Molecular Mechanism of Adult Neurogenesis and its Association with Human Brain Diseases

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ABSTRACT: Recent advances in neuroscience challenge the old dogma that neurogenesis occurs only during embryonic development. Mounting evidence suggests that functional neurogenesis occurs throughout adulthood. This review article discusses molecular factors that affect adult neurogenesis, including morphogens, growth factors, neurotransmitters, transcription factors, and epigenetic factors. Furthermore, we summarize and compare current evidence of associations between adult neurogenesis and human brain diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and brain tumors.

KEYWORDS: adult neurogenesis, molecular factors, human brain diseases

CITATION: Liu and Song. Molecular Mechanism of Adult Neurogenesis and its Association with Human Brain Diseases. *Journal of Central Nervous System Disease* 2016:8 5–11 doi: 10.4137/JCNSD.S32204.

TYPE: Review

RECEIVED: August 27, 2015. **RESUBMITTED:** April 07, 2016. **ACCEPTED FOR PUBLICATION:** May 30, 2016.

ACADEMIC EDITOR: Alexander Rotenburg, Editor in Chief

PEER REVIEW: Five peer reviewers contributed to the peer review report. Reviewers' reports totaled 1,826 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

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Introduction

According to traditional belief, mammals do not produce new neurons from precursors (neurogenesis) into adulthood. In 1965, Altman and Das published groundbreaking anatomical evidence indicating the existence of adult neurogenesis in rats.[1] Since then, the research field of adult neurogenesis has exploded. It is now widely accepted that neurogenesis occurs in limited regions such as the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricle/striatum in adult humans and rodents.[2–5] These adult-born neurons function and integrate into the rest of the brain circuit.[6] Furthermore, the number of newborn neurons has been qualified and demonstrated to be significant.[7] The physiological functions of adult neurogenesis include learning, emotions, and memory such as pattern separation, temporal separation, high-resolution memory, fear conditioning, and synaptic plasticity.[8,9] Abnormal adult neurogenesis has also been linked to diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), demyelinating disease, stroke, epilepsy, and depression.[8,10] This review article discusses the molecular factors that affect adult neurogenesis and current evidence of associations between adult neurogenesis and human brain diseases.

Molecular Mechanisms of Adult Neurogenesis

Adult neurogenesis generally includes the following four key stages:

1. Maintenance and proliferation of quiescent adult neural stem cells (NSCs).
2. Fate specification.
3. Differentiation, maturation, and survival of the immature neurons.
4. Integration into the existing brain circuit.

Here, the quiescent NSCs are slow-growing, multipotent cells with unlimited self-renewal. After NSCs become activated, they divide asymmetrically and produce transit amplifying cells (TACs) in the SVZ and transient intermediate progenitors (TIPs) in the SGZ. The TACs and TIPs are rapidly dividing cells with the potential to differentiate into neurons with limited ability for self-renewal. After a limited number of cell divisions, the TACs and TIPs give rise to the neuroblasts. The proliferating neuroblasts then exit the cell cycle, and a subpopulation survives and differentiates into newborn neurons that will then be integrated into the neuronal network in the brain (Fig. 1).[11–13] Various molecular players were found to regulate specific stages of adult neurogenesis in mammals. In this section, we focus on five groups of molecular players that play critical roles in adult neurogenesis: morphogens, growth factors, neurotransmitters, transcription factors, and epigenetic factors.

Morphogens. Morphogens are extracellular signaling molecules well known for their roles in embryonic patterning and axis formation during development.[14] In adult neurogenesis, a number of morphogens were found to be critical

