Chapter 6

Postnatal Neurogenesis in the Subventricular Zone: A Manipulable Source for CNS Plasticity and Repair

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Additional information is available at the end of the chapter

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1. Introduction

Neurogenesis is the production of new nerve cells or neurons, a specialized class of cells that make up the functional components of the central nervous system (CNS). Throughout most of the CNS this process of neurogenesis is limited to the developmental period before birth, after which time no new cells are added to the pre-established circuitry. In mammals including humans however, neurogenesis persists into the early postnatal period in two discrete brain regions: the subgranular zone in the hippocampus and the subventricular zone (SVZ) lining the lateral ventricles [1-5]. It is unknown why neurogenesis continues in such discrete locations yet is excluded from most other brain regions. A finite number of neurons is thought to afford us a stable set of circuitry that is able to accumulate and assimilate experiential information throughout our lifetimes. However, this predetermined number of neurons is also our Achilles' heel as any accidental or pathological damage to the CNS often results in irreparable damage to neurons. Consequently, there is a great unmet need for endogenous sources of brain repair, for conditions such as neurodegenerative disorders, cognitive neurological impairments, epilepsy, and cancer. This reason is one of the primary driving forces behind the study of postnatal neurogenesis and it is hoped that once the mechanisms are understood, this process can be harnessed to provide therapeutic avenues for intractable neuropathologies. Considerable progress has been made in the last twenty years to unravel the mechanisms that both define and limit postnatal neurogenesis.

In this chapter we will limit our discussion to therapeutically relevant regulators of SVZ neurogenesis. We will first start with potentially manipulable intracellular and extracellular factors that have been found to control SVZ neurogenesis. Then, we will evaluate the signaling cascades downstream of neurotransmitter receptor activity that have also been shown to play

regulatory roles within the SVZ. Finally, we will discuss the neuropathologies in which SVZ neurogenesis has been implicated.

In the two neurogenic regions, resident pools of slow-dividing, astrocyte-like stem cells generate highly proliferative transit amplifying progenitors that then give rise to fate-committed neuronal or glial precursors [1-4]. These precursors (called neuroblasts or glioblasts) then migrate to their final destinations and differentiate into postmitotic neurons, astrocytes and oligodendrocytes. In the case of neurogenesis, newborn neurons undergo additional maturation steps to develop an appropriate dendritic morphology, receive and form synapses, and survive an activity-dependent competitive process to integrate into the local circuitry [5]. Thus, neurogenesis may be broadly divided into two phases: an early phase that includes (a) stem cell proliferation, neuronal vs. glial fate commitment and migration; and a later phase that involves the (b) morphological and synaptic development and survival of newborn neurons. Throughout this chapter, astrocytic stem cells are defined as the self-renewing, multipotent cells present in the SVZ that express glial markers, including the glutamate aspartate transporter (GLAST), the intermediate filament proteins glial fibrillary acidic protein (GFAP) and nestin, and the carbohydrate Lewis X (Lex) [1;6]. Intermediate progenitors, also called transit amplifying progenitors, express epidermal growth factor receptor (EGFR) and mammalian achaete-scute homolog 1 (Ascl1/Mash1), while neuroblasts, or neuronal precursors, are defined by the presence of immature neuronal markers, including doublecortin (DCX) and βIII-tubulin (Tuj1) [7-10].

In the SVZ, astrocytic stem cells reside in-between the striatal parenchyma and the ependymal cell layer that lines the lateral ventricles [11]. These stem cells generate rapidly dividing transit amplifying progenitors, which give rise to neuroblasts that migrate by moving tangentially through the rostral migratory stream (RMS) and into the olfactory bulb (OB) [12-14]. During migration these proliferative cells travel in chains, and are ensheathed by specialized astrocytes [15]. In the OB the neuroblasts exit the RMS, change direction and migrate radially outward to differentiate into dopaminergic and GABAergic periglomerular and granule interneurons [16-20]. Granule cells form dendrodendritic reciprocal synapses with mitral and tufted neurons in the bulb and inhibit their activity to fine-tune their output, ultimately playing a role in olfactory discrimination and learning [21]. Periglomerular cells make one-way as well as reciprocal synapses with the apical dendrites of the mitral/tufted cells and the terminals of the olfactory nerves that converge into the glomeruli [20;22;23]. The progression from astrocytic stem cell to neuronal progenitor to synaptic integration requires tightly coordinated, complex regulation by a multitude of factors.

2. Progenitor proliferation, fate commitment and migration in the SVZ

2.1. Intracellular factors

SVZ neurogenesis is subject to tight regulation, confined to isolated microenvironments and sensitive to neuronal activity, stress, and aging. This control may be required to prevent network instability, maintain experience-driven memory and behavioral patterns, and prevent

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tumorigenesis. To this end, cell-intrinsic factors comprise a major component of this regulation and help coordinate neurogenesis by forming the bulwark of how cells make choices and adapt to changes in their environments. Importantly, these intracellular factors may represent clinically tractable opportunities for the treatment of neuropathologies.

