline in tauopathies like FTD and AD<sup>87</sup>.

### **Other models of acute and chronic neuropathology**

As mouse models do not always provide a full spectrum of relevant pathology, parallels to other models of neurodegeneration can assist the Alzheimer field. These findings are also mixed; increased neurogenesis is observed during ischemia[129] and trauma[130],

however functional recovery after the events due to responses in neurogenesis have not been clearly demonstrated. Additionally, these acute traumatic events have been described previously but have not provided the molecular mechanisms responsible for proliferation in neurodegenerative conditions. In models for other human neurodegenerative diseases like Parkinson's disease, neurogenesis doubled after lesioning when measured by incorporation of BrdU[131], however other investigators have explained this as a glial response[132]. Transplantation of dopaminergic neurons and stem cells has been evaluated for treatment of Parkinson's disease and the literature reflects the difficulty in successfully transplanting cells to the substantia nigra (reviewed by Deierborg et al.)[133].

While transplanted cells can survive and reverse some behavioral symptoms, the mechanisms underlying the observed benefit are unclear and there is little evidence for neuronal replacement. In most cases only a few grafted cells survive and these neurons do not show the same phenotype as the cells they are replacing in the lesion. Moreover, the functionality of these cells is unknown, afferent and efferent connections have not been established for grafted cells while also tumor formation may occur.

In stroke models, endogenous production of NSCs has been observed which is of interest for understanding the effects of stem cell or neurogenetic therapies. New neurons migrating to the site of the lesion differentiate to the appropriate phenotype, however >80% of the neurons die in the weeks following the stroke. Thus, in the weeks following the ischemic lesion only a small fraction (~0.2%) of the neuronal population has actually been replaced. The results of these experiments have been followed up by selective lesion techniques that spare the architecture of the brain using targeted apoptotic degeneration[134]. The new neurons generated under these circumstances extend axons. This implies that self-repair mechanisms of neurogenesis are restricted to the proper structure responsible for migration and survival of the new neurons.

## **Emerging areas**

### **Inflammation and the role of glia**

The AD brain is characterized by a pronounced inflammatory response and various inflammatory mediators like cytokines, complement factors and microglia cells are found to respond to amyloid

deposition. Evidence has been collected showing that reduction of proinflammatory mediators and/or microglia activation through pharmacologic treatment can restore or increase neurogenesis in different models of hippocampal insult including demyelization models of MS. Blocking inflammatory microglia has been shown to restore neurogenesis after LPS injection in adult rats[135]. So, while classically activated microglia impair neurogenesis, microglia associated with adaptive immunity have been identified as neuroprotective and participating in the regulation of neurogenesis. Environmental enrichment causes increases in CNS specific T-cells acting in concert with resident microglia contributing to progenitor cell proliferation and survival of neuroblasts[136]. Mice in enriched environment have more microglia expressing IB-4 and MHC-II proteins in the dentate gyrus. Mice with severe combined immune deficiency (SCID) housed in this enriched environment fail to show increases in proliferation or neuroblast survival, indicating impaired neurogenesis in these animals. Separate experiments confirmed that spatial learning and memory are dependent on the presence of autoimmune T cells and that brain-derived neurotrophic factor expression (BDNF) was increased, showing a positive correlation with neurogenesis and spatial learning and memory.

These findings are interesting because Alzheimer's disease is characterized by inflammation and activated microglia. A comparison of autoimmune T cells and cytokine activated microglia expressing MHC-II proteins in an Alzheimer population would provide insight regarding the status of neurogenesis during the disease state. Preventing inflammation associated with AD may create a more permissive environment that could preserve adult neurogenesis.

### **Transplantation**

Development and maturation of stem cells into functional cells of the CNS has also been explored through transplantation. Intrastratial transplantation of human fetal mesenchephalic tissue containing postmitotic dopaminergic neurons demonstrated that replacement of neurons can indeed be therapeutic[137, 138]. Grafted neurons normalized striatal dopamine release and survived despite ongoing disease destroying the endogenous population. These results highlight the exceptional potential for stem cell based therapies. Yet, there are numerous hurdles that currently limit the ability to predict the outcome

of stem cell transplantation and it is outside the scope of this report to identify the sources and potential design of stem cells transplantation studies. However, evaluating the fundamental biology of stem cells is of critical importance for attempts to replace mature cells, either by transplantation or recruitment of endogenous pools.