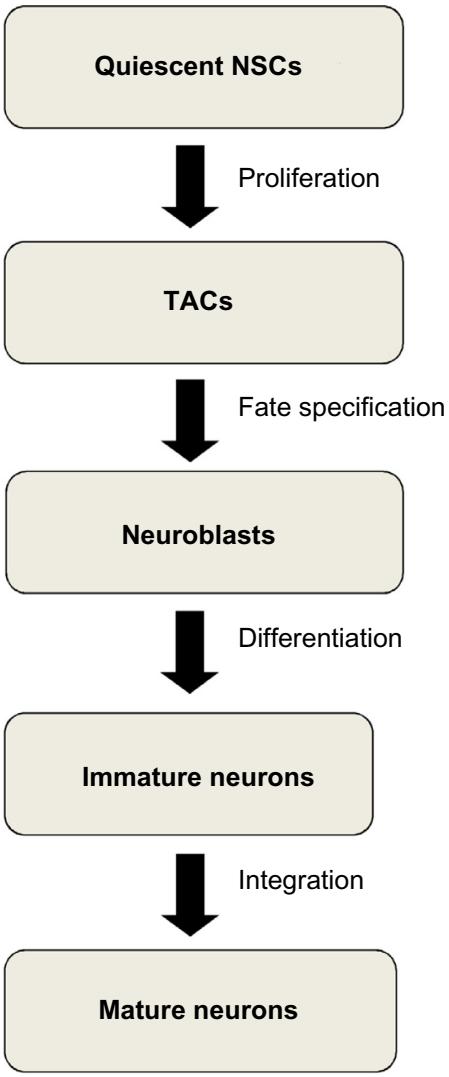

Figure 1. Key stages of adult neurogenesis. The quiescent neural stem cells (NSCs) start to proliferate to generate the transit amplifying cells (TACs). The TACs undergo fate specification and give rise to the neuroblasts. The neuroblasts differentiate into immature neurons. The immature neurons migrate and get integrated into the brain circuit to become fully mature neurons.

in establishing/regulating the stem cell niche, including Notch, sonic hedgehog (Shh), Wnts, and bone morphogenetic proteins (BMPs).

Notch signaling has been reported to regulate NSC maintenance, neurogenic niche, and newborn neuron survival and maturation in postnatal life. Inducible Notch1 loss-of-function mice had increased progenitors exiting the cell cycle, while the mice overexpressing the intracellular portion of the Notch receptor (Notch intracellular domain) had decreased progenitors exiting the cell cycle in the adult hippocampus.[15] Inactivation of the Notch ligand Jagged1 during adult SGZ neurogenesis resulted in defective neural stem cell maintenance and proliferation in mice.[16] Deletions of RBPj (recombination signal binding protein for immunoglobulin kappa J region), a downstream mediator of all Notch receptors, resulted in loss of neurogenesis accompanied by depletion of neural precursors in both SVZ and SGZ.[17,18] In the lateral ventricular walls of adult mouse brain, Notch via its downstream target EphB2 was implicated in maintaining the identity and plasticity of neurogenic niche cells.[19] Notch signaling is also implicated in the later stages of neurogenesis such as dendrite morphology[15] and synaptic plasticity[20] in newborn neurons.

Wnt/β-catenin signaling uses both paracrine and autocrine canonical mechanisms and regulates adult hippocampal neurogenesis *in vitro* and *in vivo*.[21–23] Their actions span multiple steps of neurogenesis, including maintaining multipotency of neural stem cells, enhancing neuroblast proliferation, and promoting neuronal fate specification.[24,25] Most importantly, their actions on these biological processes are linked to the functions of the adult hippocampus. Blocking Wnt signaling in the DG impaired spatial and object recognition memory in adult rats.[26]

BMPs are necessary for maintaining the quiescence of NSCs through BMPR-IA[27] in the adult DG as well as the differentiation and maturation of granule cells through BMPR-II.[28]

Growth factors. Growth factors are extracellular peptides that function as stimulants during tissue growth and development.[29] Lines of evidence support the critical roles for adult neurogenesis of the following growth factors: brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and fibroblast growth factor 2 (FGF-2).

BDNF overexpression via various methods resulted in increased neurogenesis in adult DG[30] and SVZ.[31,32] Conditional loss of TrkB, the membrane receptor of BDNF, resulted in decreased proliferation of NSCs and impaired neurogenesis in adult DG.[33] Moreover, BDNF/TrkB signaling is required for survival, dendritic arborization, and integration of newborn neurons in the adult DG.[34] Research demonstrates that an enriched environment enhances neurogenesis in the adult hippocampus. Interestingly, this enhancement was not observed in BDNF heterozygous knockout mice.[35]

