Adult Neurogenesis: A Potential Target for Regenerative Medicine

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10.1 History of Adult Neurogenesis

> "In adult. . . , the nerve paths are something fixed and immutable: . . . nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree."—(Ramón y Cajal, 1913).

For long it was considered as an established fact in neuroscience that adult brain is incapable of creating new neurons (Koelliker 1896; Cajal 1899; Ramon y Cajal 1913; Leblond 1964). Technological limitations to accurately identify the "birthdates" of neurons helped to maintain this "central Dogma of neuroscience" (Gross 2000) for most part of twentieth century. It should be noted that the idea of neural plasticity, that is, the ability of the existing nerve cells to adapt to the changes in the environment by physiological, biochemical, and morphological changes, was a known an approved notion even from the early times of neuroscience. The debate was always on the idea whether an adult brain can generate new neurons as a mechanism of central nervous system (CNS) plasticity. Classical morphological characterizations using hematoxylin and Nissl stain techniques were not efficient in accurately tracking the development of precursor cells over time into distinct populations. However, the advancements in autoradiography techniques in late 1950s allowed selective and permanent tagging DNA of neuroblasts with radioactive Thymidine (Thymidine-H^3) and thus enabling the researchers to serially track the differentiation and migration of labeled cells (Angevine Jr. 1965). The detailed autoradiographic studies of 1960s subsequently started to provide early evidences for the generation of new neurons from precursor neural stem cells in adult brain

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(Altman and Das 1965; Angevine Jr. 1965). While studying the glial proliferation in retinogeniculate area by infusing radiolabeled thymidine (precursors of DNA), Altman found that many cells that incorporated radiolabeled Thymidine were in fact morphologically similar to neurons, and such newly formed neurons were specific to the granule cell layer of Dentate Gyrus (DG) area of hippocampus. The studies opened the whole exciting field of adult neurogenesis and the discussions on the potential functional importance of generation of new neurons in adult brains and the clinical possibilities of adult formed neurons in regenerative medicine. However, the technological limitations existed with the autoradiographic techniques in convincingly differentiating the labeled neurons from glia. The early autoradiographic studies used morphological features of the labeled cells to differentiate between newly formed neurons from glia. Subjective nature of the morphological classifications induced confusions and caused strong resistance from the classical neuroscientists who believed in the central dogma of non-replicative neurons, subsequently causing the entire topic of adult neurogenesis getting pushed to the outskirts of established neuroscience field (see Gross 2000 review for a detailed historic timeline of adult neurogenesis). Series of detailed autoradiographic studies in early 1980s in primate brains exploring all major brain structures failed to detect newly formed cells with the conclusive morphological characteristics of neurons in adult animals, further suggesting that the entire concept of adult neurogenesis, may in fact, was a possible experimental error (historical review, Rakic 2002). However, things again started to change in late 80s following the emergence of novel immunohistochemistry techniques, especially the synthetic thymidine analogue BrdU (5-bromo-3′-deoxyuridine) based immunohistochemical procedures and the emergence of cell-type specific markers gave a rebirth to the topic of adult neurogenesis by avoiding the need of autoradiography and by providing more accurate methods of identifying neurons in objective, non-morphological feature dependent manner. Immunohistochemistry in adult human hippocampus using newly introduced methods detected presence of neurogenesis in anatomically similar location and in numbers, in line with the early evidences from the rodent literature (Eriksson et al. 1998). Stem cells with neurogenic potential got isolated from the adult human hippocampus and immunohistochemistry studies showed the presence of markers specific to intermediate and immature neurons, providing further experimental evidences for adult neurogenesis (Kempermann et al. 2015, for detailed review). Numerous studies also started to show the functional relevance of adult neurogenesis, and the decreases and increases in the adult neurogenesis in response to environmental factors, reigniting the excitement of potential therapeutic potentials of adult neurogenesis (Gross 2000). However, good amounts of skepticism remain in the field regarding the extent, rate and functional relevance of the newly formed neurons, especially in higher primates and humans (Rakic 2002). The debate on the timeline of adult neurogenesis and its relevance is far from a settled notion. Most notably, a recent study (Sorrells et al. 2018) suggested neurogenesis in human dentate gyrus sharply drops by childhood and rarely continue in adult DG, a finding sharply contrasting the findings of continued neurogenesis in adult DG in other