In the postnatal SVZ, progenitor fate commitment is sequentially driven by a family of proneural proteins called the basic helix-loop-helix (bHLH) transcription factors, such as Mash1/Ascl1, neurogenin2 (Ngn2), Neuro-D1, Neuro-D2, Tbr1 and Tbr2, in a pattern similar to cortical and hippocampal neurogenesis [24;25]. This bHLH-driven fate commitment is thought to develop in a temporally successive fashion, from more broadly proneural proteins (Mash1/Ascl1) to more neuronal and subtype-specifying (Neuro-D1) [26]. Although more work needs to be done to fully flesh out the role of bHLH proteins in the postnatal SVZ, *in vitro* transient expression of bHLH proteins is sufficient to induce neuronal fate commitment.

Recently, a synthetic small molecule isoxazole 9 (Isx-9) has shown promise in enhancing hippocampal neurogenesis *in vivo*, by targeting a family of regulatory interactors of Mash1/Ascl1, the myocyte-enhancer family (Mef2) [27]. This study heralds future therapies that can target and harness specific intracellular pathways within the neurogenic niche to direct neurogenesis.

The bHLH proteins are thought to induce differentiation in part by activating cyclin-dependent kinase inhibitors that then induce cell cycle exit. This finding has been shown in culture and awaits confirmation *in vivo* [28]. Cdk inhibitors p27KIP1 and p19INK4d have also been shown to modulate proliferation in the SVZ. Mice lacking p27KIP1 show increased progenitor proliferation and a reduction in neuroblast number [29;30]. Furthermore, mice deficient for both p27KIP1 and p19INK4d display renewed proliferation of post-mitotic neurons and increased cell death- causing seizures, movement disorders, and death by postnatal day 18 [31]. This indicates that cdk inhibitors positively regulate cell cycle exit in SVZ progenitors and their absence prolongs or renews cell cycling. Cdk inhibitors mediate cell cycle exit by inhibiting phosphorylation of the retinoblastoma protein (Rb) [32]. Dephosphorylated Rb binds to and sequesters the E2F transcription factor that normally functions in the nucleus to positively regulate cell cycle progression, thereby promoting cell cycle exit. In the SVZ, E2F-deficient mice show reduced progenitor proliferation and neuroblast numbers, suggesting that E2F transcriptional activity is required for cell cycle progression and the maintenance of neurogenic ability [33]. Additionally, mice lacking the gene encoding the tumor suppressor p53, another cell cycle regulator, displayed enhanced proliferative capacity and increased differentiation into neurons and oligodendrocytes [34]. Taken together, these results outline a stereotyped program of cell-intrinsic mechanisms at work within the SVZ to regulate the proliferation and fate commitment of SVZ progenitors in the early steps of postnatal neurogenesis. The development of therapies that can target these pathways within neurogenic niches is the next step for endogenous sources of brain repair.

MicroRNAs (miRs) are short, non-coding, single-stranded RNA molecules approximately 19-23 nucleotides in length that regulate gene expression by binding to complementary elements in the untranslated regions of target mRNAs and inhibiting protein synthesis. They exert epigenetic control either to maintain the status quo in a cell, (*i.e.* to maintain tissue

identity), or they act in dynamic processes occurring within cells to refine and sharpen transitional states, (*i.e.* facilitating the switch in expression profile occurring at active synapses that were previously silent) [35-37]. Their role in shaping the temporal dynamics and phenotypic outcome of gene regulatory networks means that the functions of particular miRs become especially resolvable in plastic processes like postnatal neurogenesis, and miRs have recently been implicated in regulating the fate commitment of SVZ progenitors [38]. Although as yet untested, one idea for how bHLH proteins are sequentially activated and repressed and the transitions from multipotent progenitor to post-mitotic neuron more sharply defined is the successive miR-mediated downregulation of targeted bHLH proteins. In the SVZ, microRNA-124 was shown to be upregulated upon neuronal differentiation in the SVZ, and overexpression increased the number of mature neurons at the cost of proliferative progenitors and neuroblasts, while knockdown decreased mature neuron production and increased the number of glia [38]. MiR-124 was shown to mediate these effects by antagonizing Sox9, a transcription factor that directs glial differentiation. MiR-124 has also been shown to target SCP1, a component of the REST/NRSF complex that represses neuronal genes in non-neuronal cells and PTBP1, a repressor of neuron-specific alternative splicing [39-42].

Together these results indicate that miR-124 is a critical regulator of neuronal development and tissue identity, acting early on in the shift from neuronal precursor to mature neuron. Synthetic miR anologues composed of locked nucleic acid technology (LNA) demonstrate a robust half-life and good tolerance in animal models and may prove a good strategy to induce neurogenesis in a therapeutic setting. Furthermore, transplantable cells stably expressing a complement of miRs may prove beneficial in cellular replacement strategies. Cell-intrinsic factors and their roles in the early phases of postnatal neurogenesis have only begun to become amenable to experimental dissection, and exciting developments are forthcoming.

