

Adult hippocampal neurogenesis: New avenues for treatment of brain disorders

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SUMMARY

Neurogenesis, the biological process of forming new neurons, was traditionally believed to occur only during embryonic stages in the mammalian central nervous system for a long time. Over the past few decades, due to the development of new techniques and the accumulation of supportive evidence, adult neurogenesis is now accepted as the one of the most robust forms of plasticity in the adult brain, which contributes to physiological function as well as a range of neurological or psychiatric disorders. In this review, we mainly concentrate on adult neurogenesis in the hippocampus, the most likely neurogenic niche with significant roles in various brain functions. We begin by summarizing the current fundamental knowledge of adult hippocampal neurogenesis including proliferation, differentiation, maturation, and synapse formation of neural stem cells. We then focus on the potential roles of these adult-born neurons and their contribution to learning and memory behaviors and their relevance to various diseases. Furthermore, we review regulatory mechanisms governing adult hippocampal neurogenesis, including local environmental cues, multiple molecular signaling pathways, and neural network activities. We also discuss possible therapeutic strategies and targets that can be leveraged for future clinical translations. Finally, given the substantial progress in the field of regenerative medicine aimed at harnessing the multipotent resident cells for brain repair, we address remaining challenges and propose our perspectives on future directions for treating central nervous system disorders.

INTRODUCTION

Neurogenesis, the biological process of forming new neurons, was long believed to occur only during embryonic stages in the mammalian central nervous system (CNS). However, in the late 1950s, a new technique was developed to label dividing cells with [³H]-thymidine, which incorporates into the DNA of dividing cells during the S-phase of cell cycle. Then, with the introduction of [³H]-thymidine autoradiography, Joseph Altman and colleagues (Altman, 1963; Altman and Das, 1965) provided the first evidence of [³H]-thymidine-labeled cells in various brain regions of adult rats, including the dentate gyrus (DG) of the hippocampus, neocortex, and olfactory bulb. These findings on rats were then extended to several species of mammals, where neuro-

genesis was detected in the postnatal period. Unfortunately, these early findings were given little attention due to technical limitations, including the lack of specific neuronal markers, which impeded further studies. Further support came from *in vitro* studies that successfully isolated neural stem cells (NSCs) from adult brain tissues (Palmer et al., 1995, 1997). Subsequently, the field of adult neurogenesis was revolutionized with the emergence of bromodeoxyuridine (BrdU) (another S-phase marker of the cell cycle) and retroviral-based lineage tracing, associated with immunohistochemistry and electrophysiology. These techniques contributed to the first *in vivo* convincing evidence of adult neurogenesis (Eriksson et al., 1998; Gould et al., 1998; Kuhn et al., 1996) and confirmed that adult-born neurons (ABNs) are indeed functionally and synaptically integrated (van Praag et al., 2002). However, adult neurogenesis is not wide-spread throughout the brain; instead, it is restricted to two main neurogenic niches: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal DG (Gross, 2000; Kuhn et al., 1996; Li and Guo, 2021; Ming and Song, 2005). Altogether, over the past decades, our understanding of adult neurogenesis has progressed significantly with development of new techniques. Today, adult neurogenesis is accepted as one of the most robust forms of plasticity in the adult brain, which contributes to learning and memory as well as various neurological and psychiatric disorders (Cameron and Glover, 2015; Elliott et al., 2025; Goncalves et al., 2016; Jessberger and Parent, 2015).

In this review, we mainly concentrate on the adult neurogenesis in the SGZ, as the hippocampus remains the most likely neurogenic niche to play a significant role in various brain functions. We will summarize current knowledge about adult hippocampal neurogenesis (AHN), including insights into adult human neurogenesis, a topic under heated discussion in recent years. Then, we will focus on potential functions of these ABNs, including their contribution to behaviors and their relevance to diseases. Furthermore, we will review regulatory mechanisms of AHN, discussing possible therapeutic strategies that may facilitate clinical translations. Finally, we will evaluate the therapeutic potential of regenerative medicine, which is





Box 1. Search strategy

Studies cited in this narrative review, published from 1963 to 2025, were obtained from searching the Pubmed database by using keywords including “adult hippocampal neurogenesis,” “adult-born dentate granule cells,” “adult-born neurons,” “cell proliferation,” “neural stem cell,” “neural progenitor cell,” “regenerative medicine,” “stem cell therapy,” “induced pluripotent stem cell,” “glia to neuron,” and “*in vivo* reprogramming.” Search results were further filtered by titles and abstracts. All the literature search was conducted between November, 2023 and June, 2025.

aimed at harnessing the multipotent resident cells for brain repair. The Search strategy is listed in the [Box 1](#).

NEUROGENESIS IN THE INTACT ADULT MAMMALIAN DG: PROLIFERATION, DIFFERENTIATION, MATURATION, AND SYNAPSE FORMATION OF NSCs

In general, the proliferation, differentiation, and eventual survival to maturity of newborn ABNs takes 2–4 weeks in mice and rats, but this process is longer in primates and humans ([Bergmann et al., 2015](#); [Kohler et al., 2011](#)). Most knowledge about the specific development and afferent/input of new ABNs comes from studies on laboratory animals. In the hippocampus, SGZ—a thin band between the granule cell layer (GCL) and the hilus—provides a unique microenvironment for adult NSCs. NSCs reside in SGZ and give rise to dentate granule cells (DGCs) through a multistep process: proliferation, differentiation, migration, axon/dendrite targeting, and synaptic integration.

The generation of new neurons starts from relatively quiescent NSCs, generally known as type 1 radial glia-like cells (RGLs). These cells extend a radial process through the GCL into the molecular layer (ML) and are characterized by markers such as GFAP, nestin, and Sox2. Upon activation, they produce proliferating non-radial intermediate progenitor cells, known as type 2 cells, which exhibit transient amplifying characteristics and subsequently give rise to neuroblasts (type 3 cells). Type 3 cells, characterized by the expression of doublecortin (DCX) and polysialylated neural cell adhesion (PSA-NCAM) continue to proliferate but exit the cell cycle prior to full maturation into DGCs. They migrate only a short distance into the inner GCL, projecting out a large dendritic arbor into the ML and an axon into the hilus that terminates on target cells in both the hilus and the CA3 region ([Bonaguidi et al., 2011](#); [Kempermann et al., 2004](#); [Toni et al., 2008](#); [van Praag](#)

[et al., 2002](#)). As reported by [Zhao et al.](#), GFP-expressing axons of newborn ABNs were found in the hilus as early as 7 days after retroviral infection and reached the CA3 at 10–11 days ([Zhao et al., 2006](#)). Once mature, these newborn ABNs develop into glutamatergic DGCs that share many characteristics with embryonic-generated DGCs ([Esposito et al., 2005](#); [Laplagne et al., 2006](#)).

Identifying the development of connections of ABNs is essential for understanding their integration into existing circuitry and how AHN refines these pre-existing networks. Early studies indicated that newborn ABNs initially receive GABAergic synaptic inputs during their first weeks, presumably from ambient GABA, and only later do they become targets for glutamatergic synapses as well ([Esposito et al., 2005](#)). More recent studies, utilizing rabies-virus-based monosynaptic retrograde tracing techniques, have confirmed this notion and revealed that ABNs received first GABAergic input from multiple local interneurons (~10 days), followed by modulatory cholinergic from the septal nuclei and glutamatergic synaptic input (~2 weeks) from local glutamatergic inputs, and finally integrating into the classic hippocampal tri-synaptic circuits (~3 weeks) ([Figure 1](#)) ([Amaral et al., 2007](#); [Deshpande et al., 2013](#)). Initially, GABA currents are excitatory and tonic; then, phasic GABA post-synaptic currents emerge, and immature ABNs are activated by them due to a higher concentration of intracellular chloride ions ([Ge et al., 2006](#)). The first glutamatergic inputs come from local mature DGCs and glutamatergic mossy fibers, which develop during the second week. Then, the newborn ABNs start to express NMDA receptors containing NR2B subunit that lowers the threshold for induction of long-term potentiation (LTP) and enhanced plasticity ([Kheirbek et al., 2012](#)). However, these inputs diminish as the newborn ABNs mature ([Vivar et al., 2012](#); [Vivar and van Praag, 2013](#)). This finding suggests that immature ABNs, compared with embryonically generated mature DGCs, are “young and excitable,” highlighting a unique phase of heightened responsiveness in their early development.

By the end of the first month, immature ABNs differentiate into functional neurons, acquiring passive membrane properties, forming synaptic connections, and gaining the ability to generate action potentials (APs), with most of their morphological growth also completed. However, their electrophysiological properties at this age (4 and 6 weeks post-mitosis) remain distinct from those of neighboring mature DGCs. Specifically, these immature ABNs are more excitable, exhibiting higher input resistance, lower threshold voltage, and a slower membrane time constant. Additionally, they are more prone to LTP as well as long-term depression (LTD), indicating enhanced synaptic plasticity ([Ge et al., 2007](#); [Schmidt-Hieber et al., 2004](#); [Wang et al., 2000](#)). These characteristics suggest a “critical period” during which immature ABNs and mature DGCs

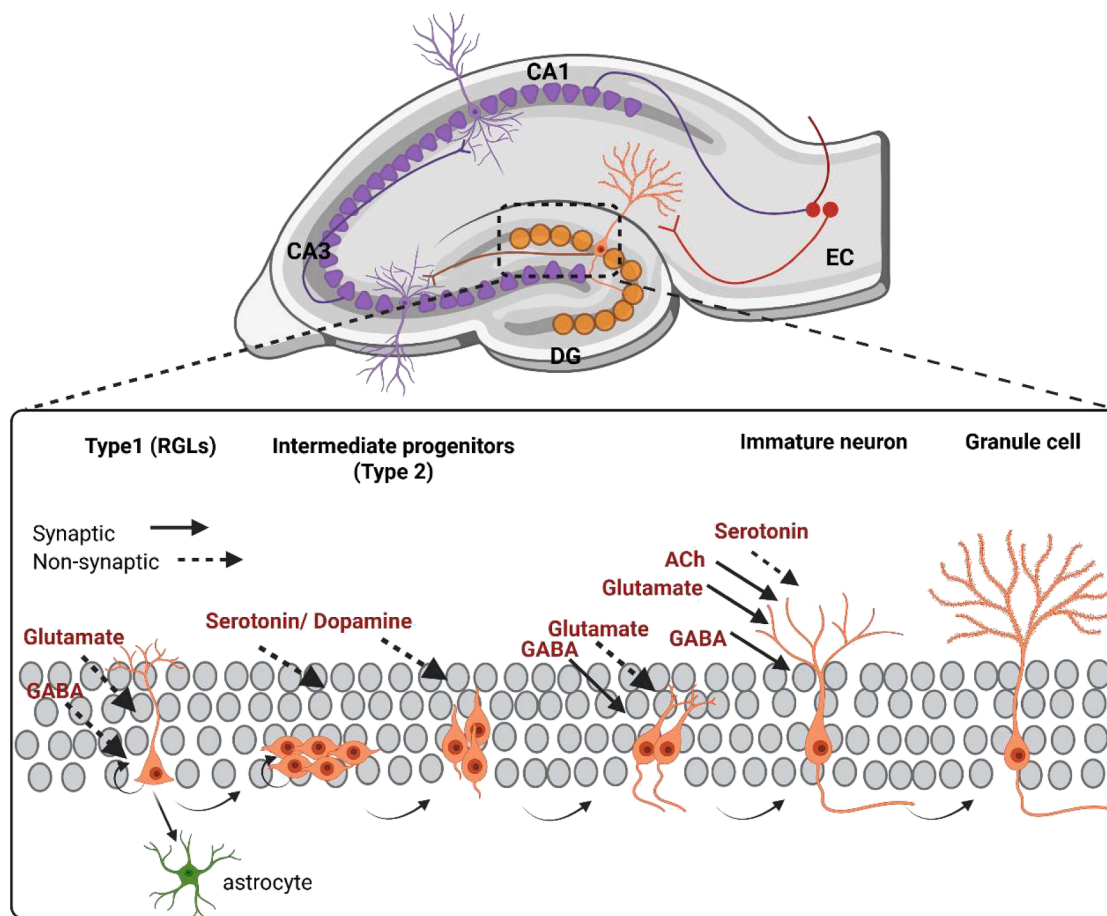


Figure 1. Adult neurogenesis in the hippocampus

Neural circuits in the hippocampus (upper panel). Adult NSCs in the hippocampus (radial glia-like cells, type 1 cells) and their differentiation in the SGZ. Multiple synaptic and non-synaptic inputs may help regulate the process of their differentiation (lower panel). This figure is created with [BioRender.com](https://www.biorender.com).

display differences in excitability and plasticity. During this time, ABNs are also likely to function differently from mature DGCs (Gu et al., 2012; Nakashiba et al., 2012), a topic that will be further explored in the section on the “functional significance of adult hippocampal neurogenesis.” However, as these ABNs mature, they tend to be under stronger inhibitory control and the range of stimuli that elicit firing narrows, resulting from sparser activity, which is typical of mature DGCs (Danielson et al., 2016; McHugh et al., 2022).

ADULT HIPPOCAMPAL NEUROGENESIS IN HUMANS

The discovery of adult mammalian neurogenesis sparked interest in exploring the existence of adult human neuro-

genesis (Gage, 2025; Simard et al., 2024). The first study demonstrating the existence of AHN in humans was published by Eriksson and colleagues in 1998 (Eriksson et al., 1998). Taking advantage of the administration of BrdU, they demonstrated the presence of a restricted population of ABNs in human DG, aligning with prior findings in rodents. Subsequent studies have quantified ABNs using immunohistochemistry with neuronal precursor markers such as nestin, Ki67, and DCX (Boekhoorn et al., 2006; Boldrini et al., 2009; Knoth et al., 2010). Meanwhile, they have revealed the dynamics of AHN, showing that a substantial number of neuroblasts decrease sharply during the first postnatal year and then decline more moderately through childhood and into adulthood. This conclusion was further supported by Spalding et al., who employed an innovative approach, using nuclear-bomb-test-derived ^{14}C dating to retrospectively birthdating cells from the



human hippocampus. They found that 1/3 of human hippocampal neurons are subject to exchange, with an annual turnover rate of 1.75% within the renewing fraction, accompanied by a modest decline during aging (Spalding et al., 2013). Despite the evidence presented above, several studies have reported scarce or even absent staining for markers of ABNs in the adult human DG, starting as early as the early 20s (Cipriani et al., 2018; Dennis et al., 2016; Sorrells et al., 2018), thereby challenging the existence of human AHN. Notably, Sorrells et al. reported that, distinct from other mammalian species, neurogenesis in human DG dropped to undetectable levels as early as childhood. Interestingly, in another study published just a few weeks after Sorrells and colleagues, Boldrini et al. came to the opposite conclusion, reporting evidence of lifelong neurogenesis in humans (Boldrini et al., 2018). There are also other contemporary publications in support of persistent presence of ABN markers in the adult human DG throughout life (Moreno-Jimenez et al., 2019; Tobin et al., 2019).

The conflicting findings are particularly intriguing given that these studies used similar detection methods. Both Sorrells et al. and Boldrini et al. calculated the number of cells expressing DCX or PSA-NCAM, two established markers for immature neurons in the adult brain, raising important technical concerns in the field. One major limitation in the field of human AHN research is the postmortem nature of the samples used, where discrepancies may arise from variations in tissue processing techniques. Seemingly trivial factors can critically affect the quantitative detection of ABN markers, such as tissue fixation procedures, postmortem delay (PTD, the interval between death and sample's immersion in fixative), and the stereological method used for cell counting (Bao and Swaab, 2018; Gallardo-Caballero et al., 2023). Specifically, different fixation periods (1–48 h) in freshly prepared 4% PFA has been reported to result in different immunohistochemistry outcomes. A controlled time course study on PTD reported that DCX staining weakened significantly within just a few hours after death, indicating that relatively long PTD would mask the DCX antigen. However, fixation with commercial formalin for several months has been a routine method used at most brain banks (Flor-Garcia et al., 2020). Therefore, due to the special nature of human brain studies, the poor performance of immunohistochemistry on postmortem samples remains a major obstacle.

Instead of immunohistochemistry on postmortem samples, more recently, single-cell/single-nucleus RNA sequencing (sc/snRNA-seq) was utilized, aided by a validated machine-learning-based analytic approach to identify immature DGCs and quantify them in the human hippocampus at different developmental stages across

the lifespan (child, adolescence, adulthood, and aging). Their findings revealed a substantial presence of immature DGCs in the adult human hippocampus via low-frequency *de novo* generation and protracted maturation (Terrerros-Roncal et al., 2023; Tosoni et al., 2023; Zhou et al., 2022). However, while Franjic et al. revealed robust transcriptomic and histologic signatures of neurogenesis in the adult mouse, pig, and macaque, they failed to identify any neurogenic populations in humans (Franjic et al., 2022). The scarcity of high-quality postmortem brain tissue, discrepancies in sample processing, experimental design, and computational analysis may also impact the reliable identification of neurogenic cell types in humans using sequencing technologies (Tosoni et al., 2023). Using spatial genomics to examine adult neurogenesis will also add more important data to this field. Further, as sc/snRNA-seq approaches start shedding light on the cellular and molecular complexities of the adult human DG, coordinated efforts are needed to reconcile findings across studies to create a unified taxonomy of cell types and specify signatures of human neural progenitor populations and their lineage trajectories, rather than relying on rodent-derived gene lists.

Overall, currently, each of the experimental strategies used to identify and visualize neural progenitors and progeny in human brains has its own limitations and potential methodological confounders, which must be carefully considered. To resolve ongoing controversies surrounding human AHN, the field must progress beyond isolated efforts and adopt a more collaborative, interdisciplinary approach. First, establishing international guidelines and standardized protocols for tissue processing, marker selection, cell clustering, and annotation is essential to reduce methodological variability and enhance comparability across studies. In addition, expanding access to large-scale, well-annotated postmortem human brain banks will ensure more consistent and high-quality tissue samples, thereby improving the reliability of findings. Meanwhile, sharing raw data from transcriptomic, imaging, and histological studies on public platforms will facilitate replication, re-analysis, and larger-scale meta-studies that can further clarify the existence and extent of adult human neurogenesis. On the other hand, definitive evidence for AHN in living human subjects will require the development of non-invasive monitoring techniques. The development of non-invasive imaging techniques (e.g., PET tracers specific to neurogenesis-related markers) or circulating biomarkers (e.g., in CSF or blood) would allow for longitudinal tracking of neurogenesis dynamics. These tools would significantly advance our ability to investigate AHN in both health and disease and may ultimately open new therapeutic avenues for neurological diseases.