mammals like rodents, thereby reigniting the fundamental questions around the notion and timing of adult neurogenesis, especially from a human clinical perspective. However, another study which came in the very same year provided a totally opposite finding, that neurogenesis persists in adult human brain (Boldrini et al. 2018), discussing the need of careful considerations on the specific timeline, quantitative analysis techniques, and the functional relevance of the adult neurogenesis. A review which looked at the techniques presented on the contrasting 2018 papers suggested that the negative neurogenesis finding in Sorrells et al. study may have been emerged from the non-optimal technical aspects used in the study like the delay in sample preparation which may have caused the diminished detection of marker proteins (Kempermann et al. 2018). A detailed metanalysis which compared timelines and rates of adult neurogenesis across multiple species, factoring in the age of the samples and techniques used, suggested that the seemingly prolong neurogenesis in rodent samples compared to primate and human samples can be understood if we consider the differences in neurodevelopmental timings, ages of sexual maturity and the overall lifespan of subjects used in different studies (Snyder 2019). The metanalysis showed comparable dentate gyrus neurogenesis during the conception to pre-birth windows and birth to sexual maturity windows across multiple species (Fig. 10.2, Snyder 2019 review), indicating that there is more alignment in terms of timing and extent of adult neurogenesis if the overall lifespan and developmental milestones are taken into consideration. However, the functional roles of newly formed neurons are still an outstanding question, especially if we consider diverse but specific foci of neurogenesis across the species.

10.2 Factors Influencing Adult Neurogenesis

Although the anatomical extent and the rate and the timeline of neurogenesis in adult brain are still ongoing research topics, it is now an accepted fact that new neurons form in subventricular zone (SVZ) of lateral ventricles and in subgranular zone of DG of adult hippocampus, across species (Gould 2007). Olfactory bulb is another important area where neurogenesis has been observed across multiple species. Adult neurogenesis in birds has extensively been studied and is shown to be different from mammalian species. While neurogenesis is limited in time and location for mammals, new neurons are added throughout most of the avian telencephalon, providing some form of plasticity to avian forebrains. Furthermore, the magnitude of neurogenesis in the avian brain is significantly higher than that seen in mammalian brains. In birds, 0.1–0.7% of all high vocal center (HVC)—an area homologous to Broca's area for speech control in human frontal lobe—neurons and 0.15–0.37% of hippocampal neurons are newly recruited per day on average while only about 0.02% of total hippocampal granule cells in mature macaque monkeys are generated per day, thereby providing evidences for species specific differences in the extent and possibly the functional relevance of adult neurogenesis (Brenowitz et al. 2015). Studies have shown conclusively that the process of neurogenesis respond to multiple external or internal factors like environmental enrichment, aging, local or

general inflammatory factors. The neural progenitor cells, first formed in sub-granular zone (SGZ) of dentate gyrus, subsequently migrate to granular cells layer to form the Dentate Granular Cells (DGC) which further project axons and make connections with CA3 region of hippocampus (Hastings and Gould 1999; Ming and Song 2005; Oomen et al. 2009; Snyder 2019). The development and maturation of neurons in DG follow multiple highly regulated steps starting from Type-1 radial glia-like cells (RGLs) population of DG neural stem cells (NSC) to the mature Dentate Granule neurons (DGN) (Gonçalves et al. 2016). RGLs under internal or external influencing factors get activated and undergo symmetric or asymmetric divisions. Under symmetric divisions RGL divides into 2 RGLs while asymmetric division leads to generation of astrocyte + RGL combination or RGL + neural progenitor combination (Ghosh 2019). The neural progenitor cells first receive GABAergic inputs followed by appearance of dendritic spines facilitating the excitatory transmission in 2–3 weeks of time. The experience dependent dendritic modifications occur during this stage and are mediated through glutaminergic inputs (Snyder 2019; Gonçalves et al. 2016). This stage of experience dependent modifications is also a critical survival phase and is susceptible to environmental factors like enrichment. The dendritic spine growth and modifications continue thereafter throughout the life time of adult formed neurons and the neurons follow a similar integration process with the rest of the existing circuitry (Ming and Song 2005; Snyder 2019). Deeper understanding of the intrinsic and extrinsic factors influencing the specific timeline and rate of neurogenesis can be critical in decoding the elusive functional roles of adult neurogenesis (Fig. 10.1).

Cell cycle transcription factors like E2F1, receptor tyrosine kinases like EphB1–3, EphA4, signaling pathways like the sonic hedgehog (SHH), adhesion molecules like neural cell adhesion molecule (NCAM) signaling pathway are among the key factors shown to be involved in regulating the timing and extent of neurogenesis (Cooper-Kuhn 2002; Conover 2000; McMahon 2003; Lledo et al. 2006). Molecular trophic factors are shown to exert mitogenic proliferative effects in adult neurogenesis and these include epidermal growth factor (EGF), bone morphogenetic protein (BMP), and glial fibrillary acidic protein (GFAP) (Abrous et al. 2005). Blockade of NMDA glutamate receptors are shown to increase the adult neurogenesis while Serotonin and nitric oxide upregulate the adult neurogenesis (Abrous et al. 2005; Lledo et al. 2006). Transcription factors like paired box 6 (PAX6) and oligodendrocyte transcription factor 2 (OLIG2) have shown to be playing potentially opposite roles in adult neurogenesis, with PAX6 promoting while the overexpression of OLIG2 resulting in the reduction in the rate of neurogenesis (Lledo et al. 2006). Other transcription factors like Repressor element 1-silencing transcription (REST), basic helix–loop–helix (bHLH) transcription factors, FoxOs, Tbr2, and CREB are also found to be critical for regulating adult neurogenesis. Epigenetic factors like histone modifiers, DNA methylase/demethylase, and microRNA, play significant roles in formation of new neurons in adult brain (Toda and Gage 2018). Adrenal corticosteroids, Gonadal hormones, especially the female gonadal hormones are studied in relation with the regulation of neurogenesis. Neurosteroids like dihydroxy epiandrosterone (DHEA) and