2.2. Extracellular factors

Neurotrophic factors have long been implicated in the dynamic regulation of postnatal neurogenesis. In the SVZ, fibroblast growth factor 2 (FGF-2) has been shown to affect the early steps in neurogenesis, positively regulating progenitor proliferation and leading to an increase in the number of neurons migrating from the SVZ into the OB [43;44]. Furthermore, FGF-2 is known to interact with epidermal growth factor (EGF) receptor signaling in neuronal progenitors, wherein prior FGF exposure is necessary for progenitors to respond to EGF or transforming growth factor β (TGFβ), the endogenous ligand for EGF receptors [45-49]. EGF has been shown to also increase proliferation specifically in the SVZ transit amplifying progenitor population at the cost of neuronal differentiation. Exposure to EGF induces transit amplifying progenitors to increase their cycling and downregulate neurogenic markers [50]. Vascular endothelial growth factor (VEGF), an angiogenic protein that can produce neurotrophic effects, has been shown to stimulate proliferation and neuroblast production in the SVZ, while insulin-like growth factor-I (IGF-I), a growth factor implicated in mediating the positive effects of exercise on adult neurogenesis, has been also implicated in enhancing proliferation and migration in the postnatal SVZ [51;52].

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Apart from modulating proliferation, diffusible factors have also been shown to affect the initial establishment of the neurogenic niche itself, by influencing stem cell self-renewal and cell fate decisions. The factors that regulate such homeostatic effects within the niche may comprise a separate class of growth factors and unlike FGF-2, VEGF and IGF-I, are not circulating systemically in the bloodstream at appreciable levels nor produced in an acute, dynamically regulated manner. Based on this hypothesis, sonic hedgehog (Shh), Wnts, bone morphogenic proteins (BMPs) and Notch/Delta are extracellular factors possibly acting in a more local fashion. Sonic hedgehog signaling is required for establishing and maintaining the quiescent pool of stem cells in the postnatal SVZ. Ablating Smoothened, the transmembrane protein required for hedgehog signaling, specifically in the SVZ results in the depletion of stem cells and proliferative transit amplifying progenitors by postnatal day 8 and the depletion of neuroblasts by postnatal day 30 [53]. The Notch-DSL (Delta/Serrate/LAG-2) pathway is a very highly conserved cell-cell signaling system that acts through single-pass transmembrane proteins. Binding of Notch to its ligand causes cleavage of an intracellular domain that translocates to the nucleus where it interacts with transcriptional regulators to initiate expression of target genes like Hes1 and Hes5. In mammals, Notch ligands like Delta-like and Jagged bind Notch on stem and proliferative cells to maintain self-renewal and prevent terminal differentiation. In the neonatal SVZ, retrovirally delivered activated Notch enhances the numbers of quiescent SVZ progenitors at the cost of migratory neuroblasts [54]. Another study shows that conditional ablation of Notch signaling in the ependymal cells reprograms these cells and enables them to leave their position in the epithelium, take on SVZ stem cell characteristics and differentiate into granule and periglomerular neurons in the OB [55]. BMPs, a family of growth factors within the transforming growth factor β superfamily, have been shown to instruct a glial lineage in SVZ stem cells, and noggin, a BMP antagonist secreted by the adjacent ependymal cells, blocks glial differentiation of stem cells in favor of neurogenesis [56]. However, deletion of Smad4, a downstream target of BMP signaling, instead of increasing neurogenesis has been shown to result in oligodendrocyte production and a neurogenic deficit [57]. Therefore, it seems that BMP signaling can have divergent effects in the SVZ.

Exciting justification for these disparate lines of research is now beginning to emerge. Small molecule inhibitors of glycogen-synthase kinase 3 (GSK-3) inhibitors have shown promise in enhancing neurogenesis in human neural progenitor cells [58]. GSK-3 is involved in the notch, Shh, Wnt/β-catenin and FGF signaling pathways and represents a movement of the field toward a more clinically oriented direction.

In the SVZ, neuroblasts have to migrate a greater distance than do their analogues in the dentate gyrus, to arrive at their ultimate destinations in the OB. Furthermore, the migration behavior exhibited by SVZ neuroblasts has two phases; it is tangential from the SVZ to the RMS-OB, and then becomes radial-like as the neuroblasts exit the RMS and begin synaptic integration into the granule cell layer. For our purposes in this review both phases of this migration are being considered within the "early" phase of neurogenesis, prior to dendritic arborization, reception of synaptic inputs, and survival. This feature of SVZ neurogenesis distinguishes it from hippocampal neurogenesis where the neuroblasts migrate very short distances, and has allowed for the isolation of a few important guidance molecules that enable