FUNCTIONAL SIGNIFICANCE OF ADULT HIPPOCAMPAL NEUROGENESIS

Studies on neurogenesis have shifted from merely questioning the existence of AHN to exploring the functional contributions that ABNs make in both healthy and diseased brains. In this section, we will briefly review the contributions of AHN to learning and memory and discuss the effects of certain pathological conditions on AHN as well as the consequences of modulating AHN levels or ABN activity, to shed light on the functional significance of ABNs.

Learning and memory

Accumulating evidence has suggested that AHN plays significant roles in cognition, learning, and memory (Chang and Hen, 2024; Toda and Gage, 2018; Toda et al., 2019). Behavioral tests such as the Morris water maze (MWM), eight-arm radial maze (RAM), and Barnes maze as well as working memory tests using the delayed matching-to-sample (DMS) or delayed nonmatching-to-sample (DNMS) protocols have been used to assess learning and memory. Strategies to enhance or ablate ABNs have often resulted in cognitive improvement or deficits, respectively, nonetheless conflicting.

Both voluntary exercise and enriched environment (EE) increase AHN; meanwhile, they have also been reported to improve performance in spatial learning (Kobayashi et al., 2002; Leggio et al., 2005) and recognition (Bruehl-Jungerman et al., 2005) while reversing the negative effects of aging and stress. In contrast, abolishing AHN using anti-mitotics, irradiation, or genetic manipulations has led to deficits in contextual fear conditioning, spatial learning and memory in various models, while negating the positive effects of EE and exercise (Dupret et al., 2008; Goodman et al., 2010; Madsen et al., 2003; Snyder et al., 2005; Winocur et al., 2006). However, other studies have shown that reduced AHN has little impact on spatial learning (van Praag et al., 2002) but may severely impair contextual memory (Saxe et al., 2006; Wojtowicz et al., 2008). In addition, reducing AHN was also reported not to affect neither contextual fear conditioning nor spatial navigation learning (Shors et al., 2002). Surprisingly, experiments with GFAP-TK transgenic mice demonstrated that ablating AHN led to improved working memory in the RAM task concurrently with impaired contextual fear conditioning (Saxe et al., 2007). Taken together, the findings from different studies are quite contradictory, possibly owing to the use of different behavioral tests, animal species, and strategies to modulate AHN, as well as variations in the duration, intensity, and efficiency of these interventions.

Several studies have associated AHN with pattern separation, a computational process by which overlapping or similar inputs (representations) are transformed into less similar, non-overlapping outputs, including spatial inputs and contextual inputs (Aimone et al., 2011; Miller and Sahay, 2019; Simard et al., 2024). Clelland et al. were the first to demonstrate the effect of ablating AHN on spatial pattern separation (Clelland et al., 2009). Using a spatial discrimination task and a delayed nonmatching-to-place RAM task, they found that hippocampal x-irradiation effectively inhibited AHN, impairing the animal's ability to make fine (but not large) spatial discriminations. In contrast, Tronel et al., using Nestin-rtTA/Tet-Bax bigenic mice to selectively deplete AHN, found that the animal's ability to discriminate between a shock-associated training context and a no-shock context was comparable to controls, as indicated by similar levels of freezing behavior in both contexts (Tronel et al., 2012). These findings indicate that AHN is essential for pattern separation across various behavioral paradigms. In a subsequent study, Sahay and colleagues not only confirmed that hippocampal x-irradiation impaired the animals' ability to discriminate between two similar contexts but also developed a genetic strategy to selectively increase AHN. They demonstrated that mice with more functionally integrated ABNs performed better in contextual discrimination tasks (Sahay et al., 2011). Overall, these results indicate that AHN is both sufficient and necessary for pattern separation.

Although the general pattern of afferent and efferent connectivity of newborn ABNs in the SGZ recapitulates that of developmentally generated DGCs, newborn ABNs exhibit heightened excitability and synaptic plasticity during a specific time window of their maturation (4–6 weeks post-mitosis) compared to mature DGCs (Ge et al., 2007; Schmidt-Hieber et al., 2004). This unique feature suggests a distinct contribution for immature ABNs in hippocampal-dependent behaviors such as contextual encoding and pattern separation (Danielson et al., 2016; Gu et al., 2012; Lods et al., 2022; Mugnaini et al., 2023; Nakashiba et al., 2012; Tuncdemir et al., 2023). Initially, it may seem quite paradoxical: the “sparse coding” of DG is essential for pattern separation as it minimizes overlap in neuronal responses, allowing similar inputs to be represented distinctly; however, immature ABNs are highly excitable and thus respond to a broader range of stimuli. Indeed, while immature ABNs are excitable themselves, they contribute to feedback inhibition in the DG, which ultimately reduces DG activity and supports sparse coding (Anacker et al., 2018; Ikrar et al., 2013; Lacefield et al., 2012; McHugh et al., 2022). Meanwhile, due to their lower activation threshold, immature ABNs preferentially respond to subtle changes in context and decrease the firing probability of mature DGCs through feedback



inhibition (Frechou et al., 2024). However, ablation or inhibition of ABNs does not always alter the overall firing rate of the DG (Tuncdemir et al., 2023). Alternatively, immature ABNs may contribute to the formation of distinct engrams by modulating the activity of hippocampal network through multiple mechanisms. For example, Luna et al. reported that the inhibitory or excitatory effects on mature DGCs depend on the excitation levels of immature DGCs (Luna et al., 2019).

Furthermore, ABNs may retain some unique properties even after reaching maturity, both morphologically (Cole et al., 2020) and functionally, including increased learning-induced plasticity (Huckleberry and Shansky, 2021; Lemaire et al., 2012).

Brain disorders

Brain disorders may arise from a variety of causes, including injuries, genetic factors, and degenerative processes. They can lead to a wide range of symptoms affecting cognitive, motor, sensory, and emotional functions. Generally, these disorders are broadly categorized into neurodegenerative disorders, seizure disorders, mental and psychiatric disorders, cerebrovascular disorders, and more. In the following section, we will discuss the roles of AHN in relation to these aforementioned major types of brain disorders.

Neuropsychiatric disorders

There is much evidence in both animal and human studies that neuropsychiatric disorders (including major depression, anxiety, schizophrenia, etc.) are linked to alterations in AHN.

Stress is a major risk factor for several neuropsychiatric disorders. Enhanced stress responses can exacerbate depression and anxiety-like behaviors with dysregulation of glucocorticoids, which not only directly affect NSCs but also influence the expression of pro-inflammatory genes and downregulate the expression of brain-derived neurotrophic factor (BDNF), a key regulator of neuronal growth, survival, and plasticity (Chen et al., 2017; Fitzsimons et al., 2016; Schouten et al., 2020). Both acute and chronic stress have been shown to decrease AHN (Borsini et al., 2023; Gould and Tanapat, 1999; Gould et al., 1998; Thomas et al., 2007; Yoshioka et al., 2022), whereas experimentally increasing AHN may increase resilience to chronic stress (Anacker et al., 2018; Culig et al., 2017) (Table 1). For instance, Anacker et al. found that chemogenetic inhibition of ABNs promoted susceptibility to social defeat stress, whereas increasing AHN conferred resilience to stress possibly through modulation of the activity of mature DGCs, indicating that AHN was both sufficient and necessary for stress resilience (Anacker et al., 2018).

Depression, the most common psychiatric disorder, is characterized by low mood, anxiety, anhedonia, and reduced ability to concentrate (Anderson et al., 2024;

Smith, 2014). A number of clinically used classic antidepressants such as fluoxetine were reported to strongly enhance AHN both in animal studies and in postmortem human brains (Planchez et al., 2020) (Table 1). A recent meta-analysis has also confirmed that chronic treatments involving most commonly used antidepressants significantly increase AHN (Lino de Oliveira et al., 2020). In turn, although neurogenesis-independent effects of fluoxetine were also reported in some behavioral paradigms (David et al., 2009), the ablation of AHN was always reported to reverse the therapeutic effects of antidepressants (Franklin and Paxinos, 2019; Li et al., 2008; Santarelli et al., 2003) (Table 2). For example, using irradiation to inhibit neurogenesis, Santarelli et al. found that the ability of fluoxetine to affect mood-related behavior in rodents was substantially reduced (Santarelli et al., 2003). However, the precise mechanisms through which ABNs might influence the antidepressant response remain elusive. Further studies not only confirmed the necessary role of AHN for the antidepressant effects of fluoxetine but also found that intact AHN was required for the ability of fluoxetine to restore hippocampal regulation of the HPA axis under chronic stress conditions (Surget et al., 2011). More recently, chemogenetic silencing of ABNs, without altering the level of AHN, was also found to abolish the antidepressant effects of fluoxetine (Tunc-Ozcan et al., 2019). These observations may also help explain why classic antidepressants always take several weeks to become effective since antidepressants-induced neurogenesis would take several weeks to become functionally integrated. However, a new antidepressant, ketamine, known for its rapid and sustained antidepressant properties (Berman et al., 2000; Zarate et al., 2006), has also been found to rapidly increase BDNF expression in the hippocampus, stimulating AHN, and accelerate the maturation of immature ABNs (Ma et al., 2017; Yamada and Jinno, 2019). Indeed, the influence of ketamine on AHN could be mostly associated with its sustained antidepressant activation; whereas synaptogenesis and neural plasticity, especially in the medial prefrontal cortex, appear to have a prominent role in the early phases of ketamine's actions (Duman et al., 2016, 2019; Ma et al., 2017; Rawat et al., 2022, 2024).

On the other hand, decreased neurogenesis has been implicated in depression and anxiety disorders in a large number of animal and human studies (Berger et al., 2020; Schoenfeld et al., 2017; Tartt et al., 2022; Wu et al., 2019) (Table 1). Various animal models, including acute psychosocial stress, unpredicted chronic mild stress (UCMS), and predator intruder stress paradigms, have been widely employed to evaluate the level of AHN in the context of depression, consistently showing its suppression (Du Preez et al., 2021; Van Bokhoven et al., 2011; Wu et al., 2019). In human studies, multiple studies using magnetic

Table 1. Selected publications showing the effect of stress/depression or antidepressant treatment on neurogenesis

Animal models				
	Species	Model	Effects on neurogenesis	References
Stress/Depression				
	tree shrews	acute psychosocial stress	decrease cell proliferation in the DG	Gould et al., 1997
	marmoset monkeys	resident-intruder stress test	decrease cell proliferation in the DG	Gould et al., 1998
	tree shrews	chronic psychosocial stress	decrease cell proliferation and survival in the DG	Czeh et al., 2002
	rats	acute/chronic restraint stress	acute restraint did not change, while chronic restraint suppressed the cell proliferation in the DG	Pham et al., 2003
	mice	CMS	decrease cell proliferation in the DG	Alonso et al., 2004
	tree shrews	chronic psychosocial stress	decrease cell proliferation in the DG	Simon et al., 2005
	mice	resident-intruder stress test	decrease cell proliferation in the DG	Mitra et al., 2006; Yap et al., 2006
	rats	acute psychosocial stress	decrease short-term survival and long-term survival of ABNs	Thomas et al., 2007
	mice	UCMS	decrease cell proliferation in the DG not SVZ	Surget et al., 2008
	mice	CORT chronic administration	decrease cell proliferation in the DG	David et al., 2009
	rats	UCMS	decrease cell proliferation, induce atrophy of dendrites of GCs in the DG without influencing the density of spines in the dendrites of the GCs	Bessa et al., 2009
	mice	CSDS	transiently decrease SGZ cell proliferation (normalized 24 h later)	Lagace et al., 2010
	mice	CSDS	decrease SGZ cell proliferation and the number of 4-week-old newborn ABNs	Surget et al., 2011
	rats	CSDS	the number of DCX+ immature neurons with long dendrites was reduced even 12 weeks after the defeat stress	Van Bokhoven et al., 2011
	mice	CSDS	decrease the survival and dendritic complexity of ABNs	Chen et al., 2015a

(Continued on next page)



**Table 1. Continued**

Animal models				
	Species	Model	Effects on neurogenesis	References
	mice	UCMS	do not impact the total DCX cells or the maturation index in the total hippocampus, while decreasing the number of DCX cells in the dorsal hippocampus	Planchez et al., 2021
	mice	neuropathic pain	manifestation of anxiety- or depressive-like behavior co-occurs with decreased survival of newly generated cells, but not with impaired proliferative activity or reduced number of immature neurons	Somelar et al., 2021
	mice	UCMS	reduced neurogenesis in the DG	Du Preez et al., 2021
Antidepressant				
fluoxetine, tranylcypromine, reboxetine	rats	–	increase cell proliferation in the DG, not SVZ, without altering the fate of ABNs	Malberg et al., 2000
fluoxetine	mice	–	increase cell proliferation in the DG without altering the fate of ABNs	Santarelli et al., 2003
fluoxetine, olanzapine	rats	–	increase cell proliferation in the DG	Kodama et al., 2004
agomelatine	rats	–	increase cell proliferation in the DG and survival of newly generated ABNs	Banasr et al., 2006
fluoxetine	mice	–	induce the proliferation of dividing type 2 and type 3 progenitor cells but ineffective on stem cells (type 1)	Encinas et al., 2006
fluoxetine	mice	UCMS	increase cell proliferation in the DG, not SVZ, in UCMS-treated mice	Surget et al., 2008
fluoxetine	mice	–	increase cell proliferation, stimulate dendritic and functional maturation of ABNs	Wang et al., 2008
fluoxetine	mice	–	increase cell proliferation when chronic fluoxetine treatment was initiated during adolescence	Navailles et al., 2008
fluoxetine	mice	CORT chronic administration	increase cell proliferation, survival, and dendritic maturation in CORT-treated mice, but not in non-CORT-treated mice	David et al., 2009

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Table 1. Continued

Animal models				
	Species	Model	Effects on neurogenesis	References
fluoxetine, imipramine, CP156,526 or SSR1494515	rat	UCMS	increase cell proliferation and attenuate dendritic atrophy in the DG in UCMS mice	Bessa et al., 2009
tianeptine	tree shrews	chronic psychosocial stress	reverse the effects of stress on SGZ proliferation	Czeh et al., 2002
SSR125543A, SSR149415 and fluoxetine	mice	CMS	reverse the reduction of cell proliferation produced by CMS	Alonso et al., 2004
fluoxetine	mice	UCMS	counteract the downregulating effects of UCMS on cell proliferation and the number of 4-week-old newborn ABNs	Surget et al., 2011
fluoxetine, R1219119, lithium	rats	–	lithium, but not fluoxetine or the CRF1 antagonist R121919, increases cell proliferation in the DG	Hanson et al., 2011
Human studies of depression				
Diseases/cases	Sex	Population assessed	Effect on neurogenesis	References
untreated MDD; SSRI-treated MDD; TCA-treated MDD; control	male and female	depressed patients postmortem	both antidepressant classes increase cell proliferation over untreated depressed patients and controls	Boldrini et al., 2009
MDD; control	male and female	depressed patients postmortem	decreased numbers of progenitor cells, while no response to ADs was found in depressed patients	Lucassen et al., 2010
untreated MDD; SSRI-treated MDD; TCA-treated MDD; control	male and female	depressed patients postmortem	both antidepressant classes increase cell proliferation over untreated depressed patients and controls	Boldrini et al., 2012
untreated MDD; SSRI-treated MDD; TCA-treated MDD; control	male and female	depressed patients postmortem	depression is associated with a decreased number of GCs, correlated with reduced DG volume. SSRI and TCA treatment increase granule neuron number and DG volume	Boldrini et al., 2013
MDD; control	male and female	depressed patients postmortem	no significant difference in number of granule cells between depressed subjects and controls	Cobb et al., 2013
MDDsui with ELA; MDDsui without ELA; control with ELA; control without ELA	male and female	depressed and resilient patients postmortem	Depression is associated with smaller DG and a decreased number of GCs; resilience to ELA is related to a larger DG and perhaps more neurogenesis	Boldrini et al., 2019
Abbreviations: CMS, chronic mild stress; UCMS, unpredicted chronic mild stress; DG, dentate gyrus; SVZ, subventricular zone; GCs, granule cells; ABNs, adult-born neurons; SGZ, subgranular zone; CSDS, chronic social defeat stress; CORT, corticosterone; CRF1, corticotropin-releasing factor receptor 1; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; ADs, antidepressants; ELA, early life adversity; MDDsui, suicide decedents with MDD.				