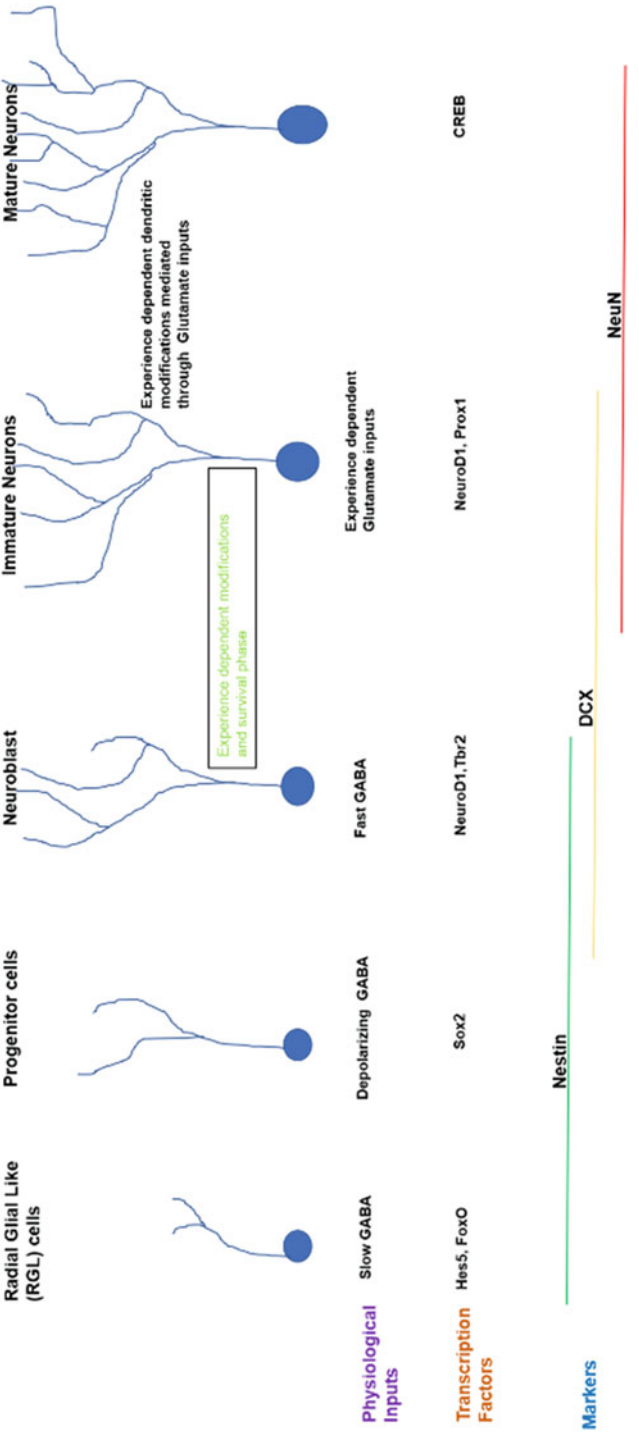


Fig. 10.1 Stages and critical players of adult neurogenesis

pregnenolone sulfate (Preg-S) facilitate neurogenesis by acting as allosteric antagonists of the $GABA_A$ receptors while allopregnanolone (AlloP), by acting as a positive $GABA_A$ receptor modulator, decrease neurogenesis in rodent DG and SVZ (Abrous et al. 2005; Lledo et al. 2006). In addition to the intrinsic factors, a variety of external factors are also known to be influencing and regulating the generation, migration, and maturation of the neurons in adult brain. Most notable external factors are physical activity, environmental enrichment, and contextual learning. These factors appear to enhance the neurogenesis, possibly through upregulation of neurotransmitters and recruitment of trophic factors (Abrous et al. 2005; Lledo et al. 2006; Toda and Gage 2018). Studies have shown increasing levels of brain-derived neurotrophic factor (BDNF) mRNA levels in the dentate gyrus within a few weeks and persistent expression of BDNF protein expression lasting several weeks. The increased BDNF expression has subsequently shown to be associated with enhancement in dentate gyrus neurogenesis and memory improvements. Furthermore, exercise when coupled with TrkB blocking (BDNF binds to tropomyosin receptor kinase B (TrkB) to affect the regulatory control over neurons), reduced the exercise-related dentate gyrus neurogenesis (Liu and Nusslock 2018). Increased neurogenesis has been observed following epilepsy, ischemia and traumatic injuries to brain. Rapid increases in neurogenesis have been observed following experimentally induced Traumatic brain injury (TBI) in mice models. However, following the initial enhancement, neurogenesis subsequently scales back to the preinjury levels and even falls below the preinjury levels indicating the potentially limited supply of neural progenitor cells and rate of adaptability of neurogenesis-mediated repair following acute injuries (Neuberger et al. 2017). Significant reductions in neurogenesis have been documented on neurodegenerative conditions like Huntington's disease, in affective disorders like major depression, and following substance abuse involving alcohol, opiates, nicotine, and cannabinoid (Abrous et al. 2005; Lledo et al. 2006; Toda and Gage 2018). The changes in adult neurogenesis in response to environmental stress factors appear to be the result of corticosteroid-related mechanisms mediated through NMDA receptor-mediated excitatory signaling pathways. However, it should be noted that the relationship between Corticosterone concentrations and the adult neurogenesis follow U-shaped dose–response relationship with complete removal of corticosterone and abnormally elevated concentrations (e.g., as in case of acute stress), both leading to significant cell loss, indicating the requirement of optimal levels of corticosterone (Hanson 2011). The environmental factors influencing neurogenesis have provided significant understandings on the potential functional implications of neurogenesis.

10.3 Anatomical and Physiological Properties of Adult Formed Neurons

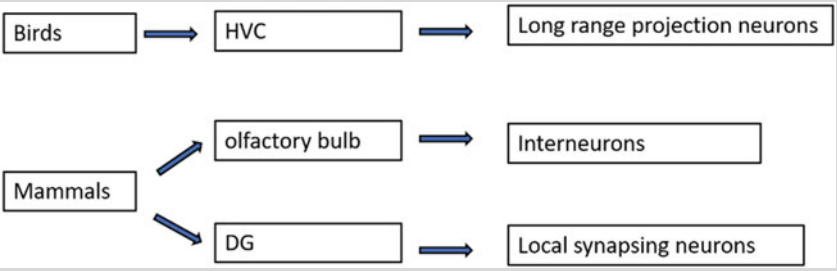
