Introduction

Adult neurogenesis is an exciting phenomenon whereby new neurons and oligodendrocytes are generated from neural stem cells located in the subventricular zone (SVZ) of the lateral ventricles of the adult brain. Newly born neuroblasts migrate long distances through the rostral migratory stream to the olfactory bulb where they differentiate into both GABAergic and glutamatergic neurons, integrate into existing circuitry and become functionally active, contributing to olfactory discrimination [1]. Oligodendrocyte progenitor cells generated in the SVZ migrate short distances into white matter tracts and contribute to normal cell turnover in this tissue [2, 3]. Neurogenesis from the SVZ has also been shown to be altered in many models of brain injury and neurodegenerative disease [4, 5], indicating the presence of an endogenous repair process which may potentially be harnessed for therapeutic application. However, before treatment strategies can be developed involving endogenous neural stem cells, the underlying mechanisms regulating their proliferation, migration and differentiation in vivo must be fully understood. Currently there is a good understanding of the multiple genes and signalling pathways involved during development of the mammalian forebrain [6, 7], but how these same genes and pathways act in the neurogenic region of the normal adult SVZ, and how this is linked to the functions of the newborn cells is only recently becoming unravelled. There is a huge level of complexity in the regulation of adult neurogenesis, with many of the well known signalling families cross talking, and promoting different cellular fates depending on the developmental stage and location of target cells. This review will focus on the essential intrinsic transcription factors that respond to extrinsic signals to regulate the generation of different progenitor cell types and direct cell fate specification, and how this is affected by brain injury.

Intrinsic regulation of adult SVZ neurogenesis by transcription factors

Transcription factors are proteins that bind DNA and control transcription of genes into RNA, either through direct binding, or with the help of
co-activators or repressors that associate with RNA polymerase and influence its binding to DNA. Proneural transcription factors that promote the expression of neural genes are some of the key intrinsic regulators of neurogenesis and neural differentiation [6]. Many of these genes were discovered through mutation and disease studies of Drosophila and mice that resulted in disruption of brain development or malformation of specific populations of cells in the brain [6]. Knock out studies, cre-lox mice and elegantly designed recombinant reporter mouse models are now helping to elucidate the complex relationships between these genes in the adult brain; how they work together to integrate positional information into the cells specific to the location and time of neuronal generation, regulate cell cycle arrest and direct differentiation.

Classes of proneural transcription factors

There are two main classes of proneural transcription factors: basic helix-loop-helix transcription factors and homeodomain transcription factors [6]. Basic helix-loop-helix (bHLH) proteins contain a structural motif of two alpha helices which allow homo and heterodimerization with other bHLH proteins and their co-factor E proteins. They are grouped into 8 families including the Achaete-Scute family (including Mash1), Neurogenin family (including Ngn1 and Ngn2), NeuroD family (including NeuroD, Math3), Atonal family (including Math1) and the Olig family (including Olig2). The majority of these basic helix-loop-helix transcription factors proteins are proneural, except the Olig family, which has been shown to suppress neurogenesis and promote oligodendrogenesis [6, 8]. Basic helix-loop-helix genes often signal to or in conjunction with homeodomain genes to control neurogenesis. Homeobox genes code for homeodomain transcription factors. Homeodomain proteins are recognised by their 60 amino acid homeodomain that binds DNA. The homeodomain is made up of 3 alpha helices plus a fourth helix, where the middle helices form a helix-turn-helix motif that binds consensus sequences in target genes. Homeodomain transcription factors are further subdivided into families depending on other conserved functional domains that they express in addition to the homeodomain. Families important in neuronal development include; the paired domain family (including Pax6, which contains both a paired box domain and a homeodomain), NK2 Box family (including Nkx2.1), Polyhistidine family (including Dlx2), and LIM domain proteins (including Lhx2) [6, 9].

The adult subventricular zone

The adult rodent SVZ is derived from a mixed population of cells originating from the embryonic telencephalic neuroepithelium, with cells found in the dorsal SVZ descendants of embryonic dorsal cortical cells and ventral SVZ cells originating from the embryonic ventral ganglionic eminence (GE) [10, 11]. Transcription factors intrinsically control telencephalon development with specific expression in patterning domains generating different cell types in a clearly defined sequence (for review see [7, 12]). Dorsal transcription factors Pax6, Ngn2, and Emx1 generate glutamatergic cell fates, while ventral transcription factors including Mash1, Dlx2, Olig2 and Gsh1/2 interact to generate GABAergic neurons and oligodendrocytes. Accordingly, many transcription factors that are expressed in the embryonic cortex and GE including, but not limited to, Pax6, Ngn2, Emx1, Mash1, Dlx2, Olig2, Gsh2 and Nkx2.1, are also expressed in the adult SVZ and RMS [2, 10, 13-17]. Transcription factor expression in different cell types allows identification of subsets of neural progenitor cells, and temporal progression from more broadly neurogenic genes, through to specific neuronal or glial cell type specific genes is indicative of how neurogenesis proceeds in this area.