### **Models of disease and neurogenesis**

Further characterization of the neurogenic micro-environment is necessary to fully understand the dynamics of the niche during aging and pathological conditions. Signaling and activity within the hippocampus are responsible for maintenance and development of granule neurons occurring only under the conditions found in the neurogenic niche. Failing functionality of this micro-environment precludes incorporation of new functional neurons. Additionally, while the function of new neurons and regulation is still poorly understood, disruptions in neurogenesis have functional consequences such as observable behavioral changes. Specific activity-dependent signaling mechanisms are of interest within this context[139, 140].

While neurogenesis can indeed increase after lesioning of the brain during acute trauma or stroke, Alzheimer disease presents a distinct problem where chronic long-term mechanisms deplete the hippocampus of activity and neurons. Given this paradigm, a proper understanding of the neurogenetic environment, including the cells interacting with NSCs, is absolutely necessary for increasing the number of functional neurons. Mouse models of AD provide an opportunity to characterize these dynamics. While preliminary studies have been completed, these models provide the foundation for more advanced study of adult neurogenesis. With continued work in this field, the essential hope for better Alzheimer's therapies will be realized.

**Table 1:** PS1, a pleiotropic gene involved with Notch and APP processing, has been evaluated through transgenic mice for the effect on adult neurogenesis. The data suggests that proliferation of NPCs can be induced when mutant PS1 is expressed by Thy1 and NSE promoters. Interestingly, increased survival of neurons has been observed in this model through different manipulations.

**Table 2:** PS1xAPP mutants provide a platform for evaluating the relationship between neurogenesis and pathology. Thus far investigators have focused on proliferative changes and survival of new neurons during aging in these animals. Attempts to restore or modify neurogenesis for therapy will need to address the special conditions found in these models.

		Hippocampal Neurogenesis				
promoter	mouse line/ conditions	mutation(s)	Neural Precursors	Neurogenesis		citation
			proliferation (BrdU+)	survival (BrdU+marker+)	age	
Thy1	C57Bl/6J x B6SJL/F1	PS1 A246E	increased	no change	3 months	Chevalier et al.
na	B6/CBA	PS1/PS2-KO	increased	increased (NeuN, GFAP)	7-9 months 18-20 months	Chen et al.
na	B6/CBA	PS1/PS2-KO	increased	increased (NeuN, GFAP)		Chen et al.
NSE	C57Bl/6J	PS1 (h)Wild-type	decreased	increased (TOAD-64, $\beta$ -tubulin III)	2 months	Wen et al.
NSE	C57Bl/6J	PS1 P117L	decreased	no change	2 months	Wen et al.
na	C57Bl/6J		control	control	2 months	Wen et al.
na	C57Bl/6J enrichment		increased (vs control)	no change	2 months	Wen et al.
NSE	C57Bl/6J	PS1 (h)Wild-type	no change	increased ( $\beta$ -tubulin III vs control)	2 months	Wen et al.
NSE	C57Bl/6J enrichment	PS1 (h)Wild-type	increased (vs no enrichment)	increased ( $\beta$ -tubulin III vs non-enriched)	2 months	Wen et al.
NSE	C57Bl/6J	PS1 P117L	no change	no change (decreased BrdU survival)	2 months	Wen et al.
NSE	C57Bl/6J enrichment	PS1 P117L	increased (vs no enrichment)	no change (decreased BrdU survival)	2 months	Wen et al.
na	129Sv/C57Bl6		control	not measured	3 months	Wang et al.
na	129Sv/C57Bl6	PS1 M146V/-	decreased (NeuN)	not measured	3 months	Wang et al.
na	CD-1	PS1 P264L KI	not measured	small decrease (DCX)	8-9 months	Zhang et al.
na	CD-1	APP KM670/671NL KI	not measured	no change	8-9 months	Zhang et al.
na	CD-1	APP/PS1 double KI	not measured	decreased (DCX)	8-9 months	Zhang et al.