this directed migration. Slit-1 and Slit-2 expression in the SVZ and septum is thought to repel neuroblasts away from the SVZ and towards the OB, while netrin expression in the mitral cells of the OB, and the coincident expression of netrin receptors neogenin and deleted in colorectal cancer (DCC) in neuroblasts may form a chemoattractive cue drawing neuroblasts towards the OB [59-61]. The secreted protein prokineticin2 (PK2) has also been shown to act as potent chemoattractant for SVZ neuronal progenitors. PK2 is expressed in the OB, and attracts SVZ cells to the OB through the two G-protein coupled prokineticin receptors (PRK1 and PRK2) [62]. Both ephrins and their Eph tyrosine kinase receptors are expressed in the SVZ and have been shown to play a role in both regulation of progenitor proliferation and neuroblast migration. EphA7, EphB2 and ephrin-B2 are associated with astrocytic progenitors in the SVZ, while ephrin-A2 is expressed in the neuroblasts. Ephrin-B2 and EphB2 signaling seem to positively regulate progenitor proliferation while also disrupting neuroblast migration in the postnatal SVZ, while ephrin-A2 seemed to positively regulate progenitor proliferation [63;64]. Tangential migration in the RMS has also been shown to involve the $\alpha 6\beta 1$ integrin [65]. Once in the OB, neuroblasts have to reorient from tangential to radial migration into the GCL. This process has been shown to involve the expression of tenascin-R, in both the GCL and internal plexiform layers of the OB, and reelin, expressed by the mitral cells [66-68].

There is now a large amount of information regarding the effects of neurotrophic factors on early stages of SVZ neurogenesis, all of which is not discussed here. Many exciting avenues are emerging for therapeutic intervention into neurodegenerative diseases and psychiatric illnesses and knowledge of how neurogenic niches are formed, maintained, and neuronal and glial programs directed is fundamental for devising a clinical paradigm of directed neurogenesis. However, these data on extracellular factor-based modulation of postnatal neurogenesis needs more critical validation within the context of *in vivo* experiments and behavioral analyses.

2.3. Dopamine

The SVZ is innervated by dopaminergic fibers originating in the substantia nigra, while the SGZ is innervated by dopaminergic fibers coming from the ventral tegmental area (VTA). Dopaminergic signaling has been shown to regulate progenitor proliferation through D2 receptors in both the SVZ and SGZ and D3 receptors in the SVZ [69-71]. In patients with Parkinson's Disease, SVZ proliferation is markedly reduced. This effect on proliferation has been shown to be mediated through the induction of EGF and CNTF secretion from SVZ stem cells in response to dopaminergic activity [72;73]. Dopaminergic deafferentiation reduces proliferation in the SVZ, and one study reports that this decrease in overall SVZ cell proliferation is nonetheless accompanied by an increase in numbers of cells expressing Pax6 in the dorsal SVZ. Pax6 is a transcription factor responsible for enabling a dopaminergic differentiation program in postnatally generated periglomerular neurons. Therefore, dopaminergic activity may not only affect proliferation but may also impact cell fate choice in the SVZ [74]. Drugs that potentiate dopamingergic signaling may represent one strategy to maintain neurongenesis postnatally. Dopaminergic regulation of postnatal neurogenesis is only beginning to be uncovered, and its role in neurogenesis has not been conclusively established as yet.

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2.4. GABA

GABA, a major inhibitory neurotransmitter in the mature CNS, has a well-established role in the development of neuronal circuits in both the embryo and adult [8;75-77]. Its ambient release in the form of spillover from synaptic and extra-synaptic sources has led researchers to its role in regulating the functional integration of new neurons into both immature and mature networks. Owing to the initial abundance of the Cl^- importer NKCC1 and the low expression of the Cl^- exporter KCC2, internal Cl^- concentrations are higher in immature neurons than mature neurons [76]. The resultant high equilibrium potential for Cl^- in neuroblasts causes GABA, acting through $GABA_A$ receptors, to depolarize immature cells in the first few weeks after fate determination. The depolarizing effect of GABA on young neurons and progenitors has been shown to regulate key stages of neurogenesis such as proliferation, migration and morphogenesis, in both the embryonic and adult neurogenic zones [78-80].

Adult neurogenesis in the SVZ recapitulates the embryonic role for GABA [8;81;82]. In the SVZ, both astrocytic stem cells and their neuroblast progeny express $GABA_A$ receptors [5;83]. Electrophysiological evidence indicates that neuroblasts release GABA in a non-synaptic and non-vesicular fashion, and that this tonically activates $GABA_A$ receptors on SVZ astrocytic stem cells [84;85]. The SVZ astrocytes also express GABA transporters that may further regulate levels of ambient GABA within the niche. Pharmacological inhibition of $GABA_A$ receptors in SVZ slice-culture preparations increases mitotic activity within the SVZ [85;86]. Blocking GABA transporters or enhancing GABA release from neuroblasts on the other hand, slows the speed of their own migration, in a paracrine/autocrine fashion in the SVZ and RMS [87]. Furthermore, knocking down Na-K-2Cl cotransporter NKCC1 and thereby reducing GABA(A)-induced depolarization in the SVZ reduced proliferation, migration as well dendrite development [79;80]. These data together suggest that GABA has a role as a negative regulator of early stages of neurogenesis in the SVZ, where it reduces neuroblasts and SVZ astrocyte proliferation and decreases the speed of neuroblast migration. This is analogous to the role of $GABA_A$ activation in the developing cortex, where it also serves to limit proliferation of ventricular zone progenitors and migration of postmitotic neuroblasts [88-90].