**Table 2. The functional importance of AHN in antidepressant efficacy of antidepressants**

Approaches	Species	Time of interventions	Model	Antidepressants	Key findings	References
Irradiation	mice	ADs were given for 27 days (day1–27); X-irradiation was given on days 1, 4, and 8; and behavioral tests were conducted on day 28	—	fluoxetine, imipramine, desipramine, haloperidol	no significant differences compared with controls; reversed the effects of ADs in NSF paradigm and UCMS	Santarelli et al., 2003
X-irradiation	mice	chronic fluoxetine was administered in the drinking water for 28 days; mice underwent irradiation on days 1, 4, and 7 of fluoxetine treatment; and behavioral tests were performed on days 30 and 31	—	fluoxetine	immobility in the FST was unaltered by irradiation; the effects of fluoxetine on immobility in the FST were not altered by irradiation	Holick et al., 2008
Irradiation	mice	animals were exposed to X-irradiation 5 weeks before UCMS (5 weeks); fluoxetine was administrated daily from the 3rd week of UCMS; and behavioral test was conducted after the completion of UCMS	UCMS	fluoxetine, imipramine, SSR125543, and SSR149415	1) no effect on animals' sensitivity to UCMS in several behavioral assays (splash test, NSF test); 2) completely blocked the effects of monoaminergic ADs but did not prevent most effects of CRF1 and the V1b antagonists	Surget et al., 2008
Transgenic mice TrkB:hGFAP: TrkB knockout in hippocampal neural progenitors (NPC)	mice	—	—	fluoxetine, imipramine	no significant differences compared with controls; insensitive to anti-depressive treatment in depression-like (TST) and anxiety-like (NSF) paradigms	(Li et al., 2008)
X-irradiation	mice	Mice were allowed 8–12 weeks to recover from irradiation before behavioral tests	—	Fluoxetine	no significant differences compared with controls; reversed the effects of fluoxetine in NSF paradigm	Wang et al., 2008
X-irradiation	mice	focal hippocampal X-irradiation was given before the start of CORT regimen (7 weeks); ADs were given during the last 3 weeks of CORT; behavioral tests were performed after the cessation of CORT	CORT chronic administration	fluoxetine, imipramine	1) no effect on animals' sensitivity to chronic CORT in several behavioral assays (OFT, NSF, and FST); 2) reversed the effects of ADs in NSF paradigm, but not in the OFT and FST	David et al., 2009

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Table 2. Continued

Approaches	Species	Time of interventions	Model	Antidepressants	Key findings	References
MAM	rat	UCMS was used for 6 weeks to induce core symptoms of depressive-like behaviors in rats; during the last 2 weeks of UCMS, ADs were administered daily combined with MAM; and behavioral tests were performed at the end of UCMS protocol	UCMS	fluoxetine, imipramine, CP156526, or SSR1494515	1) no effects in FST and sucrose preference increased latency to feed in NSF in UCMS mice; 2) reversed the effects of ADs in NSF (anxiety-related behavior), while not influencing the effects in sucrose preference and FST (depression-related behavior) in UCMS mice	Bessa et al., 2009
X-irradiation	mice	animals were exposed to X-irradiation 5 weeks before UCMS (6–8 weeks); fluoxetine was administrated daily from the 3rd week of UCMS, behavioral test was conducted after the completion of UCMS	UCMS	fluoxetine, SSR125543	1) not directly involved in the emergence of a depression-like state; 2) reversed the recovery effects of fluoxetine in UCMS mice in the cookie test as well as the sensitivity of the GCL network to novelty/glucocorticoid effects; 3) the effects of CRF1 antagonist SSR125543 were not abolished	Surget et al., 2011
MAM	mice	MAM was co-administrated with ADs during the last 2 weeks of the UCMS protocol (6 weeks), then behavioral tests were performed 1 month after the completion of UCMS	UCMS	fluoxetine, imipramine	1) precluded long-term recovery from anhedonic signs induced by ADs in the sucrose consumption test; 2) do not influence recovery from learned helplessness induced by ADs in FST; 3) attenuated fluoxetine-induced recovery from anxiety-like behavior in EPM and NSF tests, while not influenced imipramine	Mateus-Pinheiro et al., 2013
Chemogenetics, Ascl1-hM4Di transgenic mice	mice	after TAM administration (5 days), mice received 3 weeks of daily injection of fluoxetine or saline with or without chronic CNO supplementation in the drinking water, then behavioral tests were performed	—	fluoxetine	CNO reversed the effects of fluoxetine (decreased immobility in the TST, increased the distance traveled in the center of the OF)	Tunc-Ozcan et al., 2019

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Table 2. Continued

Approaches	Species	Time of interventions	Model	Antidepressants	Key findings	References
Chemogenetics, Ascl1-hM4Di transgenic mice	mice	after TAM administration (5 days), hM4Di mice underwent UCMS for 3 weeks followed by treatment with vehicle or CNO and either saline or ketamine	UCMS	ketamine	1) CNO reversed the behavioral change in ketamine-treated mice (increased social interaction ratio, increased preference for novelty, and decreased time immobile) at baseline but had no effect in saline-treated mice group; 2) CNO reversed the behavioral change (increased sociability and preference for novelty, decreased immobility) in ketamine-treated UCMS mice	Rawat et al., 2022

Abbreviations: ADs, antidepressants; NSF, novel-suppressed feeding; CMS, chronic mild stress; UCMS, unpredicted chronic mild stress; CORT, corticosterone; TST, tail suspension test; OFT, open field test; FST, forced swimming test; GCL, granule cell layer; CRF1, corticotrophin-releasing factor 1; V1b, vasopressin 1b; TAM, tamoxifen.

resonance imaging (MRI) have reported decreased hippocampal volume associated with depression (Campbell et al., 2004; Frodl et al., 2002; Huang et al., 2013), which may indirectly reflect altered AHN. Additional evidence from postmortem human studies using immunohistochemistry has provided further support for the alteration of AHN in depression (Boldrini et al., 2019; Lucassen et al., 2010). Emerging techniques, particularly sc/snRNA-seq, hold great promise for dissecting the cellular diversity and gene expression dynamics within the human DG, thus providing a comprehensive understanding of human AHN in depression/anxiety in the near future.

However, it remains unclear whether these changes are a cause or consequence of the disorder. Ablating neurogenesis in healthy experimental animals often failed to induce depressive phenotypes (Hill et al., 2015; Mateus-Pinheiro et al., 2013; Petrik et al., 2012); only a few studies in mice following acute and chronic stress have shown that abolition of AHN can induce depressive-like symptoms (Mateus-Pinheiro et al., 2013; Snyder et al., 2011) (Table 3). Using transgenic and radiation methods to decrease adult neurogenesis, Snyder et al. found that neurogenesis-deficient mice showed more severe depressive behaviors after acute stress, and their glucocorticoid levels were slower to recover after moderate stress compared with mice with intact neurogenesis (Snyder et al., 2011). Selectively activating newborn ABNs was reported to mimic the effects of fluoxetine, reversing the adverse effects of UCMS, indicating a direct protective role of ABNs in depression (Tunc-Ozcan et al., 2019). Thus, impairment of AHN may not be sufficient to induce a depression phenotype but could act as a risk factor, contributing to depression when concomitant with stressful experiences.

Epilepsy

Epilepsy is a multifarious and deliberating disease, characterized by hypersynchronous or excessive spontaneous recurrent seizures (SRSs), affecting ~1% of the population (Collaborators, 2019; Devinsky et al., 2018; Thijs et al., 2019). Epileptogenesis is usually triggered by an initial epileptogenic insult, such as status epilepticus (SE), stroke, or head trauma. This is followed by a prolonged latent period, lasting for months to years before the onset of SRS. During this latency, a variety of cellular changes including neurogenesis often occur in the hippocampus. It has been found that even a single injection of pilocarpine or kainic acid (KA) can cause a robust increase in the proliferation of neural progenitors in the DG (Nakagawa et al., 2000; Parent et al., 1997; Scott et al., 1998). However, this increased AHN after acute seizures decreases sharply following the initial seizure episode as reported in both animal and human studies (Ammothumkandy et al., 2022; Chen et al., 2023; Hattiangady et al., 2004; Heinrich et al., 2006). These findings indicate a transient increase

Table 3. The role of AHN in depressive and anxiety-like disorders

Approaches	Species	Time of interventions	Model	Influence on depression/ anxiety/stress resilience	Performance in behavioral models	References
Increase						
Irradiation	mice	X-irradiation was given on day 1, 4, 8 and behavioral tests were conducted on day 28	—	no effects on anxiety and depression-related behavior	no effects on anxiety and depression-related behavior in NSF and unpredicted chronic stress tests	Santarelli et al., 2003
Irradiation	mice	mice underwent irradiation on day 1, 4 and 7 and behavioral tests were performed on days 30 and 31	—	no effects on depression-related behavior	immobility in the FST was unaltered by irradiation	Holick et al., 2008
Irradiation	mice	animals were exposed to X-irradiation 5 weeks before UCMS (5 weeks), behavioral test was conducted after the completion of UCMS	UCMS	no effects on baseline anxiety and depression-related behavior; no effects in UCMS mice	no effects on anxiety and depression-related behaviors (splash test and NSF test) at baseline and in UCMS mice	Surget et al., 2008
Irradiation	mice	focal hippocampal X-irradiation was given before the start of CORT regimen (7 weeks), ADs were given during the last 3 weeks of CORT, behavioral tests were performed after the cessation of CORT	CORT chronic administration	no effects on baseline anxiety and depression-related behavior; no effects in chronic CORT treated mice	no effects on anxiety and depression-related behaviors (OFT, NSF and FST) at baseline and in chronic CORT treated mice	David et al., 2009
MAM	rat	UCMS was used for 6 weeks to induce core symptoms of depressive-like behaviors in rats, MAM was administered during the last 2 weeks of UCMS, behavioral tests were performed at the end of UCMS protocol	UCMS	no effects on anxiety and depression-related behavior in FST and sucrose preference; increase the latency to feed in NSF	1) no effects in FST, while increasing the latency to feed in NSF at baseline; 2) no effects in FST and sucrose preference, increased latency to feed in NSF in UCMS mice	Bessa et al., 2009
Transgenic mice: rtTA-Bax	mice	doxycycline was added to the drinking solution starting 6 weeks before behavioral testing	—	increased anxiety-related behaviors, but no changes in the FST or food avoidance in NSF	1) increased the time spent in the open arms in EPM test and longer latencies to emerge from the protective cylinder in the light/dark emergence test; 2) the latency to feed in NSF and immobility time in TST was unaltered	Revest et al., 2009

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Table 3. Continued

Approaches	Species	Time of interventions	Model	Influence on depression/ anxiety/stress resilience	Performance in behavioral models	References
Irradiation	mice	irradiation was given 4 weeks before social defeat and behavioral tests were performed thereafter	CSDS	inhibited stress-induced social avoidance	1) no effects on social avoidance, passive avoidance or juvenile interaction behavior at baseline; 2) irradiated mice were unsusceptible to defeat stress and did not display social avoidance compared with sham-irradiated mice	Lagace et al., 2010
Transgenic mice: GFAP-TK	mice	mice were treated with GCV chow for 12 weeks before behavioral tests	restraint	no effects on baseline anxiety and depression-related behavior; more severe anxiety- and depressive-like behaviors in response to stress	1) increased food avoidance in an NSF test after acute stress (restraint), similar feeding latencies under normal conditions; 2) increased behavioral despair in the FST at baseline; 3) decreased sucrose preference after restraint, similar preference at baseline	Snyder et al., 2011
X-irradiation	mice	animals were exposed to X-irradiation 5 weeks before UCMS (6–8 weeks), fluoxetine was administered daily from the 3rd week of UCMS, behavioral test was conducted after the completion of UCMS	UCMS	no effects on baseline depression-like state; no effects in UCMS mice	no effects on baseline depression-like state (cookie test) at baseline and in UCMS mice	Surget et al., 2011
MAM	mice	mice were administered with MAM for 2 weeks, then rest for 4 weeks before behavioral tests	—	elicited signs of depression and anxiety	reduced sucrose preference, increased immobility in the FST, increased latency to feed in the NSF test, increased percentage of time spent in the open-arm in the EPM test	Mateus-Pinheiro et al., 2013
Transgenic mice: Norbin KO	mice	all behavioral studies were performed using adult (3- to 6-month-old) male mice	—	elicited depressive-like behaviors	increased immobility in the FST and TST, reduced sucrose preference	Wang et al., 2015a
Decrease						

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Table 3. Continued

Approaches	Species	Time of interventions	Model	Influence on depression/ anxiety/stress resilience	Performance in behavioral models	References
Transgenic mice iBax: inactivation of the pro-apoptotic Bax gene in nestin-positive cells	mice	mice were injected with either vehicle or TAM for 5 consecutive days, 6 weeks before behavioral testing	CORT chronic administration	no effects on baseline anxiety and depression-related behavior; reduced anxiety and depression-related behavior in mice treated chronically with CORT	no effects on anxiety and depression-related behaviors (OPT, EPM, and TST); reversed the effects of CORT in the OPT, EPM, and TST	(Hill et al., 2015)
Transgenic mice iBax	mice	a 10-week UCMS model was used; in the 3rd week of UCMS, mice were treated with TAM or vehicle; in the 8th week of UCMS, behavioral tests were performed; CORT was assessed 3 days before the end and on the last day of the UCMS protocol	UCMS	increased stress resilience after exposure to chronic stress in some behavioral paradigms and decreased elevated basal CORT levels	1) no effects on anxiety and depression-related behaviors (splash test and NSF test) at baseline; 2) improve the coat state of animals exposed to UCMS, reduce the time spent in the dark box of the light- dark box test, lower the heightened basal corticosterone levels in mice exposed to UCMS; lack of significant differences in locomotor activity and in the sucrose preference test	Culig et al., 2017
Transgenic mice iBax	mice	mice were treated with TAM for 1 week, then after 6 weeks they were subjected to a chronic version of social defeat stress paradigm (10 days), behavioral tests were performed thereafter	a 10-day chronic social-defeat paradigm	reversed the chronic social defeat-induced social avoidance and anxiety-like behavior	while chronic defeat for 10 days produced robust social avoidance and anxiety- like behavior, defeated iBax mice with increased neurogenesis showed control levels of social interaction and center exploration in the OFT	Anacker et al., 2018
Administration of the small molecule XAV939	mice	30 days after the induction of XAV939 administration, behavioral tests were performed	—	ameliorated some depression- like behavior (learned helplessness)	exhibited significantly less immobility in the FST; no obvious difference from control mice in motor or exploratory activity in the OFT and sucrose preference test	Chen et al., 2019b
		mice were exposed to CRS for 7.5 h/day for 50 days, XAV939 was administered from the 15th day, behavioral tests were performed 30 days after the induction of XAV939	CRS	buffered stress-induced depression-like behaviors, mimicking the antidepressant effects of fluoxetine	XAV939-treated mice exhibited reduced latency to feed in the NSF, increased sucrose consumption in the sucrose preference test, and reduced immobility in the FST	

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Table 3. Continued

Approaches	Species	Time of interventions	Model	Influence on depression/ anxiety/stress resilience	Performance in behavioral models	References
Transgenic mice iBax	mice	mice received five consecutive injections of TAM and were housed in an enriched environment for 4 weeks, and then underwent UCMS protocol for 4 weeks before behavioral testing	UCMS	promoted stress resilience on some stress-induced depressive-like symptoms	1) not sufficient to prevent the coat state degradation induced by UCMS; 2) not sufficient to prevent UCMS-induced increased frequency and time spent in the dark box; 3) prevented UCMS-induced increased immobility in TST; 4) promoted nest-building and increased entries in the dark box at baseline	Planchez et al., 2021
Transgenic mice tph2-BDNF:overexpress BDNF in serotonergic neurons	mice	6 weeks after TAM (5 days), mice were exposed to CSDS (10 days) and then behavioral tests were performed	CSDS	no effects on baseline depressive-like behavior in the FST but increased social interaction; reversed CSDS-induced depressive-like behavior, mimicking the antidepressant effect of fluoxetine	displayed similar degree of immobility as WT animals treated with fluoxetine after CSDS; reversed reduction of social interaction after CSDS	Leschik et al., 2022
Activation						
Chemogenetics, Ascl1-hM3Dq transgenic mice	mice	3 weeks after TAM (5 days), the effects of acute activation of newly generated ABNs with CNO were evaluated in behavioral tests; CNO was injected 2 h before behavioral testing	—	acute activation of newly generated ABNs led to behavioral phenotypes similar to fluoxetine treatment	CNO-treated hM3Dq mice showed decreased total immobility in TST and increased exploration in the center of the OFT chamber	Tunc-Ozcan et al., 2019
		after TAM (5 days), mice were exposed to 3 weeks of UCMS and then evaluated behaviorally with or without acute CNO treatment	UCMS	sufficient to promote stress resilience	CNO-treated UCMS mice exhibited control levels of total immobility in the TST and center exploration in the OFT	
Retrovirus expressing Cre recombinase in combination with AAV-hM3Dq or hM4Di	mice	6 weeks after the injection of virus cocktail, clozapine was administered for 9 days before the behavioral tests	—	induced anxiety-like behavior but not depression-like behaviors	significantly decreased the time spent in the center in OFT and the entire into the open arms in EPM but had no effect on the total immobile time in TST and the total traveled distance in OFT	Wang et al., 2021a

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Table 3. Continued

Approaches	Species	Time of interventions	Model	Influence on depression/ anxiety/stress resilience	Performance in behavioral models	References
Chemogenetics, Ascl1-hM3Dq transgenic mice	mice	mice were treated with TAM for 5 days, 2 days after TAM injections, hM3Dq mice were exposed to UCMS for 21 days, then mice were given a single dose of either CNO, ketamine, or vehicle 24 h prior to behavioral tests	UCMS	mimicked the antidepressant effects of ketamine	increased preference for social interaction and novelty and decreased immobile time in TST	Rawat et al., 2022
Inhibition						
Chemogenetics, Nestin-hM4D transgenic mice	mice	mice were treated with TAM for 1 week, then cannula-mediated delivery of CNO was given directly into the vDG every day during the 5-day subthreshold social-defeat paradigm, behavioral tests were performed thereafter	5-day subthreshold social-defeat paradigm	promoted susceptibility to social defeat stress	not sufficient to alter behavior at baseline; resulted in robust avoidance of a novel mouse in a social interaction test and reduced center exploration in the OF in defeated hM4D mice	Anacker et al., 2018
Chemogenetics, Ascl1-hM4Di transgenic mice	mice	after TAM administration (5 days), mice received 3 weeks of daily injection of saline with or without chronic CNO supplementation in the drinking water, then behavioral tests were performed	—	elicited signs of depression and anxiety	CNO treatment of hM4Di increased immobility in the TST, reduced the distance traveled in the center of the OF chamber	Tunc-Ozcan et al., 2019
Abbreviations: NSF, novel-suppressed feeding; UCMS, unpredicted chronic mild stress; FST, forced swimming tests; GCV, ganciclovir; CORT, corticosterone; OFT, open field test; SUM, supramammillary nucleus; EPM, elevated plus maze; TST, tail suspension test; BDNF, brain-derived neurotrophic factor; CSDS, chronic social defeat stress; CRS, chronic restraint stress; TAM, tamoxifen.						





of AHN after seizures. According to Sierra et al., the long-term decline in neurogenesis may be explained by the “exhaustion” of the NSC pool or alterations in the neurogenic niche (Sierra et al., 2015). In addition, AHN is differently regulated by the severity of seizures, including the frequency of convulsive seizures and the extent of seizures as well as the developmental state of the brain at the time of initial seizure induction (Mohapel et al., 2004; Shi et al., 2007; Xiu-Yu et al., 2007).

Apart from the quantitative changes in neurogenesis after acute SE, significant qualitative alterations have also been reported (Chen et al., 2020c). Retroviral fluorescent protein labeling of proliferating neuroblasts and their progeny has been used as a successful strategy to enable detailed morphological analysis. Different from ABNs born under physiological conditions, which typically extend a single dendrite arising from the apical portion of the cell body branching into the outer GCL or inner ML, seizure-generated ABNs tend to develop additional basal dendrites extending toward the hilus (known as hilar basal dendrites, HBDs) (Ribak et al., 2000; Shapiro et al., 2005). The morphological features of these newborn ABNs (varying degrees of HBD formation) depend on their stage of neuronal maturation, especially their specific age relative to SE induction (Jessberger et al., 2007; Kron et al., 2010; Walter et al., 2007). Moreover, ABNs with HBDs were reported to have reduced dendritic spine density and received significant recurrent inputs from neighboring DGCs, as evidenced by both anatomical and electrophysiological studies (Kelly and Beck, 2017; Murphy et al., 2011; Ribak et al., 2000; Shapiro et al., 2008). These findings suggest that ABNs may contribute to epileptogenesis.