IGF-1 regulates various processes during adult neurogenesis including progenitor cell proliferation, neuronal differentiation, and maturation.[36–40] Peripheral infusion of IGF1 increased progenitor cell proliferation and increased production of new neurons in the adult rat hippocampus.[40] IGF-1 overexpression in NSCs in transgenic mice increased NSC proliferation in the SGZ and SVZ via MEK/ERK pathway, and at the same time it induced differentiation of NSCs via the PI3K/Akt pathway.[36] Blocking IGF-1 using antibodies in adult NSC cultures inhibited differentiation into neurons.[38] Interestingly, an *in vitro* study showed that the diverse actions of IGF-1 could be dosage dependent. At high dose (100 ng/mL), it increased adult rat hippocampal progenitor cell proliferation and decreased differentiation, while at low dose (1 ng/mL), it stimulated differentiation.[39] The expression of endogenous IGF-1 in the adult hippocampus naturally decreases with age and the rate of neurogenesis.

Research demonstrates that restoration of IGF-1 levels by intracerebroventricular infusion increased the rate of neurogenesis by approximately threefold. This suggests that changes in endogenous IGF-1 levels may underline age-related decline of neurogenesis.[37] A recent study identified another IGF – IGF2 – as a novel adult neurogenesis regulator. Transcriptome analysis showed that IGF2 was expressed in the DG NSCs at a significantly higher level than in immature neurons in adult mice, and it governs NSC proliferation *in vitro* and *in vivo* via AKT-dependent pathway.[41]

Conditional overexpression of an activated FGF receptor in adult neural precursor cells increased the production of new neurons, whereas conditional deletion of the FGF receptors in these cells decreased NSCs, progenitor cells, and immature neurons in mice. Interestingly, overexpression of the activated FGF receptor in older mice was able to restore the age-related decline in neurogenesis.[42] Similarly, intracerebroventricular FGF-2 infusion increased production of new dentate granule cells and their dendritic growth in the hippocampus in middle-aged rats.[43]

Neurotransmitters. A number of neurotransmitters are involved in adult neurogenesis including gamma-aminobutyric acid (GABA), dopamine, glutamate, and serotonin.[44]

GABA, an inhibitory neurotransmitter, was shown to be a critical niche signal regulating activation and proliferation of quiescent adult NSCs, granule cell maturation, and migration. It is secreted from neuroblasts, and its receptor $GABA_A$ ion channel is present on NSCs and their progeny. The neuroblast-derived GABA inhibits NSC proliferation, forming a negative-feedback mechanism in maintaining neurogenesis homeostasis.[45,46] Similarly, GABA derived from local parvalbumin-expressing interneurons in the DG restored quiescence of NSCs following proproliferative neuronal activities such as social isolation.[47] $GABA_A$ receptor loss-of-function caused NSCs to rapidly exit from quiescence and start symmetrical self-renewal.[47] In the anterior SVZ, GABA was also released from astrocyte-like cells, which surround the migrating neuroblasts. Here, it slowed down neuroblast migration en route to the olfactory bulb (OB) through the same receptor.[48]

Transcription factors. A number of transcription factors including sex-determining region Y-box 2 (Sox2), Orphan nuclear receptor TLX, forkhead box O proteins (FoxOs), prospero homeobox 1 (Prox1), neuronal differentiation (NeuroD), Kruppel-like factor 9, paired box protein (Pax6), and neurogenin 2 (Neurog2) were found to regulate adult neurogenesis.[44]

TLX is required for NSCs to self-renew and maintain undifferentiated state in both adult SVZ[49] and hippocampus[50] through the canonical Wnt pathway.[51] Furthermore, deletion of TLX resulted in impaired spatial learning in adult mice.[52]

Sox2 regulates different stages of adult neurogenesis including precursor cell proliferation, neuronal maturation, and migration. Sox2 null mutant mice had impaired precursor cell proliferation with a decreased production of new neurons.[53] Sox2 *knockdown* mutant mice had impaired neuronal maturation, abnormal morphology and migration, and diseased number of GABAergic neurons.[54]

Epigenetic factors. Epigenetic factors are molecules that modify gene expression via mechanisms such as DNA methylation and histone modification. Those modifications are heritable but do not involve DNA mutations and are therefore termed *epigenetic*.[53] Various epigenetic factors were reported to regulate adult neurogenesis including methyl-CpG-binding domain protein 1 (Mbd1), MYST family histone acetyltransferase Querkopf (Qkf), mixed-lineage leukemia 1 (Mll1), polycomb complex protein (Bmi-1), histone deacetylase 2 (HDAC2), and microRNAs (miR124, 137, 184, 185, and 491-3p).[44,55–57]