GABA's role in regulating early phases of neurogenesis such as proliferation and migration has been examined more extensively in the SVZ where it has been shown to act as a negative regulator of early neurogenesis. Whether these effects are corroborated in the SGZ is as yet unknown. An attractive hypothesis explaining GABA's disparate roles in development, postnatal neurogenesis, and at the synapse is that neurotransmitter-based signaling may serve as a bridge that brings an activity-dependence to cell-autonomous and locally present instructive signals that drive neurogenesis and network plasticity. In this way, neuronal and metabolic activity may loop back onto the SVZ and SGZ.

2.5. Glutamate

During embryonic neurogenesis, glutamate signaling has been shown to influence proliferation, fate commitment, and migration of newborn neurons [88;89;91-93]. During postnatal neurogenesis, in the SVZ neuroblasts have been shown to express functional NMDA receptors as well as functional mGluR5 and GLU_{k5}-containing kainate receptors, using both electro-

physiology and calcium imaging [94;95]. Evidence from our lab suggests glutamate released spontaneously from SVZ-RMS astrocytes generates phasic NMDA receptor activity in neuroblasts migrating towards the OB [96]. Both mGluR5 and GLU_{k5} activation have also been shown to mediate increases in intracellular Ca^{2+} transients in SVZ neuroblasts [95;97]. A mosaic of $GABA_A$, NMDA, mGluR5, and GLU_{k5} (now known as GluK2) receptor-expressing cells reside in the SVZ, where most cells express $GABA_A$ receptors in caudal SVZ and moving rostrally, a greater proportion of cells begin to express a combination of receptors. Ultimately, nearly half of all cells in the rostral RMS express all four types of receptors, indicating the continuing maturation of newborn cells along the SVZ-OB neurogenic axis. Mice lacking mGluR5, or in which mGluR5 was pharmacologically blocked, displayed a marked decrease in the number of proliferating cells in the SVZ [98]. This indicates a role for glutamate -acting tonically through metabotropic receptors- in positively regulating SVZ progenitor proliferation and antagonizing tonic $GABA_A$-ergic receptor-induced anti-mitotic activity; perhaps acting as a positive regulator of early neurogenic processes. Blocking GLU_{k5} in the RMS on the other hand, increased the speed of neuroblast migration, suggesting that tonic GLU_{k5}-mediated glutamatergic transmission decreases neuroblast clearance from the SVZ and acts in concert with GABA's effect on migration in the SVZ [97]. mGluR5 activity however, does not influence migration speed. It could be that GLU_{k5}-mediated signaling activated different Ca^{2+}-dependent intracellular cascades than mGluR5 signaling. It remains to be seen whether AMPA/kainate or NMDA receptor activity can have a positive effect on migration in the SVZ/RMS. These data together suggest that although glutamate receptor heterogeneity and the multiple intracellular pathways they may activate introduce ambiguity into what role glutamate may play in early neurogenesis in the SVZ, metabotropic glutamate receptor signaling enhances proliferation, while AMPA/kainate receptor signaling acts together with GABA to decrease migration of neuroblasts. More work is needed to fully flesh out the roles that the three different glutamate receptor families (NMDA, mGluR and AMPA/kainate) have in the SVZ. Work also is needed to elucidate how glutamate receptor heterogeneity parses among the different SVZ sublineages (Emx-1, Gsh2, Nkx2.1).

The diversity of glutamate receptors, the myriad intracellular pathways that they may activate and the many mechanisms by which levels of ambient glutamate are regulated suggests that glutamate, despite being nearly ubiquitously present, can have very specific and differential effects on SVZ cells. The data so far suggests glutamate may regulate the early phases of neurogenesis in manner that reflects this complexity. However, further work will involve clarifying some of the associated ambiguity surrounding glutamate availability, the receptor complement, the different intracellular pathways, and their effects on neurogenesis.

3. Morphogenesis, synaptogenesis and circuit integration in the OB

3.1. Intracellular factors

Later stages of neurogenesis include the survival, synaptic integration and dendritic elaboration of neuronal precursors within their target sites. CREB (cAMP response element binding)