Another notable qualitative alteration is the generation of ectopic ABNs. They are born after SE and migrate to the hilus after maturation instead of the GCL, which is a normal position for the newborn ABNs (Hattiangady et al., 2004; Parent et al., 1997; Shapiro et al., 2008). Similar ectopically located ABNs have also been observed in the epileptic human hippocampus (Parent et al., 2006). Accompanying with their aberrant location, these hilar ectopic ABNs exhibit distinct electrophysiological properties compared to their normotopic counterparts. For example, intracellular recordings from pilocarpine-treated rats showed that hilar “granule-like” neurons burst synchronously with CA3 pyramidal cells, a phenomenon not observed between normal DGCs and CA3 pyramidal cells in non-epileptic animals (Scharfman et al., 2000). Additionally, electrophysiological studies demonstrated that these hilar ectopic ABNs showed higher ratios of excitatory to inhibitory inputs than normal DGCs (Althaus et al., 2015; Zhan et al., 2010). Although the appearance of hilar ectopic newborn ABNs varies depending on the seizure model used (Jakubs et al., 2006), indicating that they may

not be necessary for epileptogenesis, they are generally considered to play a pro-epileptic role (Scharfman et al., 2002). While intriguing, current findings are based solely on correlation studies, and direct evidence for their functional significance remains lacking due to the absence of selective methods to manipulate hilar ectopic ABNs (Hester and Danzer, 2013; Zhou et al., 2019).

With the development of technologies to manipulate the level of AHN and modulate the activity of ABNs, accumulating evidence from both animal models and human studies supports a critical role for AHN in epilepsy (Table 4). Initially, unselective antimitotic agents and X-irradiation were commonly used, yielding conflicting results. Suppressing AHN was found to accelerate epileptogenesis in a kindling model (Raedt et al., 2007), reduce SRSs in a pilocarpine-induced TLE model (Jung et al., 2004, 2006), and show no effects sometimes (Iyengar et al., 2015; Pekcec et al., 2011; Zhu et al., 2017). Negative results could potentially be attributed to factors including off-target effects, toxic effects of antimitotic drugs, and insufficient reduction of neurogenesis; however, they may also be attributed to the heterogeneity of ABNs. Indeed, due to the heterogeneous and dynamic nature of ABNs, the reported conflicts of their effects are not unexpected. The use of non-selective techniques to manipulate may further obscure the precise functional roles of ABNs, highlighting the need for more refined and selective approaches.

Recently, advances in transgenic mouse models have provided more selective methods to manipulate and investigate the role of ABNs in epilepsy. For instance, Cho et al. used a transgenic mouse model to block neurogenesis 1 month prior to SE induction and observed a significant reduction in SRS, along with improved cognitive function (Cho et al., 2015). Subsequently, Varma et al. performed continuous and concurrent ablation of seizure-induced neurogenesis for over 4 weeks following SE, which is a clinically relevant time period, and also found a reduction in SRS (Varma et al., 2019). Interestingly, Jain et al. also reported a reduction in chronic seizures after selectively increasing nestin-expressing progenitors 6 weeks prior to the pilocarpine-induced SE (Jain et al., 2024). These findings further indicated the need for a more comprehensive view of the heterogeneous roles of ABNs generated at different time points relative to epileptogenesis. Meanwhile, similar to antimitotics, using these approaches to ablate ABNs may also disrupt the formation of their native neural circuits during development of epilepsy.

In contrast, optogenetic and chemogenetic methods provide inducible, reversible, and spatially/temporally precise interventions to modulate the activity of ABNs, making them more suitable for dissecting functional roles without permanently altering the neurogenic niche. Zhou et al.

Table 4. Functional relevance of adult neurogenesis in epilepsy

Species	Animal models	Interventions	Timepoints of intervention	Findings	References
Rat	pilo-induced epilepsy	inhibition of neurogenesis by antimitotic Ara-C	from 1 day before SE for 14 days	reduced frequency and duration of seizures no obvious difference of neuronal damage	Jung et al., 2004
Rat	pilo-induced epilepsy	inhibition of neurogenesis by COX-2 inhibitor	from 1 day after SE to 14 or 28 days after SE	reduced frequency and duration of seizures neuroprotective effect	Jung et al., 2006
Rat	hippocampal kindling model	inhibition of neurogenesis by radiation	1 day before starting kindling	decreased ADT and developed more severe seizure more rapidly	Raedt et al., 2007
Mouse	KA-induced epilepsy	inhibition of neurogenesis by Levetiracetam	from 1 day after SE for 25 days	decreased the mean duration of seizures 58 days later	Sugaya et al., 2010
Rat	amygdala kindling model	inhibition of neurogenesis by radiation	1 day before starting kindling	no effects on kindling acquisition and kindled seizures	Pekcec et al., 2011
Mouse	pilo-induced epilepsy	genetic ablation of neurogenesis (Nestin-TK)	GCV for 4 weeks until injection of Pilo	reduced frequency of SRS; restored cognitive function	Cho et al., 2015
Mouse	KA-induced epilepsy	reduction of neurogenesis by X-irradiation or genetic ablation (GFAP-TK)	from 6 weeks of age (3 doses of X-irradiation, 3 days between doses) followed by KA 7 weeks later from 6 weeks of age (VGCV for 6 weeks) followed by KA 2 weeks later	increased the acute effects of KA (decrease in the latency to the first convulsive seizure, increased number, duration and mortality)	Iyengar et al., 2015
Mouse	pilo-induced epilepsy	genetic ablation of neurogenesis (NestinCreER ^{T2} ::DTr)	from 3 weeks of age for 4 weeks (tamoxifen, weekly), followed by pilocarpine 1 week later DT began the 3rd day after SE daily for 5 days	reduced seizure frequency increased seizure duration	Hosford et al., 2016
Mouse	pilo-induced epilepsy	inhibition of neurogenesis by MAM	both 4 weeks ahead of and after SE with intervals of 48 h for 4 weeks	ectopic GCs, MFS, and HBDs were eliminated no alterations in frequency, duration, and severity	Zhu et al., 2017
Rat	pilo-induced epilepsy	inhibition of neurogenesis by ephrin-B3	from 7 days after SE for 7 days	reduced seizure frequency reduced amplitudes and mean duration of EEG seizures	Liu et al., 2018

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**Table 4. Continued**

Species	Animal models	Interventions	Timepoints of intervention	Findings	References
Mouse	pilo-induced epilepsy	chemogenetic excitation/ inhibition of newborn neurons (RV-hM3Dq/RV-hM4Di)	3 days after SE, RV-hM4Dq/hM3Di injected 2.5 months later, EEG recording, 1–3 days baseline, 4–6 CNO	Inhibition reduced epileptic spikes and SRS activation increased epileptic spikes and SRS	Zhou et al., 2019
Mouse	pilo-induced epilepsy	genetic ablation of neurogenesis (Nestin-TK)	GCV for 4 weeks post-SE, EEG recording from 5 to 7 weeks post- SE GCV for 8 weeks post-SE, EEG recording from 5 to 7 weeks post- SE or EEG recording from 18 weeks to 20 weeks post-SE	4 weeks of ablation, no effect on SRS frequency or duration 8 weeks of ablation, 65% reduction of SRS frequency, last for 10 days	Varma et al., 2019
Mouse	pilo-induced epilepsy	suppression: genetic ablation of neurogenesis (GFAP-TK) enhancement: conditional deletion of pro-apoptotic gene Bax in Nestin-expressing progenitors	starting at 6 weeks of age, chow containing VGCV for 6 weeks, pilo was injected at 15 weeks of age; starting at 6 weeks of age, tamoxifen for 4 consecutive days, 6 weeks after the last tamoxifen injection, pilo was injected	pilo-induced SE was longer and neuronal damage was greater SE shorter and less neuronal damage	Jain et al., 2019
Mouse	hippocampal kindling model and KA-induced epilepsy	optogenetic/chemogenetic excitation/inhibition of newborn neurons (pUX-ChR2/Arch/hM4D)	3 days after fully kindled, 3 weeks after fully kindled, 1 week before fully kindled, pUX-ChR2/Arch was injected; 7 days after SE, pUX- hM4D was injected	activation of ABNs born at 3 days after fully kindled prolonged ADD, inhibition curtailed ADD; activation/inhibition of ABNs born at 3 weeks after or 1 week before fully kindled, no effect on ADD; inhibition of ABNs generated 7 days after SE, reduced SRS and ADD	Chen et al., 2023
Mouse	PTZ-induced epilepsy model	optogenetic/chemogenetic excitation/inhibition of newborn neurons (pUX-ChR2//hM4D)	4 weeks before PTZ-induced seizure induction	activation of ABNs generated 4 weeks before seizure induction reduced seizure susceptibility	Li et al., 2024b
Mouse	pilo-induced epilepsy model	conditional deletion of pro- apoptotic gene Bax in Nestin- expressing progenitors	6 weeks before pilo-induced SE	selective Bax deletion increases ABNs, reduces experimental epilepsy, and the effects show a striking sex difference	Jain et al., 2024

Abbreviations: pilo, pilocarpine; Ara-C, antimitotic agent cytosine- β -D-arabinofuranoside; SE, status epilepticus; KA, kainic acid; ADT, after discharge threshold; SRS, spontaneous recurrent seizures; GCV, ganciclovir; PTZ, pentylenetetrazol; ADD, after discharge duration; ABN, adult-born neuron; HBD, hilar basal dendrite; MAM, methylazoxymethanol acetate; MFS, mossy fiber sprouting.



found that chemogenetic silencing of newborn ABNs generated acutely post-SE induction reduced both epileptic spikes and SRs, revealing an essential role for newborn ABNs in the production of epileptic spikes and SRs (Zhou et al., 2019). Moreover, our recently published work supported the role of newborn ABNs in seizure maintenance and provided direct evidence for the downstream circuit mechanism underlying pro-epileptic role of newborn ABNs generated acutely after seizures (Chen et al., 2023). In contrast, our subsequent work demonstrated a protective role for ABNs generated under enriched environment (EE), highlighting the heterogeneity of ABNs (Li et al., 2024b). Further studies are still in need to precisely distinguish the detrimental and protective ABNs, assisted by advances in neuro-technologies.

Alzheimer disease

Alzheimer disease (AD), a leading cause of dementia, is characterized by progressive neuronal cell death, atrophy of specific brain areas, and histopathological hallmarks. These include the extracellular senile plaques containing β -amyloid peptide (A β), derived from amyloid precursor protein (APP), and intracellular neurofibrillary tangles composed of hyperphosphorylated Tau protein (Mufson et al., 2016; Scheltens et al., 2021; Viola and Klein, 2015). These pathological alterations lead to progressive neuronal dysfunction and degeneration, resulting in severe cognitive deficits.

In human brains, the number of DCX-positive cells was found to decrease with age (Boldrini et al., 2018; Moreno-Jimenez et al., 2019). Thus, in neurodegenerative diseases like AD, AHN has been speculated to decline earlier and more rapidly in AD patients. However, findings from both human and animal studies have been contradictory (Lazarov et al., 2024; Salta et al., 2023). In human studies, early studies of AHN reported an increase in AHN in AD patients (Jin et al., 2004b; Ziabreva et al., 2006), indicating a compensatory mechanism. However, more recent studies have suggested a predominant decrease in AHN in AD patients (Crews et al., 2010; Moreno-Jimenez et al., 2019; Tobin et al., 2019). For instance, using high-quality, short PTD samples, Tobin et al. reported a significant decrease in the number of DCX/PCNA-colabeled neuroblasts in individuals with both mild cognitive impairment and AD (Tobin et al., 2019). Additionally, the decrease was also confirmed by employing single-cell transcriptomics in the AD human postmortem DG (Zhou et al., 2022). Indeed, the controversy can at least partly be blamed on different staining methodologies and inconsistency in postmortem human samples as we have discussed in the above part “adult hippocampal neurogenesis in humans.”

On the other hand, a number of animal models recapitulating AD have been generated based on human mutations and phenotypes, investigating the impact of AD on

AHN. There are also contradictory results among animal studies. The majority of animal studies using transgenic mouse lines include familial Alzheimer disease (FAD)-associated mutations in *amyloid precursor protein* (APP) and/or *presenilin-1* (PS1), as well as in the microtubule-associated protein Tau (MAPT) and have reported decreases in AHN, consistent with initial hypotheses (Wang et al., 2004; Wen et al., 2004; Zeng et al., 2016). However, several studies have found increased AHN (Chevallier et al., 2005; Ermini et al., 2008; Jin et al., 2004a), whereas others have reported no change in similar AD models (Yetman and Jankowsky, 2013). Triple transgenic (3 $\times$ Tg) and 5 $\times$ FAD mouse models are among the most widely used AD models (Belfiore et al., 2019; Hamilton et al., 2015; Oddo et al., 2003). In both models, the extent of AHN increases at an early age, prior to amyloid deposition, but decreases significantly in the elder (Hanspal and Gillotin, 2022; Moon et al., 2014; Rodriguez et al., 2008). However, the precise timing of these changes is highly variable. Taken together, discrepancies in transgenic mouse lines, technical issues such as mouse handling, experimental paradigms, especially the timing to detect AHN, and the types of markers used may help explain the observed controversies.

In addition, the morphology and functional integration of newborn ABNs in AD mouse models have been reported to be abnormal. For instance, in *hAPP* transgenic mice, newborn ABNs exhibited increasing dendritic length, spine density, and functional responses compared with controls early in development. However, during later maturation, these ABNs exhibited both morphological and functional impairments (Sun et al., 2009).

Accumulating studies suggest that in AD mouse models, the dysregulation of AHN occurs before the onset of classical AD pathology (e.g., A β deposition), implying a causative role of AHN in the cognitive decline (Demars et al., 2010). However, the direct evidence supporting a role for AHN in AD has remained inconclusive. Hollands et al. reported that selective ablation of AHN in an AD mouse model exacerbated cognitive deficits (Hollands et al., 2017). Subsequently, Choi et al. demonstrated that genetically and pharmacologically stimulating AHN, in combination with elevating BDNF levels, ameliorated cognitive deficits in 5 $\times$ FAD mice without reducing A β burden. Conversely, suppressing AHN at very early stages of life worsened cognitive performance and led to the loss of pre-existing DGCs later in life (Choi et al., 2018). In contrast, a more recent study by Zhang et al. reported that ablating AHN in the *APP/PS1* transgenic mice restored the cognitive and synaptic deficits to normal levels (Zhang et al., 2021b). In addition, enhancing maturation and functional integration of ABNs into the existing network, without increasing their number, has also been shown to improve cognitive function in AD (Richetin et al., 2015).



More recently, using reversible and selective optogenetic/chemogenetic stimulation, Li et al. found that activation of supramammillary nucleus (SuM)-enhanced ABNs rescues memory and emotion deficits in 3×Tg and 5×FAD AD mice (Li et al., 2023b).

Stroke

Stroke is one of the leading causes of mortality and disability worldwide (Collaborators, 2018; Feigin et al., 2014; Li et al., 2024a). Approximately 5.5 million people die from stroke annually, and most of the stroke survivors are left with permanent neurological disabilities, leading to heavy social and economic burdens (Huang et al., 2022; Tater and Pandey, 2021). Stroke is caused by the disruption of blood supply to the brain and is classified into two main types: ischemic stroke and hemorrhagic stroke. Ischemic stroke is the most common form of stroke (Saini et al., 2021).

Stroke induces changes not only in the brain regions directly affected by the disrupted blood vessel but also in brain areas that are distant from the infarct core, such as the hippocampus (Passarelli et al., 2024). Previous studies indicated that both global and focal brain ischemia induced a transient increase in AHN bilaterally (Jin et al., 2001; Kluska et al., 2005; Liu et al., 1998). Generally, the elevated division rate of neural progenitors peaks within the first week, declines during the second week, and falls back to the baseline level within a few weeks (Liu et al., 1998; Yagita et al., 2001). The exact dynamics of this neurogenic response is possibly dependent on the specific stroke model used (Kunze et al., 2006; Tanaka et al., 2004). Moreover, the increase in neurogenesis tends to be higher in cases of larger infarcts (e.g., those induced by temporary occlusion of the middle cerebral artery) compared to small, narrowly circumscribed infarcts (e.g., those induced by photothrombosis) (Niv et al., 2012).

Further, morphological maturation, migration, and functional integration of retrovirally labeled newborn ABNs were also studied. Using two well-established models, photothrombosis (PT) and middle cerebral artery occlusion (MCAO), Niv et al. found that most neurons displayed normal migration, with an increased total dendritic length and a higher number of apical dendrites in MCAO animals. However, approximately 5%–10% of newborn ABNs displayed significant morphological abnormalities including the formation of additional HBDs in both models, whereas ectopic ABNs were exclusively found in animals with larger territorial infarcts, such as those induced by MCAO (Niv et al., 2012). On the other hand, a more recent study by Cuartero et al. demonstrated that ipsilateral ABNs displayed reduced branching and dendritic length, whereas contralateral ABNs showed enhanced branching and increased dendritic length (Cuartero et al., 2019). Both morphologically normal and aberrant ABNs displayed den-

dritic spines, suggesting network integration and functional recruitment. In addition, Geibig et al. demonstrated the c-fos expression in newborn ABNs (without distinguishing aberrant and normotopic ABNs) 8 weeks after stroke, indicating functional recruitment. Their activation was context-specific, being greater in “spatiotemporal” tasks compared with “sensorimotor” tasks (Geibig et al., 2012). More recently, Ceanga et al., demonstrated that stroke accelerated the maturation of the intrinsic electrophysiological properties of DCX⁺ ABNs, although this was not coupled with development of glutamatergic inputs (Ceanga et al., 2019).

Therapies to enhance neurogenesis following stroke have been tried to improve neurological functions, including stem cell therapy, rehabilitation, and pharmacotherapy (Tang et al., 2023). For instance, experiments using neural progenitors in animal ischemic models have provided support for the use of cell transplantation to treat stroke (Daadi et al., 2009; Fukunaga et al., 1999; Wei et al., 2005). Further, short-term and long-term clinical follow-up studies have shown that the infusion of autologous mesenchymal stem cells (MSCs, which will be further discussed in the section “advances in regenerative medicine”) is feasible and safe with regard to improving functional recovery and survival in patients with ischemic stroke (Bang et al., 2005; Lee et al., 2010), damage of capillary, and increased AHN, while improving functional performance in the MWM (Zhan et al., 2020). Additionally, EE was also shown to improve functional recovery and exert a small but significant reduction on lesion size in aged stroke rats by promoting neurogenesis and reducing post-stroke inflammation (Gresita et al., 2022). High-frequency repetitive transcranial magnetic stimulation, a widely used post-stroke rehabilitation method for ischemic stroke, was also reported to promote neurogenesis and improve functional recovery (Luo et al., 2017; Zong et al., 2022). Additionally, medical treatments enhancing neurogenesis have also shown neuroprotective effects in stroke (Jin et al., 2014; Luo et al., 2025; Yang et al., 2019; Zhang et al., 2002). For instance, treatment with sildenafil, a phosphodiesterase type 5 inhibitor, increased neurogenesis in both SVZ and DG, as well as reduced neurological deficits, although no significant difference of infarct volume was observed in MCAO animals (Zhang et al., 2002).