Recent immunohistochemical and electrophysiological studies on the adult formed neurons have provided extensive data on the morphological characteristics and the physiological properties of these newly formed neurons, giving insights on the

potential functional role of adult neurogenesis. Newly formed cells become more complex morphologically and functionally within the first few weeks after their birth. The specific process of maturation depends on the site of neurogenesis and the anatomical and functional inputs of the neurogenic focus.

10.3.1 Distinct Timeline of Evolution of Morphological Features in Adult Formed Neurons

Labeling studies using retroviral vectors showed distinct differences in the timeline of development of morphological features in adult formed neurons when compared with their neonatally born counterparts. The dendritic complexity and initiation of dendritic spine growth appear to be delayed by ~4 days in mice DG in comparison with the adult formed neurons. Given that the dendritic spines serve as the major receptive points for the glutamatergic inputs, the delayed dendritic spine formation subsequently leads to delays in physiological maturations (Zhao et al. 2006). Similarly, axonal growth was also found to be delayed in adult formed neurons. The mossy fiber axons of neonatally formed neurons migrate to positions more distal to the dentate compared adult neurons of similar duration from differentiation indicating a delayed or differential integration of adult formed neurons in the larger network from the site of origin (Zhao et al. 2006). However, it should be noted that, although the developmental trajectory of adult formed neurons is delayed, eventually it catches up to acquire features of developmentally born neurons. Neonatally born cells mature faster than adult-born neurons but then do not undergo additional dendritic growth beyond ~5–6 weeks of cell age. The delayed but extended developmental trajectory of adult formed neurons brings distinct morphological and functional properties providing critical plasticity features for the adult formed neurons. For example, the size of the cell soma and nucleus of adult formed neurons surpass that of neonatally formed neurons over the course development and integration. Over the course of lifespan, the adult-born neurons acquire greater dendritic spine density, larger presynaptic terminals, and more putative efferent filopodial contacts onto inhibitory neurons (Cole et al. 2020). The protracted morphological development timeline in the adult formed neurons may be critical in contributing the physiological basis for the neurogenesis-mediated plasticity within the hippocampal network. Species specificity is also striking while comparing the morphological characteristics of adult formed neurons between mammals and birds. Most of the new neurons added to the adult HVC in birds have long axons projecting 4 mm or more to synapse on target cells in RA nucleus while the newly formed neurons in the olfactory bulb of mammals are interneurons and those added to the DG are granule cells primarily involved in making local synapses (Brenowitz et al. 2015) (Box 10.1).