is a long-studied transcription factor known for underlying the later stages of synaptic plasticity and memory formation, as well as for linking neuronal activity to survival. In the postnatal SVZ-OB, CREB has been shown to be important in the survival and dendritic arborization of SVZ neuroblasts [99]. CREB phosphorylation is transient and parallels maturation, increasing during migration towards the OB and decreasing once radial migration and synaptic integration are completed. CREB-deficient mice show deficits in neuroblast survival in the OB, and CREB inhibition *in vitro* severely attenuates neurite outgrowth, suggesting that CREB positively modulates survival and dendritic elaboration in the OB and plays an important role in the later phases of SVZ neurogenesis. Data from our lab and others suggests that a CREB-regulated microRNA, miR-132, is involved in mediating some of the effects seen by impairing CREB activity in the SVZ. miR-132 expression is upregulated along the migratory route of the SVZ neuroblasts, peaking in the OB, and miR-132 overexpression enhances morphological complexity, spine density and survival of newborn neurons *in vivo* [100]. These data suggest that CREB and a CREB-regulated miRNA may form the basis of a structural plasticity program seen in SVZ postnatal neurogenesis. Intrinsic mechanisms regulating later stages of neurogenesis are some of the least elaborated aspects of postnatal neurogenesis. Additionally, with the emergence of inducible and conditional manipulation techniques, it has become possible to discretely assay the roles of many factors within the context of postnatal neurogenesis. Work is also emerging that utilizes the stop-flox-mediated overexpression of factors in a conditional and inducible manner. MiR-132 and other recently identified miRs that promote synapse maintenance because of their ease of delivery represent therapeutic strategies for the stable maintenance of newly generated neurons in disease states.

3.2. Extracellular factors

Later stages of postnatal neurogenesis have also been shown to be responsive to neurotrophic factor signaling. A single nucleotide polymorphism in the human brain derived neurotrophic factor (BDNF)-encoding gene (Val66Met) has been shown to correlate with mood disorders and memory deficits, and knock-in mice possessing the human SNP showed reduced activity-dependent BDNF secretion ultimately resulting in reduced survival of SVZ neuroblasts and impaired spontaneous olfactory discrimination [101]. In this study, activity-dependent BDNF signaling in the SVZ was shown to exert its effects on survival and olfactory function through TrkB receptors on neuroblasts. BDNF signaling and Trk receptor activity have been widely shown to have neurotrophic and synapse-potentiating effects in neurons and may represent a general strategy to promote the survival and maintenance of newly generated neurons.

Later stages of neurogenesis are poorly studied in the SVZ. Knowledge of molecules regulating the survival, synaptic integration and morphogenesis of newborn cells is more limited in comparison to the literature covering the DG. However, BDNF-signaling is an example of emerging data within the field that unites hypotheses between the two neurogenic niches. It is also interesting to note the sustained differences between the two niche microenvironments. NT-3-signaling is exclusive to the DG and may promote excitatory versus inhibitory neurogenic potential. It has also been suggested that the convergence of dopaminergic and serotonergic fibers defines the SVZ, while convergence of noradrenergic and serotonergic projections may define the SGZ [68].

3.3. GABA

GABA-mediated depolarization of immature neurons has been shown to be critical for synapse formation in the developing cortex [102]. Postnatally, following migration into the OB SVZ neuroblasts begin the process of integrating into the local circuitry by radially migrating out of the RMS core, elaborating a complex dendritic structure and establishing appropriate synapses [5;103]. A role for $GABA_A$ signaling in the initiation, elongation and stabilization of dendritic structures in immature neurons has been established in the OB. Specifically, it was discovered that ambient GABA-induced depolarization and Ca^{2+}-influx was necessary for the stabilization of emerging dendritic protrusions and enhanced the number and length of preexisting dendrites, in SVZ culture as well as OB slice preparations [104]. This effect was specific to the immature neuron population because six days following plating, KCC2 levels had increased sufficiently to block the depolarizing effects of GABA and the modulatory effects of GABA-depolarization on dendrite development. Furthermore, GABA activity promoted initiation and elongation of immature neuroblast dendrites in culture by stabilizing tubulin in its polymerized form. Knockdown of NKCC1 and prevention of GABA-mediated depolarization in immature neurons also resulted in dendritic morphological deficits. However, this effect was transient and dendritiric morphology recovered in adults [80].

This regulation by GABA in both the OB and DG helps shape neurogenesis as an activity-dependent process where GABA is involved in regulating later stages of postnatal neurogenesis orchestrating synapse formation and dendritic outgrowth. However, although GABA's role in the synaptic integration of postnatally generated neurons is becoming clearer, more work is needed to fully flesh out the internal mechanisms by which GABA activity leads to modulation of actions as disparate as proliferation, migration, synaptic integration, and dendritogenesis.

3.4. Glutamate

Glutamate has been shown to be important for neuroblast survival, dendritic development, and synaptogenesis in the developing CNS [105]. In the postnatal SVZ, spontaneous glutamate release from astrocytes onto neuroblasts results in phasic NMDAR activation that increases in frequency and amplitude upon migration towards the bulb. Genetic ablation of the NR1 subunit in migrating neuroblasts results in 60% of these NR1-deficient newborn neurons entering apoptosis, suggesting that NMDAR-dependent glutamatergic signaling is an important factor in regulating neuroblast survival and numbers of new neurons in the OB [106]. Once in the bulb, newly generated neurons begin to integrate synaptically into the local circuitry, generate action potentials and first establish GABAergic inputs followed by glutamatergic inputs ~4 weeks after birth [103]. Recently, newborn granule cells in the OB were shown to express a transient form of LTP in response to focal glutamatergic stimulation in the granule cell layer. This type of LTP was not present in mature granule cells and was observed in cells between 2 and 8 weeks old, implying that new neurons have a capacity for synaptic plasticity that is different from their mature counterparts [107]. Perhaps this sort of synaptic enhancement can help explain the positive effects olfactory learning has on SVZ neuroblast survival, as well as the negative effects anti-mitotic activity in the SVZ has on olfactory discrimination.