Altogether, these findings suggest that neurogenesis may represent a promising target for developing new treatments for ischemic stroke. Nevertheless, there seems not yet evidence solid enough to demonstrate the relationship of increase in neurogenesis and functional recovery of stroke, owing to the lack of results produced by more selective and more precise interventions to modulate neurogenesis. Employing approaches such as targeted radiation or transgenic mouse models may stand out as powerful tools to



help address this question and clarify the role of neurogenesis in stroke recovery.

FACTORS REGULATING ADULT HIPPOCAMPAL NEUROGENESIS

As mentioned above, AHN possesses functional significance under both physiological and pathological conditions, indicating a promising target for clinical translation. However, adult neurogenesis is naturally restricted, with overall efficiency remaining relatively low. Therefore, finding out practical and effective approaches to regulate AHN may provide alternative options for clinical treatment in the future.

Molecular signaling pathways

NSCs are maintained in a quiescent state in the SGZ, with a fraction dividing symmetrically to expand the neurogenic pool (Bonaguidi et al., 2011). However, once activated, quiescent NSCs become active and enter the cell cycle (as we have discussed in the section “neurogenesis in the intact adult mammalian DG: proliferation, differentiation, maturation, and synapse formation of NSCs”). The equilibrium between quiescence and activation is tightly regulated by intrinsic and extrinsic factors within the DG (Goncalves et al., 2016; Lugert et al., 2010; Matsubara et al., 2021).

Over the past decades, numerous studies have identified several key factors and signaling mechanisms that regulate adult neurogenesis, including the processes of proliferation, differentiation, migration, and synaptic integration. These findings are summarized in Table 5. Recently, using birthdating and snRNA-seq, Rasetto et al. delineated a continuous transcriptional trajectory from RGLs through postmitotic immature neurons to fully mature ABNs. They defined four discrete developmental stages—quiescent RGLs, proliferative progenitors, immature ABNs, and mature ABNs—and uncovered the molecular programs orchestrating neuronal differentiation and integration in the adult hippocampus (Rasetto et al., 2024).

Morphogens

Notch signaling. The mammalian genome contains four Notch receptors (Notch1-4) and five ligands. Notch receptors have been reported to express throughout the DG, with canonical Notch signaling being particularly prominent in both radial and horizontal NSCs (type 1 cells) but absent from type 2 cells and immature neuroblasts (type 3 cells) (Ehm et al., 2010; Lugert et al., 2010; Stump et al., 2002). Notch signaling is activated by interactions between Notch receptors and their ligands, leading to sequential proteolytic cleavages in the receptor that release the active Notch intracellular domain (NICD). The NICD is then

translocated into the cytoplasm, traversing into the nucleus, where it interacts with the DNA-binding CSL protein (Rbpj in mice). This interaction forms the Notch/RBPJk transcriptional regulator complex, which activates the expression of target genes, including members of the hairy and enhancer of split (*Hes*) and hairy and enhancer of split-related with YRPW motif (*Hey*) families.

Numerous studies have reported that Notch signaling is critical for the maintenance of NSCs and the control of their fate in the embryonic CNS (Hitoshi et al., 2002; Louvi and Artavanis-Tsakonas, 2006; Mizutani et al., 2007). Similarly, in the adult brain, Notch signaling is also found to be required for self-renewal and maintenance of NSCs (Ables et al., 2011; Imayoshi and Kageyama, 2011; Zhang et al., 2018). Previous studies have demonstrated a significant reduction in NSC proliferation within the DG in aged mice, with the quiescence of Notch-dependent NSCs contributing to the age-related decline in neurogenesis (Lugert et al., 2010). Moreover, ischemia stroke has been reported to upregulate the expression of *Hes* genes, leading to an expansion of neurogenic pool and increased neuronal differentiation (Kawai et al., 2005; Wang et al., 2009).

Gain- and loss-of-function experiments have further provided more direct evidence for the role played by Notch signaling in AHN. Overexpression of the NICD maintained the GFAP-expressing, undifferentiated states of NSCs *in vivo*; conversely, genetic ablation of *Notch1* or *Rbpj* promoted cell-cycle exit, contributing to a transition from NSCs to transient amplifying cells or neurons (Ables et al., 2010; Breunig et al., 2007; Ehm et al., 2010). Down-regulation of *Hes1*, a downstream target of Notch signaling, also significantly increased neuronal production and differentiation in the adult DG, while improving the spatial learning and memory capacity following traumatic brain injury (Zhang et al., 2014). Although previous studies investigated the role of Notch1 and its transcriptional effector RBPJk, a more recent study has highlighted the role of Notch2 signaling in the DG. Notch2 signaling was found to maintain NSC quiescence by blocking cell-cycle entry, with Id4 identified as its major effector (Zhang et al., 2019). Moreover, in a pilocarpine-induced epilepsy model in adolescent SD rats, Yuan et al. observed that administering DAPT, a Notch γ -secretase inhibitor, into the lateral ventricles, suppressed abnormal neurogenesis during the acute phase following SE (Yuan et al., 2020).

Wnt signaling. Wnts are secreted signaling molecules that activate signaling cascades involved in different aspects of embryonic development (Inestrosa and Varela-Nallar, 2015; Machon et al., 2007; Mulligan and Cheyette, 2012). The Wnt signaling pathway is activated by Wnt ligands to activate different signaling cascades: the canonical Wnt/ β -Catenin signaling pathway and the

**Table 5. Important signaling pathways regulating adult hippocampal neurogenesis**

Molecules	Species	Interventions	Effects on AHN	References
Morphogens				
Notch	mouse	TAM-inducible overexpression of activated Notch1 in NSCs; conditional inactivation of Notch1 in NSCs	induces expansion of NSC pool required for maintenance required for dendritic arborization	Breunig et al., 2007
	mouse	TAM-inducible conditional inactivation of Rbpj in NSCs	required for NSC self-renewal, maintenance	Imayoshi et al., 2010 ; Ehm et al., 2010
	mouse	TAM-inducible conditional inactivation of Rbpj in glial cells, including NSCs	required for NSC self-renewal, maintenance	Lugert et al., 2010
	mouse	TAM-inducible Notch1 knockout in NSCs	required for NSC self-renewal, maintenance	Ables et al., 2010
	mouse	overexpression of Hes1: Ad5-Hes1 injection; knockdown: Hes1-siRNA injection	enhancing Hes1 inhibits the proliferation and differentiation downregulation Hes1 increases proliferation, promotes differentiation as well as improves the spatial learning and memory capacity following TBI	Zhang et al., 2014
	mouse	TAM-inducible Notch2 knockout in Hes5 ⁺ NSCs conditionally expressing the active form of Notch2 (Notch2ICD) in Hes5 ⁺ NSCs	required for maintenance of quiescent NSCs and increases progenitor proliferation maintains quiescent NSCs and decreases neuroblast production	Zhang et al., 2019
	mouse	overexpression of microRNA-153 to suppress Notch	by suppressing Notch, overexpression of microRNA-153: enhances AHN prevents NSC gliogenesis alleviates cognitive impairment in aged mice	Qiao et al., 2020
Wnt	rat	LV-dnWnt was injected into the DG to reduce Wnt3-initiated β -catenin signaling in AHPs LV-Wnt was injected to increase Wnt signaling	LV-dnWnt results in a marked reduction in AHN LV-Wnt increases neurogenesis	Lie et al., 2005
	mouse	transgenic mice (POMC-cre) were used to specifically knock out β -catenin in newborn neurons	required for dendritic development	Gao et al., 2007
	mouse	β -catenin cKO mice (Ctnnb1 ^{loxP/loxP}) Ctnnb1 shRNA to knock down β -catenin	required for neuronal differentiation	Kuwabara et al., 2009
	mouse	forced induction of Wnt signaling in Shh-responding NSCs	leads to expansion of the IPC pool	Choe and Pleasure, 2012

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Table 5. Continued

Molecules	Species	Interventions	Effects on AHN	References
	mouse	Wnt7a knockout mice	required for NSC self-renewal, maintenance required for neural progenitor cell-cycle progression required for neuronal differentiation	Qu et al., 2013
	mouse	sfrp KO mice (sFRP3 is a Wnt inhibitor)	activates quiescent NSCs and promotes newborn ABNs maturation, dendritic growth and dendritic spine formation in the adult hippocampus	Jang et al., 2013
	mouse	deletion of Dkk1 in NSCs (Dkk1 is a Wnt antagonist)	increases progenitor proliferation ameliorates affective behavior in the TST restores AHN and cognition in old age	Seib et al., 2013
Shh	rat	overexpression of Shh using rAAV-Shh pharmacological inhibition of Shh using cyclopamine	promoted progenitor cell proliferation reduced progenitor cell proliferation	Lai et al., 2003
	mouse	mutant mice lack primary cilia	required for formation of adult NSCs	Breunig et al., 2008
	mouse	conditionally ablation of primary cilia/Smo from a subset of NSCs	required for formation of adult NSCs and postnatal neurogenesis	Han et al., 2008
	mouse	forced induction of Shh signaling in Shh-responding NSCs	promotes neurogenesis without significant expansion of IPCs	Choe and Pleasure, 2012
	mouse	mutant mice lack Smo or Shh	required for NSC self-renewal, maintenance	Li et al., 2013
	mouse	administration of Smo agonist	increases surviving newborn ABNs improves functional recovery after stroke	Jin et al., 2017
	mouse	Ptch1 ^{+/-} mice heterozygous mice	reduction of quiescent NSCs, newborn neurons accumulation of proliferation IPCs	Antonelli et al., 2018
	mouse	genetic ablation of Shh from hilar mossy cells	increased migration of immature neuronal precursors into the GCL	Gonzalez-Reyes et al., 2019
	mouse	conditionally knockout of Smo from NSCs	decreases neurogenesis in SGZ accelerates age-related depletion of NSC pool abolishes stroke-induced neurogenesis	Wang et al., 2022b
	mouse	mossy cell-selective conditional Shh knock-out (Shh-cKO) mice	attenuates seizure-induced neurogenesis, reduces the self-renewal of NSCs, prematurely depletes the NSC pool after seizure-induced neurogenesis accelerates age-related decline of the NSC pool	Noguchi et al., 2023

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**Table 5. Continued**

Molecules	Species	Interventions	Effects on AHN	References
BMP	mouse	transgenic Noggin overexpression to inhibit BMP signaling	expands NSC pool required for self-renewal of NSCs	Bonaguidi et al., 2008
	mouse	blockade of BMP signaling by intracerebral infusion of Noggin selective ablation of Bmpr1a in hippocampal NSCs inactivation of BMP canonical signaling in conditional Smad4 knockout mice	recruits quiescent NSCs into the cycle and increases neurogenesis transiently enhances proliferation but later leads to a reduced number of precursors	Mira et al., 2010
	mouse	virally mediated overexpression of BMP4 (LV-BMP4) overexpression of the BMP inhibitor noggin (LV-noggin) ablation of BMPRII in NSCs	causes NPC cell-cycle exit and slows the normal maturation of NPCs promotes NPC cell-cycle entry and accelerates NPC maturation accelerates maturation into neurons without depleting the NSC pool	Bond et al., 2014
	mouse	Smad1 shRNA to inhibit BMP4 in NSCs selective deletion of Bmpr1a in NSCs	enhances proliferation in 18-month-old mice	Yousef et al., 2015
	mouse	viral overexpression of BMP4 viral overexpression of noggin genetic deletion of the BMPRII in NSCs	blocks the effects of fluoxetine on proliferation and depressive behavior exerts antidepressant and anxiolytic activity along with an increase in AHN promotes neurogenesis and reduces anxiety- and depression-like behaviors	Brooker et al., 2017
Neurotrophins				
BDNF	mouse	heterozygote BDNF knockout mice	required for survival of newborn neurons	Linnarsson et al., 2000
	rat	using riluzole to increase BDNF in the hippocampus	increases neurogenesis	Katoh-Semba et al., 2002
	rat	intrahippocampal BDNF infusion	increases neurogenesis	Scharfman et al., 2005
	mouse	heterozygote BDNF knockout mice	reverses the enhancement of AHN	Rossi et al., 2006
	mouse	conditional ablation of TrkB in AHPs	impair proliferation and neurogenesis mice become insensitive to anti-depressive treatment	Li et al., 2008
			required for survival, dendritic arborization, and functional integration of newborn neurons impaired neurogenesis-dependent LTP and increased anxiety-like behavior	Bergami et al., 2009

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Table 5. Continued

Molecules	Species	Interventions	Effects on AHN	References
	mouse	conditional knockout BDNF in ABNs	less dendritic branches, shorter dendritic length, and lower density of dendritic spines	Gao et al., 2009a
	mouse	RNA interference and lentiviral vectors to knockdown BDNF in the DG	reduces neurogenesis affects behaviors associated with depression	Taliaz et al., 2010
	mouse	deletion and overexpression of BDNF in ABNs	reduction and elevation of dendrite growth, respectively	Wang et al., 2015b
Inflammatory cytokines				
IL-1 β	mouse	administration of exogenous IL-1 β and IL-1 β receptor antagonist mice with a null mutation of the IL-1 β receptor	decreases neurogenesis, which is blocked by IL-1 β receptor antagonist the decrease in neurogenesis after acute/chronic stress is blocked	Koo and Duman, 2008
	mouse	repeated intra-hippocampal infusion of IL-1 β	increases cellular proliferation but not influence DCX expression	Seguin et al., 2009
	mouse	IL-1 β (XAT): A mouse model with an IL-1 β activated transgene	impaired DCX+ cells at 1 and 3 months after IL-1 β induction, which is reversed by the deletion of the IL-1 receptor	Wu et al., 2012
IL-6	mouse	transgenic mice to chronically express IL-6 in astroglia	reduces proliferation, survival, and differentiation of NPCs	Vallieres et al., 2002
	mouse	repeated intra-hippocampal infusion of IL-6	increases cellular proliferation but not influence DCX expression	Seguin et al., 2009
	mouse	IL-6 knockout mice	reduces proliferation and survival of NPCs	Bowen et al., 2011
IFN	rat	administration of IFN- α	decrease neurogenesis, which is blocked by the co-administration of IL-1 receptor antagonist	Kaneko et al., 2006
	mouse	intracerebral injection of IFN- α	inhibits proliferation of NPCs	Moriyama et al., 2011
TNF- α	mouse	systemic administration of TNF- α	decreases neurogenesis	Seguin et al., 2009
	mouse	mouse models with loss of TNF-R1 and TNF-R2	in the intact brain, the number of new ABNs was elevated in TNF-R1(–/–) and TNF-R1/R2(–/–) mice, whereas no significant changes were detected in TNF-R2(–/–) after SE, TNF-R1(–/–) and TNF-R1/R2(–/–) mice produced more ABNs, whereas TNF-R2(–/–) showed reduced SE-induced neurogenesis	Iosif et al., 2006

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**Table 5. Continued**

Molecules	Species	Interventions	Effects on AHN	References
	mouse	mouse models with loss of TNF-R1, TNF-R2, and TNF- α	TNFR1(–/–) and TNF α (–/–) animals have elevated baseline neurogenesis in the hippocampus, whereas absence of TNFR2 decreases baseline neurogenesis following radiation injury, loss of TNF α or TNFR2 worsens the effects of radiation injury on neurogenesis and loss of TNFR1 has no protective effects on neurogenesis	Chen and Palmer, 2013
Growth factors				
FGF-2	mouse	using mice genetically deficient in FGF-2	decreases neurogenesis after KA or MCAO rescued by intraventricular injection of HSV carrying FGF-2 gene	Yoshimura et al., 2001
	mouse	intracerebroventricular injection of FGF-2	increases neurogenesis in the aged hippocampus	Jin et al., 2003
	rat	intraventricular infusion of FGF2	increases neurogenesis enhances dendritic growth	Rai et al., 2007
	mouse	conditional knockout FGF1 from AHPs	required for progenitor proliferation	Zhao et al., 2007
	mouse	express activated Fgfr3 transgene in AHPs delete the FGF receptors from AHPs	increases neurogenesis, rescues the age-related decline in neurogenesis required for NSC maintenance	Kang and Hebert, 2015
IGF-1	rat	peripheral injection of IGF-1	increases neurogenesis	Aberg et al., 2000
	rat	intracerebroventricular injection of IGF-1	increases neurogenesis	Lichtenwalner et al., 2001
VEGF	rat	intracerebroventricular administration of VEGF	increases neurogenesis	Jin et al., 2002
	rat	two selective and potent Flk-1 inhibitors SU5416 and SU1498; intracerebroventricular infusion of recombinant VEGF	VEGF signaling through the Flk-1 receptor is required for antidepressant-induced cell proliferation; VEGF infusion stimulates SGZ cell proliferation	Warner-Schmidt and Duman, 2007
NGF	rat	chronic intracerebroventricular infusion of NGF	increase neurogenesis in DG	Birch and Kelly, 2013
	rat	6 or 20 days intracerebroventricularly NGF infusion	not affect proliferation of progenitor cells in the DG, but increase their survival	Frielingsdorf et al., 2007

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Table 5. Continued			
Molecules	Species	Interventions	Effects on AHN
NT-3	mouse	conditional deletion of NT3	differentiation rather than proliferation of neuronal precursor cells is significantly impaired in DG lacking NT-3
	mouse	overexpression NT-3 in the ventral DG by AAV-NT-3	the number of proliferating cells and immature neurons in the SGZ are significantly decreased

Abbreviations: TAM, tamoxifen; NSC, neural stem cell; TBI, traumatic brain injury; IPC, intermediate progenitor cell; DCX, doublecortin; AHN, adult hippocampal neurogenesis; SGZ, subgranular zone; NPC, neural progenitor cell; MCAO, middle cerebral arterial occlusion.

non-canonical β -Catenin-independent signaling cascades (Gordon and Nusse, 2006; Veeman et al., 2003).