Mbd1 is critical for adult hippocampal neurogenesis and spatial learning by inhibiting proliferation and promoting differentiation.[58–60] Mbd1 functions through at least two arms. It directly binds to the FGF-2 promoter and induces its methylation. As a result, the mitogen FGF-2 expression was downregulated allowing for differentiation to occur.[60] The second arm involves the downregulation of miR-184 by Mbd1. miR-184 is a microRNA that promotes proliferation and inhibits differentiation by inhibiting the expression of Numb1 (Numblike 1, a regulator of brain development). When miR-184 is downregulated by Mbd1, it results in inhibition of proliferation.[59]

Qkf is a MYST family histone acetyltransferase expressed in the SVZ of the adult brain. The Qkf-deficient mice had reduced adult neurogenesis. The number of interneurons in the OB decreased, accompanied by a reduction in the number of NSCs and migrating neuroblasts in the rostral migratory stream. Furthermore, NSCs isolated from Qkf-deficient mice exhibited reduced both self-renewal and the ability to differentiate into neurons.[61]

Adult Neurogenesis in Brain Diseases

The association between adult neurogenesis and brain diseases is studied in both human and animal models. This section focuses on reports directly related to human, either by immunohistochemical labeling of neurogenic markers in postmortem brain tissues or by magnetic resonance imaging (MRI).

Alzheimer's disease. AD is characterized by widespread neurodegeneration throughout the basal forebrain, the cortex, and the limbic system. The hallmarks of AD include deposition of amyloid plaque and formation of neurofibrillary tangles.[62,63] Some studies have found reduction of neuronal progenitor proliferation with bromodeoxyuridine labeling in aging rats[64] and AD mouse models.[65,66] However, to date, studies on postmortem brain tissues of AD patients using immunohistochemical staining against neurogenic markers showed alternations in neurogenesis with inconsistent patterns. Elevated hippocampal expressions of neurogenic marker proteins, such as DCX, PSA-NCAM, TUC-4, and NeuroD, were found in particular in the granule cell layer of SGZ,[67] suggesting higher

level of neurogenesis in AD. In another study, both Nestin and PSA-NCAM showed significantly higher immunoreactivities in patients, and the increase correlated with the progression of the disease.[68,69] However, the neurogenic marker Musashi-1 (Msi1) immunoreactivities were significantly lower in the AD patients,[68,69] as well as choline-acetyltransferase, which is an indicator of a reduction of cholinergic activity.[68] Another study showed that neurogenic markers Sox 2 and DCX were downregulated accompanied by an increase in NSC quiescence regulator BMP6.[70] These discrepancies might be due to the differential expression of certain biomarkers but not others (for example, Msi1 vs. Nestin).[63] The differences reflect particular stages of AD progression or glial and vascular-associated changes independent of modulation of neurogenesis.[71,72] Furthermore, a recent study identified proliferating cell nuclear antigen (PCNA)-positive cells within the CA regions that lacked amyloid beta pathology. These cells were not colabeled with astrocyte maker glial fibrillary acidic protein (GFAP) but with Iba1, a microglial marker, in the CA regions as well as the DG and SGZ.[73] Iba1-positive cells often formed a concentric ring around amyloid plaques and were found in proximity of plaque pathology.[73]

In general, microglia are activated by brain damage to release cytokines such as toll-like receptors (TLR-2 and TLR-4), tumor necrosis factor α, and interleukin 1 beta.[74,75] These cytokines activate astrogliosis.[76,77] During AD progression, degradation of astrocytes and the migration and congregation of microglia within neuritic and dense-core plaques are commonly seen.[78] The proliferation of microglia is likely to be a critical step to initiate these changes.[79] In fact, the microglial activity could regulate neurogenesis in its own right.[79,80]