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4. Responsiveness and involvement of postnatal neurogenesis in distinct neuropathologies

4.1. Alzheimer's disease

Alzheimer's disease (AD) is a late-onset neurological disease with a heritable component characterized by deposition of β-amyloid peptides (Aβ), formation of neurofibrillary tangles, reactive astrocytosis, activation of microglial cells and cholinergic deficits [108]. The effect of AD is a progressive neurodegeneration throughout the neocortex and hippocampus, and severe dementia [109]. SVZ neurogenesis is reduced in mouse models of AD and has also been shown to be diminished in postmortem tissue from human AD patients. Mice harboring familial mutations in amyloid precursor protein (APP) and presinilin 1 (PS1) show decreased proliferation in the SVZ [110;111]. Infusion of Aβ peptide into the lateral ventricles also decreases proliferation in the postnatal SVZ [112]. SVZ-derived neural progenitor cells from PS1 mutants and the APPSwe/PS1ΔE9 double-mutants showed decreased cycling *in vitro* [112; 113]. In postmortem tissue, AD patients showed decreased numbers of proliferative ($Ki67^+$) cells in the SVZ [114]. Anosmia or hyposmia, the inability or reduced ability to perceive smell, are predictive indicators of Alzheimer's progression in the clinic. However, it remains to be conclusively established whether altered SVZ neurogenesis is the cause of this disrupted olfaction in AD patients.

4.2. Parkinson's disease

Parkinson's disease (PD) develops due to the specific loss of dopaminergic neurons in the substantia nigra (SN) and results in impaired regulation of movement, mood, and motivation [69]. In mouse models of PD SVZ proliferation is reduced. This is thought to be due to the loss of dopaminergic inputs to the SVZ from the SN via the nigrostriatal pathway, as chemical ablation of these fibers results in decreased proliferation in the SVZ and decreased numbers of mature granule neurons in the OB [69;74]. This effect on proliferation was partially rescued with the application of the dopamine precursor levodopa. Furthermore, in postmortem tissue from human AD patients SVZ proliferation was reduced, as were numbers of immature neurons in the granule cell layer of the OB [69]. However, increases in numbers of periglomerular dopaminergic neurons have also been reported in mouse models of PD using chemical ablation, and in PD postmortem human tissue [74;115]. Because dopaminergic activity of periglomerular cells generally inhibits the transmission of olfactory information, it is thought that the decreased numbers of granule cells and the increased numbers of periglomerular cells together contribute to the hyposmia and disturbed olfaction seen in PD patients.

4.3. Huntington's disease

Huntington's disease (HD) is caused by expansions in CAG repeat elements in the gene encoding huntingin. This leads to aggregation of mutant huntingtin and neurodegeneration in the striatum [116]. In mouse models of HD there is little striatal neurodegeneration and consequently SVZ neurogenesis remains unchanged. However, in rat models of striatal

degeneration SVZ proliferation is increased [117;118]. Some cells from the SVZ are seen to ectopically migrate into the damaged striatum and begin expressing markers of newborn neurons, although any functional recovery was not reported [118]. In HD patients an increase in proliferation in the SVZ is observed that corresponds with the number of CAG repeats, and SVZ cells are seen to migrate into the damaged striatum where they express both proliferative as well as mature neuronal markers. It remains to be seen whether the expression of both proliferative and mature markers in SVZ-derived cells within the HD-damaged striatum is symptomatic of HD or in fact, can contribute to functional recovery [119-121]. However, the potential for endogenous repair for HD can still be seen as promising, as newborn neurons would take a long time to develop huntingtin inclusions and in the meantime participate in the maintenance of striatal circuitry.