Recently, Wnt pathway has also been suggested to play a critical role in the adult brain with regard to neurogenesis (Arredondo et al., 2022). For example, Wnt3, which is produced by local hippocampal astrocytes and hilar cells, has been shown to stimulate Wnt/ β -Catenin signaling and thereby plays a crucial role in promoting proliferation, differentiation, and survival of neural progenitors as well as rescuing impaired neurogenesis in aged animals (Lie et al., 2005; Okamoto et al., 2011). Additionally, Wnt7a has been shown to promote self-renewal of NSCs, cell-cycle progression of neural progenitors, and neuronal differentiation, possibly through separate activation of the β -Catenin-cyclin D1 pathway and β -Catenin-neurogenin2 pathway (Qu et al., 2013). Conversely, inhibition of Wnt signaling in the SGZ has been associated with reduced proliferation and neuronal differentiation (Kuwabara et al., 2009; Lie et al., 2005; Song et al., 2002). Zhou et al. found that chronic restraint stress (CRS) significantly reduced the expression of both Wnt2 and Wnt3 selectively in the ventral hippocampus, rather than the dorsal hippocampus. Further, knocking down Wnt2 or Wnt3 in the ventral hippocampus led to impaired Wnt/ β -Catenin signaling pathway, neurogenesis deficits, and depression-like behaviors, whereas overexpression of them reversed the depression-like behaviors (Zhou et al., 2016). In addition, Qiu et al. reported that Wip1 gene knockout inactivated the Wnt/ β -Catenin signaling pathway, impairing neurological functional recovery and reducing DCX expression in animals with MCAO. Meanwhile, pharmacological activation of the Wnt/ β -Catenin signaling pathway compensated for the Wip1-knockout-induced deficit in neuroblast formation (Qiu et al., 2018).

On the other hand, non-canonical β -Catenin-independent Wnt signaling has also been implicated in controlling the differentiation and development of ABNs (Arredondo et al., 2020, 2022; Schafer et al., 2015). Specifically, Schafer et al. revealed a remarkable transition in Wnt signaling responsiveness (from the canonical branch to the non-canonical branch) in the course of neuronal differentiation; while canonical Wnt signaling progressively faded, the emerging non-canonical (PCP pathway) became essential for late stages of maturation, such as dendrite initiation and patterning.

In addition, Wnt antagonists such as sFRP3 and Dkk1 have demonstrated to regulate neurogenesis in the adult hippocampus (Jang et al., 2013; Seib et al., 2013). More recently, Dkk3 was found to increase with aging in the adult hippocampus, and Dkk3 deletion from DGCs was found sufficient to restore AHN in old or AD model mice, while counteracting the cognitive decline (Martin Flores et al., 2024). This important finding further supports the



well-established notion that dysregulation of Wnt signaling is associated with the decline of neurogenesis in both aging and AD hippocampus (Heppt et al., 2020; Okamoto et al., 2011), making Wnt signaling an attractive therapeutic target for AD.

Hedgehog signaling. Sonic hedgehog (Shh) is the primary activating ligand that initiates Hedgehog signaling in the brain. The Shh receptor Patched (Ptch) and the transmembrane protein Smoothened (Smo), key components of the Shh pathway, are expressed in the neurogenic niches, including the adult SVZ and SGZ, by NSCs and transient amplifying cells. This pathway is best recognized for its diverse roles during embryonic and early postnatal development, including the formation and maintenance of NSCs in the SGZ (Ahn and Joyner, 2005; Britto et al., 2002; Machold et al., 2003; Ruiz i Altaba et al., 2002). Early studies demonstrated that exogenous Shh directly promoted progenitor proliferation *in vitro*. Overexpression of Shh within the DG resulted in a marked increase in adult hippocampal progenitor cell proliferation *in vivo*, whereas pharmacological inhibitor of Shh signaling reversed its proliferative effects (Lai et al., 2003). In addition, administration of an Smo agonist was found to promote neurogenesis in stroke mice and improve post-stroke behavioral recovery (Jin et al., 2017).

Adult NSCs in the DG appear to originate from Shh-responsive embryonic neural progenitors in the ventral hippocampus, which subsequently relocate into the dorsal hippocampus (Ahn and Joyner, 2005; Li et al., 2013). Studies have demonstrated that embryonic ablation of *Smo* or ciliary genes in postnatal NSCs and neural progenitors prevents their expansion and development, underscoring the essential role of Shh signaling—mediated via the primary cilia—in establishing and maintaining the postnatal hippocampal NSC pool as well as promoting proliferation of progenitors (Breunig et al., 2008; Choe and Pleasure, 2012; Han et al., 2008; Machold et al., 2003). In addition, by conditionally knocking out Shh signaling receptor *Smo* in NSCs, Wang et al. reported a decrease in AHN and an acceleration of age-related depletion of NSC pool. Meanwhile, they also found that stroke-induced neurogenesis was abolished, leading to delayed motor function recovery and increased anxiety levels following stroke (Wang et al., 2022b).

On the other hand, the Shh molecular pathway was also shown to be expressed in calretinin positive (CR⁺) neurons in the early postnatal brain (dorsal hippocampus), and ablation of it from CR⁺ neurons can significantly lead to decrease in proliferation and the number of NSCs (Li et al., 2013). Further, a recent study demonstrated that Shh was expressed by hilar mossy cells (MCs), which constitutes a major population of CR⁺ neurons, in the adult DG. However, genetic ablation of *Shh* from hilar MCs

decreased numbers of MCs but increased neural progenitor proliferation and migration of immature neuronal precursors into the GCL (Gonzalez-Reyes et al., 2019). More recently, Noguchi et al. found that deletion of *Shh* from MCs attenuated seizure-induced neurogenesis while reducing self-renewal of NSCs, resulting in a premature depletion of NSC pool after seizure-induced neurogenesis. Meanwhile, *Shh* from MCs also accelerated age-related decline of the NSC pool (Noguchi et al., 2023).

Bone morphogenetic protein signaling. Bone morphogenetic protein (BMP) signaling is also implicated in the regulation of adult neurogenesis. BMPs are a subgroup of the transforming growth factor β (TGF- β) superfamily of cytokines, which are chronically secreted by DGCs, NSCs, and other neurogenic niche cells.

In SGZ, BMPs act as short-range morphogens, playing a crucial role in regulating the balance between proliferation and quiescence of NSCs. This regulation is mediated possibly through BMP receptors such as BMPR-Ia and downstream signaling components like Smad4. In addition, BMPs influence the amplification and maturation of intermediate progenitor cell pool through BMPRII (Bonaguidi et al., 2008; Bond et al., 2014; Mira et al., 2010). Negative regulation of BMP activity can be achieved through BMP inhibitors, such as Chordin and Noggin, which are present in the hippocampal niche and are thought to locally adjust the levels of BMP signaling. Bond et al. found that virally mediated BMP4 overexpression caused neural progenitors to exit the cell cycle and slowed their normal maturation, resulting in a long-term reduction in neurogenesis. Conversely, overexpression of Noggin produced the opposite effects, indicating that inhibition of BMP signaling is a mechanism for rapidly expanding the hippocampal neurogenic pool (Bond et al., 2014). Similarly, attenuation of BMP signaling with transgenic perturbations in aged mice increased the proliferation of neural progenitors, highlighting its inhibitory effect on neurogenesis during aging (Yousef et al., 2015). This study also identified an age-related increase in BMP signaling, indicating that alongside with Wnt, BMP signaling is another contributor to the decline in neurogenesis with aging. Moreover, in addition to impairing neurogenesis, increased BMP signaling was found to contribute significantly to age-related cognitive decline (Meyers et al., 2016). More recently, Frazer et al. found that knocking out Gremlin 2 (Grem2), which is the most potent natural inhibitor of BMP signaling expressed in the adult brain, decreased AHN and contributed to development and progression of anxiety and epilepsy (Frazer et al., 2024).

Neurotrophic factors, growth factors, and inflammatory cytokines

Neurotrophic factors are extracellular signaling proteins that interact with tyrosine kinases receptors (Trk receptors)



and their co-receptors to regulate various cellular functions. They are one of the key mediators of neural plasticity and functional recovery (Gibon and Barker, 2017), including BDNF, nerve growth factor (NGF), and neurotrophin-3 (NT-3).

Among the identified neurotrophic factors, brain-derived neurotrophic factor (BDNF) has been mostly extensively studied and is recognized as a critical regulator of adult neurogenesis (Goncalves et al., 2016; Leschik et al., 2022; Wang et al., 2022a). Firstly, BDNF was reported to be required for the survival of the continuously regenerating neural populations in the adult DG (Lee et al., 2002; Linnarsson et al., 2000) and play a key role in promoting neurogenesis (Taliaz et al., 2010), including the enriched environment (EE)-related neurogenesis (Rossi et al., 2006). Additionally, studies have demonstrated that increasing hippocampal BDNF levels, either by using riluzole (Katoh-Semba et al., 2002; Usmani et al., 2023) or through chronic infusion of BDNF directly into the adult DG, significantly enhances the proliferation of ABNs (Scharfman et al., 2005). Moreover, deletion and overexpression of BDNF in ABNs separately resulted in the reduction and elevation of dendrite growth (Gao et al., 2009b; Wang et al., 2015b). Deletion of TrkB, the receptor of BDNF, in adult neural progenitors also impaired neurogenesis and reduced the dendrite and spine growth in ABNs while increasing anxiety-like behaviors (Bergami et al., 2008; Li et al., 2008). More recently, through intrahippocampal injection of AAV-shRNA-BDNF to inhibit the BDNF/TrkB pathway, Chen et al. found that the advantageous effects of dexmedetomidine on AHN, neuronal survival, and cognitive improvement in hypoxic-ischemic neonatal rats were counteracted (Chen et al., 2024b).

Growth factors are a diverse group of extracellular proteins that regulate cell growth and maintenance, with several of which identified as key regulators of AHN, including fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), and NGF. For instance, intracerebroventricular infusion of FGF has been shown to stimulate AHN in both 3-month-old and 20-month-old mice, indicating that the aged brain retains the capacity to respond to exogenous growth factors (Jin et al., 2003). Similarly, Kang et al. demonstrated that conditionally expressing an activated form of an FGF receptor in neural precursors increased the neural proliferation and rescued the age-related decline in neurogenesis in older mice. Conversely, by deleting the FGF receptors, they found that FGF receptors were required for NSC maintenance (Kang and Hebert, 2015). VEGF is another potent modulator of AHN, known for its ability to enhance neurogenesis in the DG under both physiological and pathological conditions (Fournier and Duman, 2012; Han et al.,

2015; Jin et al., 2002; Warner-Schmidt and Duman, 2007). In addition, emerging evidence has shown that IGF-1 is critical for neural proliferation and neuronal differentiation in the hippocampus (Aberg et al., 2000; Lichtenwalner et al., 2001). More recently, PDGF-mediated signaling has also been shown to regulate AHN. Li et al. found that overexpression or exogenous administration of PDGF-BB in DG rescues the effect of chronic stress on NSC proliferation and dendritic growth of ABNs. Conversely, knockdown of PDGF-BB facilitates CSDS-induced deficit of AHN and promotes the susceptibility to chronic stress in mice (Li et al., 2023a).

Although being less explored, a few studies that focus on the actions of NGF and NT-3 also strongly suggest an important role these neurotrophic factors play in modulating AHN (Ribeiro and Xapelli, 2021). NGF is highly expressed in the adult hippocampus; however, its role in AHN remains controversial. For example, chronic intracerebroventricular infusion of NGF for 6 weeks has been reported to enhance cell proliferation in the DG, upregulate the expression of TrkA, and improve recognition memory (Birch and Kelly, 2013). In contrast, shorter NGF treatments (6 or 20 days) in adult and aged male rats intracerebroventrically improved survival of newborn neurons in the GCL of adult but not aged rats, without significantly affecting the proliferation of progenitor cells (Frielingsdorf et al., 2007). Similar to NGF, NT-3 expression is largely confined to the hippocampal DG. Conditional deletion of NT-3 in the brain significantly impaired the differentiation of neural progenitor cells in the DG, whereas proliferation remained unaffected (Shimazu et al., 2006). However, Kasakura et al. demonstrated that overexpression of NT-3 in the hippocampus suppressed the early phase of neurogenic processes (Kasakura et al., 2023).

Inflammation has also been known to be closely associated with AHN (Amanollahi et al., 2023; Borsini et al., 2015; Kohman and Rhodes, 2013). Studies using lipopolysaccharide (LPS), a method commonly used to stimulate the innate inflammatory responses, have shown that LPS disrupts progenitor proliferation, reduces neuronal differentiation, and decreases the survival of neuroblasts (Bastos et al., 2008; Ekdahl et al., 2003; Fujioka and Akema, 2010; Jakubs et al., 2008). Conversely, inflammatory blockade has been reported to restore neurogenesis by decreasing the survival of newborn ABNs (Bastos et al., 2008; Monje et al., 2003). The influence of inflammation is possibly exerted through release of various inflammatory cytokines (Borsini et al., 2015), including pro-inflammatory cytokines released by activated microglia, such as interleukin-1 (IL-1), IL-6, interferons (IFNs), and tumor necrosis factor alpha (TNF- α). For example, using transgenic mice to overexpress IL-6 in astroglia, Vallieres et al. found that overall AHN was decreased by 63%, suggesting an



inhibitory role of IL-6 in AHN (Vallieres et al., 2002). Conversely, adult IL-6 knockout mice exhibited compromised neurogenesis (Bowen et al., 2011). In addition, Iosif et al. found that TNF- α acted as a negative regulator of neural progenitor proliferation through TNF-R1 (Iosif et al., 2006). A subsequent study confirmed these findings by revealing that elevated baseline AHN was detected in TNF-R1 (–/–) and TNF- α (–/–) mice, whereas absence of TNF-R2 decreased AHN (Chen and Palmer, 2013). However, for neurogenesis following radiation injury they found that immunomodulatory signaling of TNF- α mediated by TNF-R2 is more significant than through TNF-R1, indicating the differential roles of TNF-R1 and TNF-R2 under different contexts. Indeed, inflammation is the common underlying mechanism shared by the brain disorders mentioned above. Given the close relationship between inflammation and AHN, modulating them could be crucial for the treatment of these disorders and further investigations are still required.

Cellular components of the SGZ

The neurogenic niche, SGZ, is a specialized and dynamic microenvironment composed of both complex cellular and non-cellular components of the DG. The cellular components provide a complex regulatory architecture that allow the proper development of NSCs, promoting their integration into the pre-existing hippocampal circuits. The process of AHN consists of sequential steps that are tightly controlled by both cell-autonomous mechanisms and the interaction with the molecular and cellular niche components (Artegiani et al., 2017; Bonafina et al., 2020; Viciomini et al., 2020).

Neuronal cells and neurotransmitters

First, NSCs act as key regulators of their own niche through distinct autocrine and paracrine mechanisms, influencing the development of their progeny across different neurogenic stages (Kirby et al., 2015; Viciomini et al., 2020; Zhou et al., 2018). For instance, conditional ablation of VEGF in Nestin+ cells led to a transient increase in NSC proliferation, followed by partial depletion of the NSC pool (Kirby et al., 2015). Many NSC-derived ligands, including VEGF, have receptors that are expressed not only in NSCs themselves but also in their progeny, neuroblasts, and immature ABNs and other niche components like microglia. This suggests that NSCs may regulate multiple stages of maturation of ABNs either directly through their secreted factors or indirectly through modulation of niche factors (Tang et al., 2019a).

Meanwhile, accumulating evidence has suggested that neurotransmitters released by DG local neurons, including interneurons, hilar mossy cells, and mature DGCs, or by axons arising from long-range projecting neurons may modulate different aspects of AHN (Ge et al., 2008; Song

et al., 2016). For example, direct GABAergic inputs were reported to promote neuronal differentiation by enhancing dendritic development and synaptic integration of immature neurons (Ge et al., 2006; Tozuka et al., 2005). Although NSCs appear to lack functional GABAergic synapses, local parvalbumin (PV)-positive interneurons help maintain NSC quiescence by tonic inhibition mediated by GABA spillover from PV-DGC synapses (Song et al., 2012). In contrast to NSCs, neural progenitors received immature GABAergic synaptic inputs from local PV⁺ interneurons, and the activation of PV⁺ interneurons was found to promote their survival (Song et al., 2013). Hilar mossy cells provide the first glutamatergic synaptic inputs onto newborn ABNs as well as disynaptic GABAergic inputs via interneurons (Deshpande et al., 2013; Scharfman, 2018; Vivar et al., 2012). However, their role in regulating AHN was not examined until 2018, when Yeh et al. demonstrated that mossy cells regulate the quiescence and maintenance of adult NSCs through a dynamic balance of direct glutamatergic and indirect GABAergic signaling onto NSCs (Yeh et al., 2018). In addition, mature DGCs have also been reported to accelerate the functional integration of newborn ABNs through recruiting dentate PV interneurons (Alvarez et al., 2016).

In addition to local neuronal cells that have been shown to coordinate neurogenesis and network activity, AHN can also be influenced by distal circuitry. EC provides the primary long-range excitatory input to the DG through the medial and lateral perforant path (van Groen et al., 2003; Witter, 2007). Newborn ABNs compete with mature DGCs to receive glutamatergic synaptic inputs from the EC to integrate into the circuit (Toni et al., 2007). This integration relies on NMDA-receptor-mediated responses to glutamate, which are essential for the survival of immature neurons in a time-dependent manner (Tashiro et al., 2006). Moreover, the induction of LTP has been shown to promote the proliferation of adult neural progenitors and enhance the survival of newborn neurons (Bruehl-Jungerman et al., 2006; Stone et al., 2011). In addition, DG also receives dense serotonergic projections originating from brainstem raphe, especially in the SGZ, where synapses are preferentially formed on interneurons (Bjarkam et al., 2003; Cheng et al., 2022; Vertes et al., 1999). Given the diversity of serotonin (5-HT) receptor families (Alenina and Klempin, 2015; Clemett et al., 2000; Sharp and Barnes, 2020), previous studies have produced inconsistent results regarding the effects of 5-HT on AHN, indicating a region-dependent and receptor-type specific roles of 5-HT mechanisms in AHN (Banar et al., 2004; Higuchi and Arakawa, 2023; Jha et al., 2006; Soumier et al., 2010). Furthermore, DG also receives cholinergic and GABAergic inputs from the septum, which target different cell types: GABAergic inputs terminate preferentially on GABAergic



interneurons, whereas cholinergic inputs primarily target glutamatergic DGCs. Bao et al. demonstrated that long-range GABAergic inputs from the septum, mediated by dentate PV interneurons, were both sufficient and necessary for maintaining NSC quiescence; ablating them depleted NSC pool and finally impaired AHN (Bao et al., 2017). Previous studies have indicated that adult neural progenitors and their progeny are stimulated by cholinergic activation (Campbell et al., 2010; Itou et al., 2011; Kaneko et al., 2006). Furthermore, Chen et al. found that stimulation of the cholinergic circuits projected from the septum to the DG promoted proliferation and morphological development of NSCs, providing direct evidence for how cholinergic inputs from the septum regulate AHN (Chen et al., 2024c). On the other hand, SuM of the hypothalamus has also been reported to send dense axonal projections to the DG, modulating various hippocampal-dependent behaviors (Chen et al., 2020a; Ito et al., 2018; Root et al., 2018) while regulating AHN. Recent work by Li and colleagues demonstrated that chronic patterned optogenetic stimulation of SuM-DG projections robustly increased production of NSCs and behaviorally relevant ABNs with enhanced maturity, possibly via interactions with DGCs (Li et al., 2022b).