Box 10.1 Species Specific Differences of Adult Formed Neurons



10.3.2 Physiological Features of Adult Formed Neurons

In general, GABA-mediated synapses are the first formed connections followed by glutaminergic connections. The order of voltage-dependent currents during the maturation process and the specific sequence of synaptic connections formed decide the physiological properties of newly formed neurons from different sites of neurogenesis (Lledo et al. 2006). In periglomerular cells, the maturation of the voltage-dependent sodium current and the ability to generate fully formed action potential appear before the development of synaptic contacts while in newly formed cells of granular zone, the sodium current is generated only after the formation of extensive synaptic connections. The delayed development of action potential generation in adult formed neurons in DG possibly carries a functional importance by not disrupting the pre-formed circuits within the DG (Lledo et al. 2006). The neurogenesis in DG and the physiological properties of adult formed neurons in DG assumes special functional relevance given the causal role of hippocampus in the memory formation, consolidation and retrieval. It is interesting to note that only about 25% of adult formed DG neurons end up integrated in the circuit. This may appear as a waste of resources, but the distinct physiological features of immature neurons during the pathway of adult neurogenesis may be functionally contributing to the normal memory processes of brain even without eventually getting integrated to the circuit (Ghosh 2019). The smaller population of adult formed neurons which eventually get integrated to the circuit also show physiological characteristics that are distinct from the developmentally formed neighboring ones. Most notable features of the newly formed neurons are the enhanced excitability and the lower thresholds for Long-Term Potentiation (LTP) and Long-Term Depression (LTD)—two fundamental neural plasticity mechanisms. These neural plasticity-related features appear to be stemming from the presence of low-threshold T-type Ca^{2+} channels and the low expression of Ca^{2+} binding proteins. These two specific channel characteristics, in combination, effectively lead to the temporal summation of Ca^{2+} signals (Schmidt-Hieber et al. 2004; Ming and Song 2005). However, whether or not the adult formed neurons retain such enhanced plasticity throughout

the lifetime is still an active area of research (Ming and Song 2005; Lledo et al. 2006). While rodent studies have suggested long lasting plasticity in the adult formed neurons (Lemaire et al. 2012), extending such results to primate brain will require more extensive research (La Rosa et al. 2020). Studies using immediate early genes (IEGs) like *Fos*—expression of which is closely associated with the neuronal activity—have further shown distinct physiological properties of adult born neurons. The neuronal activity (in response to physiological events or spontaneous activity) did not induce IEG expression in adult-born neurons in DG up until about 3–4 weeks of age in mice. Interestingly, the IEG expression in adult-born neurons (once it is formed) to learning related and cognitively demanding physiological stimuli was found to be significantly more when compared with the developmentally formed neurons, findings that provide potential links between the protracted morphological development of adult-born neurons and the functional relevance of such neurons (Deng et al. 2010).

10.4 Functional Roles of Adult Neurogenesis

Some of the external factors influencing the extent and the rate of the adult neurogenesis as mentioned in the previous sections also provide evidences toward the potential functional roles of the adult neurogenesis. Evidences suggest that only about 0.004% of neurons are added each day in adult humans (Spalding et al. 2013), which in absolute terms, may appear as a small, functionally insignificant number, but if we consider the evidences suggesting that neurogenesis persists throughout the lifespan, the amount of newly formed neurons can translate to functionally relevant cell mass in hippocampus (Snyder 2019). Studies have shown the functional roles of adult neurogenesis in learning, memory, especially related to the flexibility of such cognitive tasks (Toda and Gage 2018).

10.4.1 Learning and Memory

Replacement of older neurons in the HVC of songbirds with newly formed neurons is shown to be critical in unlearning of older song patterns and acquisition of newer patters, providing a critical role of adult neurogenesis in learning and memory (Thorpe 1958; Nottebohm 1984). Rodent studies in late 1990s further extended the functional roles of adult neurogenesis to learning related to spatial cues and spatial navigation. In rodents, the number of adult formed neurons in DG significantly increased in response to training on tasks which demanded spatial association learnings involving hippocampal circuits (e.g., spatial water-maze training) while the number of adult formed neurons were not significantly different when rodents were trained with tasks like cue-maze training which didn't require hippocampal circuits (Gould et al. 1999). Studies attempted to experimentally manipulate critical components of adult neurogenesis pathways to assess the causal role of neurogenesis at specific anatomical locations and during stages of anatomical development and cognitive learning. Early studies with methyl azoxy methanol acetate (MAM)—an

antimitotic agent, have showed reduction in hippocampal neurogenesis and subsequent impairments with hippocampal-mediated contextual memory learning (Toda and Gage 2018). Selective perturbance of hippocampal neurogenesis by targeted X-ray irradiation or with the usage of transgenic animals further established the causal role of hippocampal neurogenesis with the formation and flexibility of contextual memory. The physiological properties of newly formed DG neurons, specifically the enhanced synaptic plasticity features, point toward its functional role in helping the network to effectively adapt to changes by providing flexibility within the learning networks. Such network level flexibility and adaptability may also be playing important functions when comes to processing and storing new information (Lledo et al. 2006). Computational models incorporating neurogenesis in DG have shown the improvements in recall function by reducing the interactions between previously stored memories and the newly formed ones—a key concept related to the meta-plasticity or the ability of the brain networks to change to effectively adapt to the changes (Lledo et al. 2006; Ming and Song 2011).