4.4. Ischemic stroke

A stroke results from either a hemorrhage or blocked cerebral arteries, leading to diminished local blood flow (ischemia) in a brain region and loss of neurons. In stroked tissue, the core infarcted area is distinguishable from the surrounding penumbral area by the exaggerated necrosis and little potential for regeneration. In the penumbral region on the other hand, neuronal regeneration has been demonstrated as it is perfused by collateral arteries and not wholly dependent on the occluded artery for oxygen. As ischemic stroke is one of the most frequent causes of mortality in industrialized countries, a lot of research has been undertaken to probe the capacity for regeneration in this condition. In rodent and primate models of stroke where the medial cerebral artery is occluded (MCAO), SVZ proliferation and the numbers of neurons in the OB are increased [122-124]. In addition, ectopic neurogenesis is also observed in the penumbral areas, such as the striatum [125]. Some groups have also reported ectopic neurogenesis in cortical regions following stroke (Gu 2000, sun 2003) but this has been denied by others [125]. In the stroked striatum, SVZ-derived cells differentiate into medium spiny GABAergic neurons which represent 90% of striatal neurons and are lost there, although once in the striatum many of the newborn neurons undergo cell death [125]. However, this finding is greatly encouraging for the continued study of an effective neuronal replacement strategy as a means to treat stroke damage in the CNS. As proof of this idea, ablating neurogenesis in mouse models of stroke greatly exacerbated cell death and postischemic sensorimotor deficits, suggesting that neurogenesis can account for some amelioration of stroke-induced damage [126]. In human stroke patients, increased proliferation has been observed in the ipsilateral SVZ and traces of ectopic neurogenesis were seen in the cortex [127-129]. The functional recovery that this observed increase in neurogenesis following stroke is able to accomplish remains to be validated, but it does suggest that some measure of recovery is endogenously possible and may be drawn out with continued research and more-tailored therapeutic intervention.

4.5. Epilepsy

Epilepsy has also been shown to alter SVZ neurogenesis. In rats, pilocarpine-induced seizures increased SVZ proliferation as well as expanded the extent of the RMS. Ectopic migration and

increased immature neurons were also observed [130]. In humans, increases proliferation and ectopic migration have also been observed in organotypic slice preparations [131]. These effects on neurogenesis seem to be symptomatic of epilepsy, whether they can be harnessed as a way to treat the damage caused by repeated seizure activity remains to be seen.

4.6. Precancerous lesions and cortical heterotopias

It has long been suggested that the SVZ is the source of origin for malignant gliomas. The prognosis for these cancers is very poor and for glioblastoma, the most common variant in adults, the median survival rate is only 9-12 months [132-134]. A few years ago, in a mouse model of malignant astrocytoma that included a p53 deletion and a conditional disruption of the neurofibromatosis type 1 (NF1) gene, researchers conclusively established that the originating tumorigenic mutation arises within the SVZ atrocyte-like stem cell [135]. Recently it was further shown that although the mutation arises in the neural stem cell, the cancer begins at a subsequent stage, when these stem cells have committed to the oligodendrocytic lineage [136]. Studies of the molecular characteristics of low-grade human astrocytomas suggested that most often in these conditions p53 is deleted and Ras signaling is elevated. Since NF1 is a negative regulator of Ras, its deletion would result in increased Ras activity and in conjunction with the p53 deletion more accurately model human astrocytomas. In mice, this genetic strategy produced astrocytomas with complete penetrance, suggesting that NF1 and p53 deletion are sufficient to induce cancer. When tumor development was closely followed in these mice, it was discovered to arise from the SVZ in nearly every instance before dispersing to other brain regions. These results demonstrate that therapeutic intervention utilizing SVZ neurogenesis must guarantee against the elevated risk of tumorigenesis, and that continued research is necessary to manipulate the proliferation, fate choice, migration and differentiation of SVZ progenitors. Perhaps one day a therapy can be conceived to induce cell death in progenitors that have become transformed into precancerous cell types.

It has also been recently demonstrated that SVZ dysfunction can contribute to the pathophysiology of neuropsychiatric conditions like tuberous sclerosis complex (TSC). TSC is caused by loss of either one of two tumor suppressor genes, *TSC1* and *TSC2*, which encode hamartin and tuberin, respectively. Mutations in these genes lead to hyperactivity of the mammalian target of rapamycin (mTOR) signaling pathway. Neurological symptoms of TSC include seizures, autism, psychiatric problems and the presence or subendymal nodules, heterotopias and giant, ectopically localized cells with both neuronal and glial characteristics. A recent study modeled TSC in mice by conditionally ablating *Tsc1* specifically in the postnatal SVZ. This produced ectopic migration and differentiation of neuronal precursors, resulting in hetertopias and micronodules containing neurons with a hypertrophic dendritic tree in aberrant locations. Furthermore, *Tsc1*-mutant cells were shown to be rerouted to forebrain structures where they differentiated into neurons and glia. This remarkable rerouting of SVZ cells to the cortex is thought to be occurring at a very low rate under normal circumstances, but becomes elevated when mTOR activity is pathogenically increased [137]. It is hypothesized that these ectopic cells in the cortex contribute to network malfunction in higher-order cognitive function. This research also opens up the exciting idea of actively rerouting cells to the cortex, or other desired brain regions, for directed endogenous circuit repair.

5. Conclusion

New neurons continue to be produced throughout life in two regions of the mammalian CNS and a plethora of research has accumulated demonstrating how this amazing propensity for plasticity is orchestrated and regulated. Postnatal SVZ neurogenesis has been shown to make important contributions to coordinated network activity in the OB as well as serving as a sensor for different neurological disease states. But most importantly, it continues to provide tantalizing potentials for a source of endogenous repair within the CNS.

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