		Hippocampal Neurogenesis			
promoter	mouse line/ conditions	mutations(s)	Neural Precursors	proliferation (BrdU+)	survival (BrdU+ <i>marker</i> +) age citation
Thy1	Female C57Bl/6J	APP23 Swedish KM670/671NL		increased	increased (DCX) 25 months Ermimi et al.
Thy1	C57Bl/6J	APP23 Swedish KM670/671NL -PS1 L166P		no change	no change, decreased (DCX) 8 months Ermimi et al.
PDGF	C57BL/6 × DBA/2	APPSw <sub>Ind</sub> (K670N/M671L and V717F)		increased	increased (β-tubulin III) 3 month/5 month Lopez-Toledano et al.
PDGF	C57BL/6 × DBA/2	APPSw <sub>Ind</sub> (K670N/M671L and V717F)		decreased	3 month/5 month Lopez-Toledano et al.
Nestin/PD GF	C57BL/6 × DBA/2	LacZ/ APPSw <sub>Ind</sub> (K670N/M671L and V717F)	slight increase (lacZ)	no change	no change 2 months Gan et al.
Nestin/PD GF	C57BL/6 × DBA/2	LacZ/ APPSw <sub>Ind</sub> (K670N/M671L and V717F)	decreased (lacZ)	increased	increased (NeuN) 8 months Gan et al.
Nestin/PD GF	C57BL/6 × DBA/2	LacZ/ APPSw <sub>Ind</sub> (K670N/M671L and V717F)	decreased (lacZ)	decreased	increased (NeuN) 12 months Gan et al.
PDGF	C57BL/6J	APPSw <sub>Ind</sub> (K670N/M671L and V717F)		increased	increased (DCX) 3 months Jin et al.
PDGF	C57BL/6J	APPSw <sub>Ind</sub> (K670N/M671L and V717F)		increased	increased (DCX) 12 months Jin et al.
hamster PrP	C57B6/SJL	Tg2576 APPSwe K670N/M671L		decreased	not measured 3 months Dong et al.
hamster PrP	C57B6/SJL	Tg2576 APPSwe K670N/M671L		decreased	not measured 6 months Dong et al.
hamster PrP	C57B6/SJL	Tg2576 APPSwe K670N/M671L		decreased	not measured 9 months Dong et al.

murine P-P	C3H/HeJ × C57BL/6J hybrids	APP <sup>Swe</sup> K670N/M671L	no change	no change	3 months	Haughey et al.
murine P-P	C3H/HeJ × C57BL/6J hybrids	APP <sup>Swe</sup> K670N/M671L	decreased	decreased (BrdU)	12-14 months	Haughey et al.
Thy1	B6D2	APP23 K670N/M671L	not measured	no change	4 months	Bondolfi et al.
Thy1	B6D2	APP23 K670N/M671L	not measured	increased (S100B, CD11b)	24 months	Bondolfi et al.
Thy1.2	Female C57B/6 - control	APP23 670/671KM3NL	control	control	15 months	Wolf et al.
Thy1.2	Female C57B/6 - long term exercise	APP23 670/671KM3NL	not measured	no change (BrdU)	15 months	Wolf et al.
Thy1.2	Female C57B/6 - long term enrichment	APP23 670/671KM3NL	not measured	no change (BrdU) increased (Calretinin)	15 months	Wolf et al.
Thy1.2	129/C57B6	APP695 KM670/671NL, P301L, PS1 M146L	**decreased(HH) 3) female only	not measured	4 months	Rodriguez et al.
Thy1.2	129/C57B6	APP695 KM670/671NL, P301L, PS1 M146L	decreased(HH3)	not measured	9 months	Rodriguez et al.
Thy1.2	129/C57B6	APP695 KM670/671NL, P301L, PS1 M146L	decreased(HH3)	not measured	12 months	Rodriguez et al.

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