Non-neuronal cells

Astrocytes, a type of glial cell, are abundant in the hippocampal neurogenic niche that provide both structural and functional support for NSCs and maturing ABNs. Astrocytes were first reported to regulate the proliferation and neuronal fate specification of adult neural progenitors in an *in vitro* co-culture study (Song et al., 2002). They are now recognized as key regulators of cell proliferation, migration, differentiation, and synaptic integration of newborn ABNs, acting through membrane-associated molecules and by secreting various soluble signals such as FGF-2, Wnt ligands, and cytokines (Cao et al., 2013; Casse et al., 2018; Lu and Kipnis, 2010; Shetty et al., 2005; Vallieres et al., 2002). Additionally, astrocytes help control the availability of neurotransmitters in the synaptic cleft and play a critical role in synaptic integration of ABNs. Using transgenic approaches to block vesicular release from astrocytes, Sultan et al. found that ABNs, but not mature neurons, showed reduced glutamatergic synaptic input and dendritic spine density, along with lower functional integration and decreased cell survival (Sultan et al., 2015). Subsequently, in another study, genetic ablation of the cholinergic receptor CHRM1 in astrocytes was reported to result in defects in NSC survival, neuronal differentiation, and integration of newborn ABNs, along with impaired contextual fear memory (Li et al., 2022a). This highlighted a critical role of astrocytes in mediating cholinergic regulation of AHN and memory. Moreover, astrocytes may play a role in synchronizing network activity,

either through the spread of gliotransmitters or through gap junction coupling with hundreds of other astrocytes to regulate AHN distally (Adamsky et al., 2018; Araque et al., 2014; Wu et al., 2017b).

Microglia have also been shown to play a crucial role in AHN in several studies. As professional phagocytes in the adult hippocampal neurogenic niche, microglia remove newborn cells that are naturally undergoing apoptosis (Sierra et al., 2010). However, recent studies have highlighted an active role of microglia in maintaining AHN (Gemma and Bachstetter, 2013). Intracerebroventricular infusion of CX3CR1-blocking antibodies into adult rats increased hippocampal IL-1 β levels while decreasing neural progenitor proliferation (Bachstetter et al., 2011). Similarly, mice lacking CX3CR1 exhibited reduced proliferation and a decreased number of ABNs (Vukovic et al., 2012). Further studies have shown that ablation of microglia in the adult DG results in decreased survival of neuroblasts (Kreisel et al., 2019). Generally, microglia act as sensors of local cell death, dynamically modulating the balance between cell proliferation and survival in the SGZ through their phagocytosis secretome (Diaz-Aparicio et al., 2020). Additionally, in response to chronic stress, IL-4-driven microglia in the hippocampus trigger BDNF-dependent neurogenesis, helping protect against depressive-like symptoms (Zhang et al., 2021a). More recently, using 5 $\times$ FAD transgenic mice, Wang et al. found that microglial replenishment restored AHN, reversing the cognitive and synaptic deficits, by restoring the BDNF neurotrophic signaling pathway (Wang et al., 2023). Furthermore, microglia secrete inflammatory cytokines, which regulate multiple steps of AHN, as we have mentioned above in the section of “neurotrophic factors, growth factors, and inflammatory cytokines.”

Accumulating studies have indicated that blood vessels are also critical components of hippocampal neurogenic niche. Vascular cells can impact neurogenesis (Licht and Keshet, 2015) directly by producing neurogenic factors themselves or indirectly, transporting neurogenic substances produced by other cells. Several studies indicate that endothelial cells affect NSC proliferation and maturation of ABNs by secreting different trophic factors including BDNF, VEGF, and chemokines. For example, a recent study by Wang and colleagues demonstrated that endothelial cells contributed to the maintenance of lactate homeostasis while promoting neurogenesis and cognitive functions (Wang et al., 2019).

Non-pharmacological treatments

Intriguingly, one of the fundamental features of AHN is its dynamic regulation by an individual's behavior, experience, and emotional/biological status. Thus, in addition to pharmacological treatments, alternative non-pharmacological approaches such as physical activity



and EE have also been demonstrated to enhance neurogenesis.

EE refers to housing conditions that facilitate enhanced sensory, cognitive, and motor stimulation, compared to standard housing conditions. Although the exact protocols for EE vary widely among laboratories, there is a general consensus that EE significantly increases AHN (Kempermann, 2019; Li et al., 2023c; Ohline and Abraham, 2019; Toda and Gage, 2018). As early as the 1990s, Kempermann et al. found that EE exposure significantly increased the number of newborn cells and the volume of GCL, while improving the ability of spatial learning (Kempermann et al., 1997; 1998). Subsequent studies revealed that EE also promoted the survival of newborn cells (van Praag et al., 1999; 2000), however, with its effects on the survival and integration of ABNs restricted to the first 3 weeks after their birth (Tashiro et al., 2007). Moreover, EE has been found to exert beneficial effects in animal models of a range of CNS disorders, including cognitive deficits (Pereira-Caixeta et al., 2017; Veena et al., 2009), depression (Vanisree and Thamizhoviya, 2021), epilepsy (Auvergne et al., 2002; Li et al., 2023c, 2024b; Vrinda et al., 2017; Young et al., 1999), and stroke (Neves et al., 2024; Yu et al., 2014; Zhan et al., 2020), possibly through regulating multiple aspects of AHN. Importantly, with its non-invasive nature, the effects of EE have also been evaluated in several clinical studies (Amatya et al., 2020; Janssen et al., 2012; Woo and Leon, 2013). These findings suggest that EE may serve as a promising therapeutic alternative for both neuro-protection and brain repair.

Attempts have been made to assess the individual effects of different components of EE, with physical exercise being the most extensively studied (Hannan, 2014). Physical exercise is known to contribute to many of the major effects of EE, including the enhancement of AHN (Ben-Zeev et al., 2022). Most early researches focused on aerobic exercise (Fischer et al., 2014; Marlatt et al., 2012; van Praag et al., 1999, 2005), with voluntary physical exercise (usually wheel running) being the most widely adopted model, consistently demonstrating its ability to enhance AHN. For example, van Praag et al. found that neither maze training nor yoked swimming had any effect on the number of BrdU-positive cells, whereas voluntary wheel running doubled the number of surviving newborn cells, achieving levels comparable to those induced by EE (van Praag et al., 1999). Subsequently, they also reported that voluntary wheel running partially reversed age-related declines in neurogenesis and improved their learning abilities (van Praag et al., 2005). However, anaerobic resistance training was reported to exert no effect on the proliferation, maturation, or survival of new ABNs in the DG, whereas high-intensity interval training (HIIT), a combination of aerobic and anaerobic exercise, was reported to have

only modest benefits. These findings underscore the importance of sustained aerobic exercise in promoting AHN (Nokia et al., 2016). Noteworthy, forced exercise, which relies on a reward or punishment to motivate animals to perform, may induce stress, thus potentially confounding the experimental findings (Lucassen et al., 2015; Parihar et al., 2011). In addition, physical exercise is widely regarded as a non-pharmacological and holistic therapy, known to prevent and mitigate numerous neurological conditions as well as alleviate aging-related cognitive decline. Its benefits are partly attributed to its ability to stimulate neurotrophin levels (e.g., BDNF), alongside its impact on AHN (Afzalpour et al., 2015; Farmer et al., 2004; Voss et al., 2019). Intriguingly, combining genetic enhancement of AHN with pharmacological elevation of BDNF levels has been demonstrated to improve cognition in AD mouse model, mimicking the beneficial effects of exercise (Choi et al., 2018). Moreover, the positive effects of exercise on cognitive function and health-related quality of life have been validated in a number of clinical trials (Jia et al., 2019; Sanders et al., 2020; Song and Yu, 2019; Yan et al., 2023).

ADVANCES IN REGENERATIVE MEDICINE

Recently, regenerative medicine—a field focused on repairing, regenerating, or reconstructing damaged tissues and/or organs, with the ultimate goal of promoting functional recovery and adaptation—has garnered significant interest (Chen et al., 2012; Lapteva et al., 2018). Stem-cell-based therapy, a key branch of regenerative medicine, leverages the unique properties of stem cells, including their abilities for self-renewal and differentiation, to regenerate damaged cells and tissues in the human body. Alternatively, it aims to replace damaged cells with new, healthy and functional ones by delivering exogenous cells to patients (Hoang et al., 2022; Rahimi Darehbagh et al., 2024; Rahman et al., 2022). Although stem-cell-based therapies for neurological diseases remain controversial and face numerous challenges before reaching clinical application, recent preclinical and clinical studies demonstrated promising treatment effects.

Cell transplantation

By definition, NSCs are considered the most logical and promising option for stem cell therapy in treating neurological disorders, as they represent the prototype of regenerative cells for the CNS. However, endogenous AHN is temporally and spatially restricted and is generally insufficient for functional neural repair. To address this gap, cell transplantation has emerged as a viable strategy, which can be either autologous, using the patient's own cells, or



allogeneic, using cells from a healthy donor. Various types of stem cells have been explored for transplantation, including pluripotent stem cells (PSCs) and multipotent MSCs, both of which have recently emerged as key players in regenerative medicine due to their remarkable ability to differentiate into diverse cell types (Cyranoski, 2018; Hoang et al., 2022; Samsonraj et al., 2017; Tabar and Studer, 2014; Zuk et al., 2002).

The discovery of PSCs, including embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs), has revolutionized stem cell research and cell-based therapies. Numerous studies using ESCs in animal models have shown their therapeutic potential. For example, undifferentiated ESCs have been shown to differentiate into dopaminergic (DA) neurons and restore motor function in Parkinson disease (PD) models after transplantation (Bjorklund et al., 2002; Grealish et al., 2014; Takagi et al., 2005; Xiong et al., 2021). ESCs have also demonstrated effectiveness in promoting functional recovery after cerebral ischemia (Wei et al., 2005) and in spinal-cord-injured mice (Bottai et al., 2010). Additionally, in different animal epilepsy models, it has been shown that grafted medial ganglionic eminence (MGE) progenitors exhibit normal migratory activity, differentiate into GABAergic inhibitory neurons, and integrate into the neural circuitry to help suppress seizures (Arshad et al., 2022; Baraban et al., 2009; Bershteyn et al., 2023; Casalia et al., 2017; Chen et al., 2024a; Hunt et al., 2013; Shetty and Upadhyaya, 2016). However, since hESCs are derived from the inner cell mass of the developing blastocyst, and their use is limited due to the ethical concerns and the potential risk of tumor growth. To address these issues, hiPSCs were generated, offering molecular and biological properties similar to hESCs (Takahashi et al., 2007; Takahashi and Yamanaka, 2006; Yu et al., 2013), thus opening new avenues for cell replacement therapy. hiPSCs have since been widely applied in brain repair across different disease models. For example, hiPSCs, derived from human fibroblasts, have demonstrated therapeutic potential in models of stroke (Chang et al., 2013; Chau et al., 2014) and PD (Song et al., 2020; Stoddard-Bennett and Reijo Pera, 2019). Additionally, long-term survival and functional efficacy of hiPSCs-derived dopamine cells have also been observed in non-human primate PD models (Kikuchi et al., 2017). GABAergic interneurons/MGE-like interneuron precursors derived from hiPSCs have also been shown to attenuate chronic epilepsy and its associated comorbidities (Cunningham et al., 2014; Upadhyaya et al., 2019).

MSCs possess the ability to self-renew and differentiate into mesenchymal lineages (Ankrum and Karp, 2010; Nombela-Arrieta et al., 2011; Zhou et al., 2021). They have been widely reported to exhibit therapeutic effects in various neurological diseases, including stroke (Bang

et al., 2005; Gao et al., 2018; Khalili et al., 2014; Lee et al., 2010) and neurodegenerative diseases (Cova et al., 2010; Ma et al., 2013; Mostafavi et al., 2019; Wu et al., 2017a). They can be easily acquired from the host to avoid the transplant rejection (Seo and Cho, 2012) and are capable of crossing the blood-brain barrier (BBB) without disrupting its structure (Chen et al., 2015b; Kopen et al., 1999). Moreover, MSCs have displayed the ability to migrate to the injured area (Oh et al., 2018; Schmidt et al., 2006), differentiate into neurons (Wislet-Gendebien et al., 2005), and rebuild neurological functions through the secretion of various neurotrophic factors (Kawai et al., 2015; Liu et al., 2006).

A relatively limited number of small-scale clinical trials have investigated the safety and feasibility of stem cell therapies (Chung et al., 2021; Elshaer et al., 2021; Jaillard et al., 2020; Kalladka et al., 2016). A meta-analysis of early-phase clinical trials using MSCs in ischemic stroke patients reported a favorable safety profile alongside functional improvement (Li et al., 2020). However, more recently, a phase 2/3 trial investigating intravenous administration of umbilical cord blood-derived MSCs in acute ischemic stroke patients failed to demonstrate a significant functional improvement at 90 days (Houkin et al., 2024). These results underscore the need for further optimization of stem cell therapies for stroke, including the selection of patients most likely to benefit, the timing, and route of administration. Additionally, clinical trials have also evaluated the safety and feasibility of stem cell therapies for other neurological diseases, such as spinal cord injury (SCI) (Bydon et al., 2024; Curtis et al., 2018; McKenna et al., 2022; Xu and Yang, 2019) and autism spectrum disorder (Villarreal-Martinez et al., 2022).

In conclusion, cell transplantation holds great therapeutic potential for treating neurological diseases. However, it remains in its infancy as several challenges persist, including ethical concerns, immune rejection, complications, adverse reactions, and the risk of tumorigenicity. Current support primarily comes from early-stage clinical trials, which have limitations such as small sample sizes, lack of placebo controls, and short follow-up periods, making it difficult to draw definitive conclusions. In addition, a deeper understanding of the underlying mechanisms is still needed, along with solutions to control the proliferation and differentiation properties of transplanted cells, to optimize the stem-cell-based therapeutic strategies. Future directions may involve the development of personalized stem cell therapies tailored to each patient's specific needs, the use of gene editing technologies to enhance the therapeutic properties of stem cells, and the exploration of combinational approaches to enhance the efficacy of stem cell transplantation. Meanwhile, well-designed clinical



trials with larger sample sizes and more extended follow-up periods will be essential.

On the other hand, while regenerating diseased tissue/organs to restore function remains the ultimate goal of cell transplantation, a more immediate and practical application for cellular models lies in preclinical drug discovery. Cellular disease models can offer many advantages over traditional methods; for example, they can provide a renewable source of human cells with genetic background sensitive to disease pathology (Brennand et al., 2011; Israel et al., 2012; Jiao et al., 2013; Marchetto et al., 2010).

***In vitro/in vivo* reprogramming**

Recent advances in direct reprogramming of mature differentiated cells into alternative fates have provided new insights into mechanisms that define and maintain cell identities (Boudreau-Pinsonneault et al., 2023; Schaukowitch et al., 2023; Wang et al., 2021b). More than 20 years ago, retroviral-mediated expression of the transcription factor (TF) Pax6 was found to instruct neurogenesis in astrocytes *in vitro*, highlighting the role of Pax6 as an intrinsic fate determinant of the neurogenic potential of glial cells and marking the first evidence of *in vitro* reprogramming (Heins et al., 2002). Subsequently, direct astroglia reprogramming toward a glutamatergic (Neurog2 or NeuroD1) or GABAergic (Ascl1 or Dlx2) neuron fate was achieved using single TFs (Heinrich et al., 2010, 2011). Beyond astroglial cells, fibroblasts and other cell types have also been successfully reprogrammed into neurons *in vitro*. Furthermore, combinations of TFs, microRNAs, and small molecules and other factors have significantly enhanced the efficiency and functional maturity of induced neurons (iNs), representing a huge boost to the field of *in vitro* reprogramming field (Ambasudhan et al., 2011; Caiazzo et al., 2011; Inoue et al., 2014; Karow et al., 2012; Pang et al., 2011; Xu et al., 2015).

Inspired by iPSCs and *trans*-differentiation technologies that were initially developed in *in vitro* cultures, the concept of *in vivo* reprogramming have recently pioneered as a new strategy for regenerative medicine, aiming at converting endogenous non-neuronal cells into functional neurons to restore lost functions and correct neurological deficits (Heinrich et al., 2015; Li and Chen, 2016; Wang and Zhang, 2018). Compared with *in vitro* reprogramming followed by cell transplantation, *in vivo* reprogramming avoids the complications of cell culture conditions and the serious concerns such as immune rejection associated with transplantation.

While neurons are frequently lost in response to pathological conditions, glial cells typically react to injury by becoming proliferative and hypertrophic, which is a common pathological hallmark of many neurological disorders. Although these cells may initially play beneficial

roles, their persistent activation and scar formation are generally believed to hinder neural regeneration and may contribute to secondary tissue damage (Robel et al., 2011). Therefore, glial cells, which are the most abundant and ubiquitously distributed non-neuronal cells in the adult CNS, provide the predominant cell source for *in vivo* reprogramming. Initial studies have demonstrated that astroglial cells can be successfully transdifferentiated into neurons *in vivo* in an intact brain (Heinrich et al., 2010; Niu et al., 2013; Torper et al., 2013). These reprogramming strategies have since been successfully applied to diverse disease models and other types of glia cells. For example, Guo et al. reported that reactive glia cells in the cortex of stab-injured or AD model mice can be directly reprogrammed into functional iNs *in vivo* by forced expression of NeuroD1 (Guo et al., 2014). Similarly, Heinrich et al. reported the Sox2-mediated conversion of NG2 glia into iNs in the injured adult brain cortex (Heinrich et al., 2014). Matsuda et al. demonstrated that overexpressing NeuroD1 directly converted mouse microglia into neurons both *in vitro* and *in vivo*, indicating the potency of NeuroD1 in cross-lineage reprogramming. Furthermore, such *trans*-differentiation strategies have been applied to brain repair and found of great potential. For instance, reactive glia in TLE models have also been reported to be reprogrammed into GABAergic interneurons and help reduce chronic seizure activity (Chen et al., 2022; Lentini et al., 2021; Zheng et al., 2022a). More advances in the field of *in vivo* reprogramming have been summarized and presented below in Table 6.