10.4.2 Pattern Separation and Pattern Completion

Causal manipulation studies have shown the role of hippocampal neurogenesis with the blockade of hippocampal neurogenesis leading to impairments in the pattern separation functionalities, possibly stemming from the disturbances in population coding dynamics within the medial temporal lobe memory system (Toda and Gage 2018). Computational models have suggested the role of DG neurogenesis in pattern separation and pattern completion. The unique anatomy of DG with highly converging inputs from its primary input area—entorhinal cortex—and the sparse coding property of DG neurons make the DG a potential key area for the neural computational processes related with pattern separation and completion. The extended plasticity features and delayed axonal developments associated with the adult-born neurons provide the specific opportunities for rate modulations or firing specific groups of newly formed neurons, subsequently leading to unique output variations effectively separating the patterns in memory space and thereby providing enough response dissimilarity between the new patterns, resulting in an efficient computational mechanism for pattern separation (Deng et al. 2010).

10.4.3 Higher Order Cognitive Functionalities

Hippocampal neurons modulate hypothalamic–pituitary–adrenal (HPA) axis by a negative feedback loop mechanism in response to circulating stress hormones through the high levels of glucocorticoid and mineralocorticoid receptors expressed. The adult formed neurons in DG have enhanced receptors for stress hormones indicating its critical role in regulating the stress hormone-mediated mechanisms (Schoenfeld and Cameron 2014). Several studies have shown the critical role of hippocampal neurogenesis in the treatment efficiency of antidepressant agents like Fluoxetine—a selective serotonin reuptake inhibitor (SSRI). The antidepressant

effect of fluoxetine depends significantly on its pro-neurogenic action, exerted by promoting proliferation, differentiation, and survival of progenitor cells of the hippocampus (Micheli et al. 2018). The extensive anatomical connections of hippocampus with other brain nodes like hypothalamus Amygdala, and anterior thalamic nuclei further contribute to further possibilities of hippocampal neurogenesis influencing other higher cognitive functions related to emotion, mood, and attention. It has also been suggested that the proposed role of hippocampal neurogenesis in pattern recognition and completion may also be playing a role in higher order cognitive functions like mood and anxiety, by its interactions with memory and by helping to recognize dangerous and stressful signals and to resolve decision conflicts. Impairments in these cognitive pattern separation functionalities may in turn lead to triggering or aggravating anhedonic or depressive behavior (Eisch and Petrik 2012). Studies on the factors influencing the neurogenesis suggest the critical roles of neurogenesis in regulation of higher cognitive functions like emotional control and decision making. The findings of environmental enrichments and physical or social rewarding enhancing the adult neurogenesis and the correlated findings of improvements in depression and anxiety symptoms further provide evidences for the interlinks between adult neurogenesis neuropsychiatric conditions. These findings also suggest the possibility and the need of exploring the functionally relevant neurogenesis in neocortical areas in addition to the hippocampal and SVZ sites (Gould 2007; Ming and Song 2011; Cameron and Glover 2015). For example, the depressive-like state produced in rodents by removal of the olfactory bulbs and the olfactory changes are also observed in human patients with depression and schizophrenia (Schoenfeld and Cameron 2014).

10.5 Adult Neurogenesis: A Target for Regenerative Medicine

From the very early days of the emergence of the topic of adult neurogenesis, it was started being proposed as a potential target for a large variety of neurological conditions. Even with all the (still) ongoing debates on the anatomical extent, timeline, rate, and functional significance of adult formed neurons, there are promising evidences suggesting the clinical possibilities of adult neurogenesis (Fig. 10.2).

10.5.1 Stroke and Injuries

Studies have shown enhanced neurogenesis follows medial temporal lobe epilepsies, ischemia, and traumatic injuries, providing promising directions toward the possibility of natural neural repair mechanisms related to the formation and assimilation of new neurons (Abrous et al. 2005). Experiments on animal models of stroke induced by techniques like transient middle cerebral artery occlusion have shown evidences of neurogenesis following stroke episodes. The neural progenitors proliferate in response to ischemia-induced cell loss. The proliferated progenitor cells differentiate and subsequently migrate to damaged areas, most notably to striatum