Parkinson's disease. PD is a progressive, chronic neurodegenerative disorder that is associated with the degeneration of dopaminergic neurons of the substantia nigra located in the midbrain. The pathological hallmarks of PD are accumulation of alpha-synuclein and intracellular deposits to form inclusion bodies called Lewy bodies and filamentary Lewy neurites.[81,82] PD affects the neuronal activities at various regions of the brain such as the amygdala, hippocampus, and OB.[83–85] With a limited number of studies using postmortem brain tissues of PD patients, the involvement of neurogenesis is largely unclear due to inconsistent results from different reports. In two studies, the number of cells expressing epidermal growth factor receptor (EGFR)[86] and PCNA[87] in the SVZ of PD patients significantly decreased compared with age-matched controls. However, another study with older patients and shorter postmortem time observed a higher variation in the number of NSCs at SVG. The number of cells expressing PCNA or the mitotic marker phosphohistone H3 did not show significant differences in patients with PD pathology, with or without dopamine replacement therapy, compared to age- and sex-matched controls.[88] In particular, hyposmia, a reduced ability to smell and to detect odors, is one of the most prevalent symptoms of PD.[89,90] Correspondingly, the total number of tyrosine hydroxylase-immunoreactive neurons in the OB was twice as high in the PD patients.[91,92] However, the number of neural precursor cells decreased,[87] with the OB volume unchanged in some studies[83,84] but reduced in others.[85,93,94] Similar to AD, recent evidence also indicates that the proliferating cells in the hippocampus of PD patients are predominantly microglia,[95,96] probably due to the neuroinflammatory response to developing PD pathology.

Huntington's disease. HD is a progressive neurodegenerative genetic disorder caused by autosomal-dominant mutations in the form of CAG repeats in the huntingtin gene located on chromosome 4.[97,98] Increased cell proliferation defined by expression of PCNA in SVZ was identified in postmortem brains of HD patients, and the proliferating cells were colabeled by a neuronal marker beta III-tubulin or GFAP, suggesting increased neurogenesis.[35] The degree of cell proliferation correlated with the disease severity and with the number of CAG repeats in the huntingtin gene.[99] The thickness of SVZ increased with a 2.6-fold increase in the number of new neurons in SVZ.[100,101] Some PCNA-positive cells also expressed cannabinoid CB1 receptors, which are preferentially lost in HD, but not with neuronal, glial, microglial, or oligodendrocyte markers, in SVZ of both adult normal and HD brains.[102]

Brain tumors. The multipotency and self-renewal ability of neural stem cells are very similar to brain tumor stem cells in human brain tumors. It is hypothesized and supported by accumulating research that NSCs within the SVZ transform give rise to brain tumors.[103] Glioblastoma multiforme (GBM), the most common and most aggressive malignant primary brain tumor in humans, has been the focus of many studies. A study showed that in 93% of cases of GBM, the lesions contacted at least one region of the lateral ventricular wall where adult neurogenesis occurs.[104] Multiple MRI analyses of GBM cases showed that the subtypes in contact with the SVZ and involving the cortex were most likely to be multifocal at the time of initial diagnosis.[105] These patients are also more likely to have recurrent tumors at locations distant to the initial lesion,[105] with more rapid progression,[106] and have decreased overall survival rate.[106,107]

Conclusion

Adult neurogenesis is regulated by both extracellular factors (morphogens, growth factors, and neurotransmitters) and intracellular factors (transcription factors and epigenetic factors). Their functions have been identified and related to specific stages of adult neurogenesis. As our understanding on the molecular mechanism of adult neurogenesis deepens, its association with a number of human diseases begins to emerge. Accumulating evidence has shown that adult neurogenesis is altered in various brain diseases such as AD, PD, HD, and brain tumors. However, the findings are highly variable and sometimes contradicting. This is most likely due to the use of

different approaches, different markers, or the examinations of different disease stages. More efforts with standardized methods and specific stages of the diseases are necessary to elucidate the associations between adult neurogenesis and these brain diseases.

Acknowledgment

We thank Katherine Hanna, Grace Liu Anderson, and Stephanie Blackstone (Registered Nurse and president of Treasures of the Heart Inc. 501(c)(3) charity) for proofreading the manuscript.

Author Contributions

Wrote the first draft of the manuscript: HL, NS. Contributed to the writing of the manuscript: HL, NS. Agree with manuscript results and conclusions: HL, NS. Jointly developed the structure and arguments for the paper: HL, NS. Made critical revisions and approved final version: HL, NS. Both authors reviewed and approved of the final manuscript.

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