Although *in vivo* reprogramming holds considerable promise, there still remain significant controversies in the field. For instance, Rao et al. critically reevaluated the potential of NeuroD1 to convert microglia into neurons. Contrary to earlier findings suggesting successful conversion, their findings indicated that NeuroD1 overexpression did not induce microglia-to-neuron conversion but instead induced microglial apoptosis (Rao et al., 2021). Similarly, Wang et al. employed rigorous lineage-tracing techniques to reevaluate the astrocyte-to-neuron conversion in the adult mouse brain (Wang et al., 2021c). They found that neurons presumed to be derived from astrocytes via NeuroD1 overexpression (Chen et al., 2020b) or PTBP1 knockdown (Qian et al., 2020) could not be traced retrospectively to quiescent or reactive astrocytes, thus challenging the specificity and validity of these reprogramming strategies. Collectively, these findings highlight that the field is evolving from initial enthusiasm to a more nuanced understanding of the challenges involved, particularly regarding cell identity, reprogramming fidelity, and experimental reproducibility. These controversies emphasized the necessity for rigorous experimental design and validation, including the use of stringent genetic

Table 6. Advances in the field of *in vivo* reprogramming in the brain

Reprogramming strategy	Vectors	Generated cells	Reprogramming environment	Functional outcome	References
Resident astrocytes					
Ascl1/Brn2/Myt1l	LV	NeuN	intact striatum	ND	Torper et al., 2013
Sox2	LV	DCX	intact striatum	ND	Niu et al., 2013
Sox2 /BDNF-Noggin or VPA	LV	NeuN	intact striatum	immature excitability (5/18) and mature excitability (13/18); while most of them (17/18) formed synapses with endogenous striatal neurons (>10w)	
Sox2 /BDNF-Noggin or VPA	LV	CR ⁺ interneurons	intact striatum	mature excitability, synaptic input (8–40w)	Niu et al., 2015
ALN (Ascl1, Lmx1A, Nurr1)	AAV	GAD65/67, vGLUT1	intact striatum	ND	Torper et al., 2015
Ascl1		NeuN, VGLUT2, GABA, GAD67	midbrain	mature excitability, synaptic input (30–40d)	Liu et al., 2015
		NeuN	striatum	mature excitability, synaptic input (30d)	
		NeuN	cortex	mature excitability, synaptic input (30d)	
NeAL218 (NeuroD1, Ascl1, Lmx1A, miR218)	LV	TH, DCX, RBFOX3, SLC6A3	striatum in PD model (6-OHDA)	mature excitability; partial functional recovery	Rivetti di Val Cervo et al., 2017
NeuroD1	AAV (intravascular)	DCX, NeuN	intact striatum	ND	Brulet et al., 2017
NeuroD1/Dlx2	AAV	NeuN, GAD67, GABA, DARPP32	striatum, striatum in R6/2 model	immature excitability (30d), synaptic input and output (30d), alleviate neurodegeneration, reduce striatum atrophy	Wu et al., 2020
Reactive astrocytes					
NeuroD1	RV	NeuN/Tuj1	cortex, after stab injury	mature excitability, synaptic input (4w)	Guo et al., 2014
	RV	NeuN	cortex, 5×FAD mouse	synaptic input (4w)	

(Continued on next page)





Table 6. Continued

Reprogramming strategy	Vectors	Generated cells	Reprogramming environment	Functional outcome	References
NeuroD1	RV, AAV	NeuN, MAP2, Cux1, Ctip2, Emx1, Tbr1, Satb2	cortex, focal ischemic injury model	neuronal recovery, cortical tissue repair, mature excitability, synaptic input and output (60d), functional rescue of motor deficits	Chen et al., 2020b
NeuroD1	AAV	NeuN, GAD67, PV, nNOS, SST, CR, CB, CCK	cortex, CA1, DG in TLE model	rescue neuronal loss, mature excitability, synaptic input (6w), reduce seizure activity, rescue behavioral abnormalities	Zheng et al., 2022a
Resident Ng2 glia					
ALN (Ascl1, Lmx1A, Nurr1)	AAV	NeuN, MAP2, GAD65/67, vGLUT1	intact striatum	mature excitability, synaptic input (4w)	Torper et al., 2015
ALN	AAV	PV, ChAT, NPY, DARPP32	intact striatum, DA-depleted striatum, midbrain	mature excitability, synaptic input (5, 8, 12w)	Pereira et al., 2017
NgLN(Ngn2, Lmx1a, Nurr1), ANgN (Ascl1, Ngn2, Nurr1), NgND1(Ngn2, NeuroD1), AFLE (Ascl1, FoxA2, Lmx1a, En1)	AAV	PV, ChAT, NPY, GAD65/67, Ctip2	intact striatum	ND	
Reactive Ng2 glia					
NeuroD1	RV	NeuN/Tuj1	cortex, after stab injury	ND	Guo et al., 2014
Sox2	RV	NeuN/DCX	cortex, after stab injury	immature excitability, low frequency synaptic input	Heinrich et al., 2014
Unspecified reactive glia					
Neurog2/GFs	RV	DCX/NeuN/Glu/Bhlhb5	neocortex, after stab injury	ND	Grande et al., 2013
		DCX/NeuN	neocortex	ND	
		DCX/NeuN/GLU	neocortex, ischemia	ND	
Neurog2/GFs	RV	DCX/NeuN/Tuj1/MAP2/GABA/Isl1	striatum, after stab injury	synaptic output (12w)	
		DCX/NeuN	striatum	ND	
		DCX/NeuN	striatum, ischemia	ND	
NeuroD1	RV	DCX/NeuN/Tbr1/Ctip2	cortex, after stab injury	mature excitability, synaptic input (4w)	Guo et al., 2014

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Table 6. Continued					
Reprogramming strategy	Vectors	Generated cells	Reprogramming environment	Functional outcome	References
Neurog2/Bcl-2/calcitriol or α T3 (antioxidants)	RV	DCX/NeuN/Ctip deep layer neurons	cortex, after stab injury	mature excitability	Gascon et al., 2016
Ascl1/Dlx2	RV	DCX/NeuN/GAD/VIP/SST/NPY	hippocampus, at 5dpKA	properties of physiologically functional interneurons, widespread synaptic input (7w), establishment of GABAergic synapses with DGcs, reduces SRs in MTL mice	Lentini et al., 2021

Abbreviations: ND, not determined; LV, lentivirus; VPA, valproic acid; CR, calretinin; DCX, doublecortin; SST, somatostatin; DGcs, dentate granule cells; SRs, spontaneous recurrent seizures; DA, dopamine; MTL, mesial temporal lobe epilepsy.

lineage tracing, appropriate controls, and reproducibility across models, to accurately assess the true potential of *in vivo* reprogramming.

CONCLUSIONS AND PERSPECTIVES

Since the discovery of AHN, remarkable progress has been made in understanding its characteristics, functional contributions, and regulatory mechanisms. Additionally, several key directions are emerging that may shape the future of regenerative medicine.

Direction 1: Targeting endogenous adult hippocampal neurogenesis as alternatives to treat neurological diseases

Currently, therapeutic approaches primarily focus on managing symptoms and slowing disease progression, rather than targeting the underlying pathology. For example, dopaminergic medications for PD, cholinesterase inhibitors for AD, and ASMs for epilepsy, all offer limited relief. Given these limitations, there is a pressing need for innovative approaches, such as regenerative medicine, to develop disease-modifying therapies. As mentioned above, different signaling pathways, environmental conditions (EE, physical exercise, etc.), and pharmacological treatments are being studied for their potential to modulate endogenous neurogenesis—possibly through regulating NSCs—to promote neuroprotection, neuro-repair, and immunomodulation in various CNS diseases.

The signaling pathways outlined in Table 5 offer valuable insights into potential druggable targets that could modulate AHN and facilitate drug development. Additionally, many current pharmacological medications, as discussed, also hold the potential to regulate AHN, although researches are required to unravel their novel therapeutic effects in CNS diseases. However, there still remain challenges that may discourage the supposed clinical translations. First, AHN is quite a complex and dynamic process, with ABNs being highly heterogeneous, consisting of both “helpful” and “harmful” subpopulations. For instance, aberrant ABNs with HBDs and hilar ectopic ABNs are generally considered to be “harmful” (Austin and Buckmaster, 2004; Cameron et al., 2011; Kelly and Beck, 2017). In addition, ABNS generated at different time points with regard to seizure onset are also possibly heterogeneous, with conflicting results produced when modulating them (Cho et al., 2015; Jain et al., 2024; Li et al., 2024b; Zhou et al., 2019). Unfortunately, current technologies are insufficient to precisely distinguish between the heterogeneous ABNs and selectively manipulate these diverse ABN populations, making targeted interventions challenging.



On the other hand, small molecules are often reported with limited bioavailability and poor ability to cross the BBB. These issues complicate efforts to effectively deliver drugs to neurogenic niches in the hippocampus. To address these limitations, advanced drug delivery systems, such as micro/nano-particulate delivery vehicles, are being developed. These systems can be engineered for spatiotemporal control, enabling the release of multiple biomolecules at specific time points to modulate signaling pathways within the neurogenic niche more precisely. Such innovations hold promise for overcoming these barriers and enhancing the clinical utility of AHN-targeting therapies.

EE and physical exercise may offer promising non-invasive strategies with significant therapeutic potential for patients. However, the exact underlying mechanisms remain elusive. Gaining a deeper understanding of these mechanisms may help optimize the paradigms of EE/exercise and identify patients that are mostly likely to benefit. While these approaches are generally considered safe, additional clinical trials are required to assess their efficacy in patients with various neurological diseases.

Last but not least, all of the above-mentioned strategies targeting AHN can also be combined with conventional medical therapy, helping to reduce the required dosages, potentially minimizing their side effects, and accelerate patients' recovery, serving as complementary treatments.

Direction 2: Targeting adult hippocampal neurogenesis may be potential in dealing with neurological comorbidities

In clinic practice, patients often present with complex clinical conditions, where cognitive and emotional symptoms coexist with the primary disease. Such presence of comorbidities can significantly influence the severity of symptoms, treatment efficacy, and the overall prognosis. Therefore, addressing comorbidities is crucial when developing effective treatment strategies. Considering the above-mentioned universal benefits of AHN across various neurological diseases, as well as its crucial role in learning and memory, targeting AHN emerges as a promising approach to manage neurological comorbidities.

Cognitive deficits are among the most common and significant neurological comorbidities. Patients with TLE frequently experience cognitive decline alongside seizures (Kanner et al., 2020; Operto et al., 2023; Ratcliffe et al., 2020). Similarly, post-stroke cognitive impairment often arises during the chronic phase of ischemic stroke (Huang et al., 2022; Rost et al., 2022). In animal studies, modulating AHN has proven to be an effective strategy to alleviate cognitive comorbidities. For instance, Cho et al. used a transgenic mouse model to selectively ablate AHN and found a reduction in SRSs along with a restoration of cogni-

tive deficits associated with epilepsy (Cho et al., 2015). Additionally, enhancing AHN through strategies like EE has been shown to improve learning and memory, while simultaneously helping to manage epilepsy (Zhang et al., 2015). Although it is hard to manipulate the levels of adult neurogenesis in the human brain, recent research has shown that the decline in verbal learning during epilepsy progression coincides with an exponential loss of immature neurons, indicating a correlation between AHN and epilepsy-associated cognitive deficits (Ammothumkandy et al., 2024; Wang and Chen, 2025). This finding highlights an opportunity to advance regenerative medicine for patients with TLE and cognitive deficits. On the other hand, AHN modulation, for instance through EE, has been reported to facilitate functional recovery after stroke and help improve learning and memory (Gresita et al., 2022; Nagase et al., 2023; Tang et al., 2019b). HIIT has also demonstrated a preventive role on stroke severity while promoting neurogenesis, neuroplasticity, and cognitive recovery after stroke (Hugues et al., 2021).

In addition to cognitive deficits, targeting AHN may also be promising in treating comorbidities such as depression and anxiety, which also often accompany conditions like epilepsy and stroke. EE, a well-established method to promote AHN, has been shown to reduce SRSs in a chronic epilepsy model while alleviating accompanying depression (Vrinda et al., 2017). Selective IL-17a deletion was found to reduce anxiety levels in a pilocarpine-induced SE model, through hippocampal neuroprotection and the reduction of hilar ectopic ABNs, providing a novel target for TLE-associated anxiety (Choi et al., 2022). In contrast, a more recent study demonstrated that mice lacking BMP antagonist Gremlin2 showed decreased AHN, displayed a higher susceptibility to, and increased severity of seizures, together with increased anxiety levels (Frazer et al., 2024). Similarly, by conditionally knocking out Shh signaling receptor *Smo* in NSCs, Wang et al. found a decrease of intact AHN and stroke-induced neurogenesis, with mice displaying delayed motor function recovery and increased anxiety level after stroke (Wang et al., 2022b). On the one hand, these findings further support the idea that targeting AHN via manipulating related signaling pathways may be of great potential to address comorbidities in neurological diseases. On the other hand, their conflicting results also re-emphasize the challenges of clinic translation provided by the heterogeneity of ABNs.

By targeting AHN, regenerative medicine offers a promising approach to treat not only the primary neurological conditions but also the associated cognitive and emotional comorbidities, making it a valuable therapeutic avenue for improving the overall quality of life in patients with complex neurological disorders. However, the causal relationship between AHN and comorbidities remains to be further



explored, understanding of which may help clarify the underlying mechanisms of comorbidities.

Direction 3: Sequencing technologies may be used to distinguish the heterogeneous neurogenic cell populations and identify targets for precise regenerative manipulation

Sequencing technologies, particularly scRNA-seq, are a powerful genomic technology that allows researchers to analyze the transcriptome (gene expression profile) of individual cells (Lu et al., 2024; Slovin et al., 2021). They offer groundbreaking potential to distinguish the heterogeneous neurogenic cell populations. Additionally, these technologies provide an unprecedented level of detail in understanding the cellular and molecular diversity within the neurogenic niches of the adult brain, such as the hippocampus and SVZ (Artegiani et al., 2017; Ayhan et al., 2021; Zywitzka et al., 2018). Importantly, enhancing the “fitness” of these neurogenic niches in individuals at elevated risk for certain neurological diseases may also emerge as a promising preventative or disease-modifying strategy.

Previous studies have highlighted the heterogeneity of ABNs in seizures at multiple levels: (1) in contrast to normotopic ABNs, those with aberrant morphologies or locations tend to be pro-epileptic; (2) ABNs generated at different time points relative to seizure onset may function differently in seizures due to variations in their input and output neural circuits. Thus, conflicting findings regarding the roles played by ABNs in seizures can likely be attributed to this heterogeneity (pro-epileptic, anti-epileptic, and non-functional ABNs co-exist). Using sequencing technologies, it may be possible to identify molecular signatures for these heterogeneous ABNs, paving the way for selective manipulation of ABN in future epilepsy research and treatment. In addition, by analyzing the DG transcriptome from drug-resistant epilepsy patients, as well as from epilepsy patients and non-epileptic individuals, we may find more both cellular and molecular potential targets to further elucidate the pathological mechanisms underlying epileptogenesis.

As highlighted by Salter et al., key mechanistic questions as to what renders an individual more susceptible or resilient against developing neurological diseases, such as AD, may be addressed by utilizing sequencing technologies in the brains of a unique group of elderly individuals who maintain cognitive function despite substantial AD pathology. Sequencing technologies may facilitate the understanding of the specific characteristics of neurogenic cell populations, distinguish heterogeneous subpopulations, and reveal how they contribute to brain functions. Moreover, single-cell and spatial transcriptomic approaches can uncover how the transcriptional profiles of these cells are altered during the progres-

sion of AD disease and whether they are involved in cognitive reserve (Salta et al., 2023). For example, a recent study employing single-cell transcriptomics in the post-mortem DG of AD patients not only confirmed a decrease in a neuronal population with immature transcriptional profile but also identified 14 downregulated genes in AD associated with synaptic plasticity and signaling (Zhou et al., 2022). Gaining such insights could greatly facilitate biomarker discovery and guide the development of precision medications aimed at restoring neurogenesis, promoting neuronal repair, or even reversing the decline in neurogenic potential associated with AD and other diseases (Kalamakis et al., 2019; Uzuner et al., 2024; Zheng et al., 2022b).

Sequencing technologies may also help revolutionize the field of stem-cell therapy. By profiling gene expression at the single-cell level, scRNA-seq allows researchers to identify distinct NSC subtypes based on their activation states, differentiation potential, and regional identities (Artegiani et al., 2017; Hochgerner et al., 2018; Llorens-Bobadilla et al., 2015). This precision facilitates the selection of the NSCs with proliferative potential and identification of key molecular signatures that define neurogenic capacity, which can be further exploited for regenerative medicine. Furthermore, scRNA-seq may be used to identify subpopulations within cell sources that exhibit different differentiation potentials. By identifying and characterizing these subpopulations, researchers can select the most suitable cell source based on specific therapeutic goals. For instance, subpopulations with a propensity to differentiate into GABAergic interneurons can be selected to treat conditions like epilepsy. Moreover, scRNA-seq contributes to the understanding of differentiation processes, revealing the gene expression dynamics and identifying key transcription factors that regulate the transition to a neural lineage. This information not only improves our understanding of differentiation but also may provide insights into how culture conditions can be optimized to control the fate of stem cells during cell transplantation or *in vivo* reprogramming. Last but not least, sequencing technologies allow for the identification of specific genetic mutations responsible for various diseases. This capability enables the creation of personalized gene-edited iPSCs or autologous stem cell therapies, where the patient's own cells are reprogrammed and corrected for specific mutations, offering a precise and tailored approach to treatment.

Taken together, sequencing technologies are transforming stem cell therapy by providing deep insights into stem cell biology, enhancing precision, and enabling personalized treatments. These innovations allow for a more targeted approach to stem-cell-based therapies, paving the way for more effective, safe, and sustainable regenerative treatments for a wide range of diseases.



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AUTHOR CONTRIBUTIONS

L.Y.C. compiled literature research, conceptualized, and wrote the manuscript. Z.X.L. compiled literature research and produced the figures. W.Q.W., Y.T.Z., and W.L.L. reviewed and edited the manuscript. Y.W. conceptualized, reviewed, and edited the manuscript. All authors read and approved the final manuscript as submitted.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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