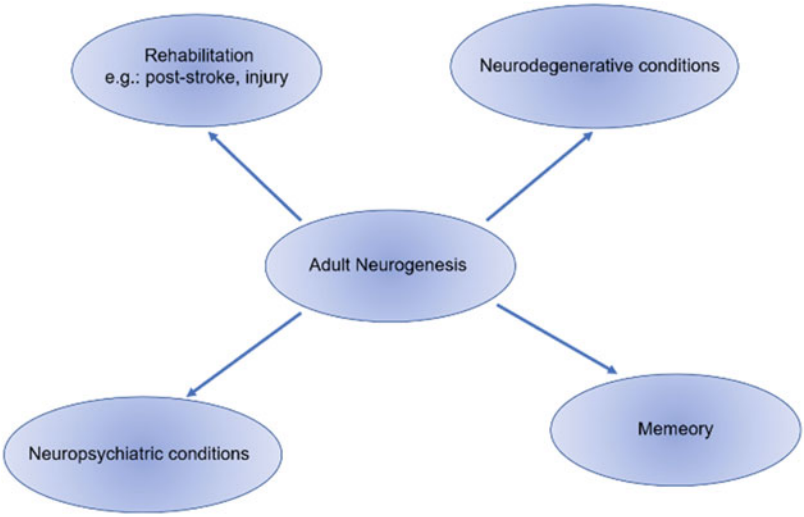


Fig. 10.2 Potential clinical targets of adult neurogenesis

(Lindvall and Kokaia 2015). The migration of neuroblasts from the neurogenesis foci to damaged areas appear to be mediated through the blood vessels. Compared to the post-stroke neurogenesis evidences in striatum, the cortical neurogenesis is less conclusive. Significant regeneration of neocortex out of neurogenesis has not yet been observed in humans. It has been shown that neurogenesis can be induced in stroke damaged cortical areas by introducing agents like growth factors, but it should be noted that majority of the newly differentiated striatal neurons following stroke undergo programmed cell death within the first 2 week of their formation and fails to survive. Ischemia-related inflammatory changes which induced the initial proliferation of progenitor cells also contribute to the poor survival of the newly formed striatal neurons, indicating that limitations of neurogenesis dependent post-stroke self-repair mechanisms (Lindvall and Kokaia 2015; Lu et al. 2017). It has been suggested that reducing ischemia-related inflammatory substrates in critical windows of survival of newly formed neurons and also be stimulating the differential of cells using growth and neurotrophic factors could be potential workarounds for using the potential of neurogenesis as effective post-stroke repair mechanism (Lu et al. 2017). However, it should be noted that inflammatory factors are critical for proliferation of the progenitor cells and the angiogenesis which ultimately control the migration of newly formed neurons to damaged areas. Striking a balance between the interconnected processes is critical for being able to use neurogenesis for post-stroke repair (Rahman et al. 2021). A recent review exploring the role of neurogenesis in post-stroke functional recovery, discuses several factors which needed to be considered and solved before translating the finding of increased post-stroke neurogenesis as a valid treatment pathway for the post-stroke functional recovery (Ceanga et al. 2021). The extent to which the newly formed neurons can

migrate from the currently established foci of neurogenesis to the distant cortices critical for the post-stroke functional recovery being the most important factor to be considered. The timing of neurogenesis is also important given numerous neural network plasticity processes and functional neural compensation mechanisms that occur within a short time window following the stroke events. Efforts to accelerate the neurogenesis, in the hopes for faster and efficient functional and cognitive repair and recovery, need to be approached carefully given our limited understanding on the migration and functional assimilation of newly formed neurons. Careful considerations should be made regarding maladaptive versus beneficial reorganizations, especially when considering motor recoveries (Ceanga et al. 2021).

10.5.2 Neurodegenerative Conditions

Neurodegenerative diseases are another avenue where adult neurogenesis is extensively investigated as a potential therapeutic target. Significant changes in adult neurogenesis have been observed in multiple neurodegenerative diseases like Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD). Although the pathology of these neurodegenerative diseases is linked to different proteins and distinct neuronal populations, the early symptom complexes of these conditions are strikingly similar and include memory and learning-related cognitive impairments, emotional imbalances, and depression, all of which can be linked to hippocampal and olfactory complexes, the primary areas of adult neurogenesis, suggesting a possible causal link between the adult neurogenesis and onset of pathophysiology of the neurodegenerative conditions (Winner and Winkler 2015). Experimental evidences support this hypothesis. Transgenic animal models of PD showed impairments in proliferative activity and survival of newly generated neurons. Similarly, decreased proliferation in correlation with the increase in β-amyloid plaques has been observed in AD models (Winner and Winkler 2015). Impaired hippocampal neurogenesis in Alzheimer's disease and Impaired maturation of striatal neurons in the striatum have been observed (Cheyuo et al. 2019). Postmortem studies on human subjects with neurodegenerative conditions showed abnormal morphological development and changes in differentiation markers in adult hippocampal neurogenesis (Therreros-Roncal et al. 2021). Based on the potential link between the impairments in the adult neurogenesis and the development of pathophysiology of neurodegenerative conditions, strategies aimed at enhancing neurogenesis have been suggested as potential treatment options for neurodegenerative conditions. Milk fat globule-epidermal growth factor-factor VIII (MFG-E8), a secretory glycoprotein that has been shown to be promoting neural stem cell proliferation and migration toward the ischemic brain tissues in post-stroke brains has also been explored as a potential therapeutic agent for repairing neurogenesis impairments in neurodegenerative conditions (Cheyuo et al. 2019). Animal studies on the neurodegenerative models do provide early promising results of functional improvement with enhanced neurogenesis (Winner and Winkler 2015). However, the functional recovery with neural stem cells or artificially

enhancing the in vivo neurogenesis will largely depend on the rate, anatomical extent and the functional integration of newly formed neurons to the existing network, similar to the recovery possibilities discussed with the post-stroke conditions (Ceanga et al. 2021).

10.5.3 Neuropsychiatric Conditions

Decreased neurogenesis in a number of neuropsychiatric conditions including major depression, anxiety, and the reversal of pathologically reduced neurogenesis with existing treatment options point toward yet another therapeutic aspect of adult neurogenesis (Abrous et al. 2005; Ghosh 2019). Pharmacological innervations and other treatment modalities have shown to enhance the neurogenesis and the findings of the dependence of treatment efficacy level of neurogenesis provide direct links between the role of neurogenesis and development of neuropsychiatric conditions (Schoenfeld and Cameron 2014). Decrease in cell proliferation within the dentate gyrus and reduced hippocampal volume have been reported in a number of neuropsychiatric conditions along with impairments in hippocampus-dependent functionalities (Kang et al. 2016). It has been shown that DISC1 gene, a major susceptibility gene for schizophrenia is involved in regulating adult hippocampal neurogenesis, further providing evidences for the neurogenesis related origin of schizophrenia (Eisch et al. 2008). Given the role of anatomical connections between hippocampus and limbic system in reward and motivation, hippocampal neurogenesis was hypothesized to play roles in drug addiction and substance abuse and experimental evidences indeed suggest the possibility of such an association (Eisch et al. 2008). Although these evidences suggest the potential role of neurogenesis in the pathophysiology of a variety of neuropsychiatric conditions, targeting neurogenesis in treatment options is not straightforward as in the case of stroke rehabilitation and neurodegenerative conditions. Many unknown factors remain to be revealed related to the rate of proliferation, survival, and integration of the newly formed neurons within the existing network—the factors which critically determine the potential clinical role of adult neurogenesis in neuropsychiatric conditions.

10.5.4 Potential Roles in Learning and Cognitive Functionalities

It has been shown that environmental factors like enrichment and learning affect adult neurogenesis (Shohayeb et al. 2018). These findings provide a potential avenue of a reverse clinical application, that is, enhancing cognitive abilities related to learning and memory by enhancing hippocampal neurogenesis. Genetically driven expansion of neural stem cells compensated the age-related decline in neurogenesis enhanced navigational learning strategies in mice models (Berdugo-Vega et al. 2020). Interestingly, enhanced hippocampal neurogenesis and related plasticity also leads to a memory reorganization and neurogenesis-induced forgetting as in

the case of contextual fear conditioning experiments in mice models (Evans et al. 2021). Further studies suggest that the neurogenesis-mediated forgetting is not limited to contextual fear memories but extends to broader array of learned memories including spatial, context, or object memories (Scott et al. 2021). These findings while suggesting the potential possibilities for modulating cognitive functionalities using factors influencing hippocampal neurogenesis, also shows the complicated interconnections between the memory and learning nodes within the hippocampal and medial temporal lobe memory system.

While existing research works on the adult neurogenesis do indicate the prospects of adult neurogenesis being emerging as the potential target for many neurological conditions, its limitations, based on what we currently know (and don't know) about the extent and the specific mechanisms, also need to be considered while aiming for therapeutic applications. Manipulating the adult neurogenesis will most possibly bring functional effects related to the local microenvironments at the foci of neurogenesis, but the clinical relevance of such local effects and the causal roles of adult formed neurons in the wider neural networks and in the global brain functionalities will require extensive future research works. Such works will eventually better define the clinical potentials of adult neurogenesis in vascular, neuropsychiatric, or neurodegenerative conditions (Box 10.2).

Box 10.2 Outstanding Questions and Future Directions

- **Search for the other potential loci of adult neurogenesis:** comparative studies with other species showing varying loci of neurogenesis in adult organisms suggest the need of considering developmental milestones and embryological parallelism while exploring the potential neurogenesis loci.
- **Precise mechanisms of migration and integration of adult formed neurons in the existing networks:** A better understanding on these mechanisms are critical for exploring the therapeutic potentials of adult neurogenesis.
- **Physiological and computational mechanisms of adult formed neurons in cognitive domains:** although current evidences show the links between adult neurogenesis and memory functionalities, the network reorganizations with which newly formed neurons involved in new learning while simultaneously affecting the storage of existing memories need to be explored.

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