The adult SVZ is made up of four main cell types and is closely associated with the ventricular vascular plexus [18, 19]. These cells are; Ependymal cells, Type B neural stem cells, Type C transit amplifying precursor cells (TAPs), and Type A cells which are neuroblasts. Displaced ependymal cells, mature astrocytes, and microglia are also located in the adult SVZ, but in lesser numbers [20, 21]. These different cell types can be morphologically identified through ultrastructural analysis, and each also express a different set of cell surface and transcriptional markers to allow for experimental identification. In vitro and in vivo experimentation has shown that lineage progression evolves from the slow dividing Type B stem cell, to fast dividing TAP, to neuroblast or oligodendrocyte precursor cell [14, 22-25]. This progression occurs through a combination of asymmetrical and symmetrical
divisions that maintains self renewal of a stem cell pool while also driving neurogenesis.

Within this specialised neurogenic niche of the adult SVZ, close contacts and signalling occurs between the Type B cells, TAPs, neuroblasts, ependymal cells, vasculature and cerebrospinal fluid. As with the development of the adult SVZ from the embryonic forebrain, extrinsic signalling pathways active during forebrain development have also been shown to be important in regulating adult neurogenesis. Specifically, Notch, BMP, Wnt, FGF and EGF signalling are important in the adult SVZ [26-30]. However, even with these extracellular signals present in the adult SVZ, the intrinsic genetic programme of lineage progression and cell fate specification is strongly coded within adult neural progenitor cells. This can be readily seen when adult SVZ cells are cultured in a monolayer with no added growth factors or in vivo niche signals present and lineage progression of Type B to C to A cells with predictable rates of asymmetric and symmetric division continues to occur [22]. Heterotopic transplantation of adult NPCs to alternate SVZ areas has also shown to generate olfactory bulb cell types specific to the site origin, not the destination, despite the presence of a different range of external cues in the transplanted region [31].

**Intrinsic control regulating B cell lineages**

Type B cells are the slow dividing stem cell pool in the adult SVZ. They are identified by GFAP expression, and share some ultrastructural characteristics with astroglia [32, 33]. Through Cre-lox fate mapping, transcription factors expressed in the neuroepithelium of the embryonic cortex (Emx1), and lateral GE (Gsh2) have been shown to contribute to specific pools of B cells residing in different areas of the adult SVZ, all of which contribute to olfactory bulb neurogenesis [34]. In addition, each embryonic area contributes to a different proportion of Type B stem cells versus neurosphere forming TAPs, with Gsh2+ lateral GE-derived stem cells potentially generating more TAPs compared to cortically derived ones. Furthermore, B cells retain intrinsic lineage determinates from development, as different embryonic zones contribute to different populations of differentiated olfactory bulb interneurons. Specifically, cortically-derived adult stem cells generate the majority of the calretinin olfactory bulb neurons, with the remaining olfactory bulb neurons, including calbindin-expressing neurons are exclusively generated from lateral GE-derived progenitors. Tyrosine hydroxylase-positive neurons are made from a combination of cortical and lateral GE-derived progenitors [10, 31, 35]. Further, when radial glia (cells that generate the adult Type B cells) lining the lateral ventricle were targeted at P0 (postnatal day 0) in mice and the progeny analysed 4 weeks later, cells from different anatomical locations generated specific subsets of olfactory bulb interneurons [31]. Extending these observations, when adult Type B cells at different locations in the SVZ were targeted at P60, the cell progeny generated olfactory bulb neurons in a very similar pattern to the P0 generated cells indicating the persistence of region-specific intrinsic regulation through postnatal neurogenesis. Neuronal sub-type specification was not altered even when the labelled neonatal radial glia were heterotopically transplanted into different regions lining the ventricle or when cultured under adherent conditions that mimicked postnatal neurogenesis [31].

These experiments indicate a previously unknown complexity within the Type B cells of the adult SVZ and their ability to retain intrinsic control over neuronal subtype specification at the earliest steps in adult SVZ neurogenesis. Although evidence that strong intrinsic cues remain present in Type B cells, they are also affected by external signalling changes in their microenvironment. A high fraction of Type B cells express the transcription factor Smad4, with Id1 and Id3 expression also observed in the SVZ [29, 36]; all downstream targets of the BMP signal pathway. Deletion of Smad4 specifically in Type B cells leads to reduction in neuroblast generation with a concurrent increase in oligodendrocyte generation and migration into the corpus callosum [36]. This is thought to occur via intrinsic changes in Dlx2 and Olig2 transcription factor expression in TAPs [36, 37]. This effect was driven from intrinsic Type B cell signalling, as when Smad4 deletion was targeted to the fast dividing TAPs and neuroblasts, instead of the Type B cells, no significant changes were found in the doublecortin neuroblast population. Smad4 signalling is therefore required for the transition from Type B cell to TAP [36].

**Intrinsic control over transit amplifying precursor cell lineages**

TAPs are fast proliferating cells that are generated through symmetric and asymmetric divi-
Intrinsic regulation of adult SVZ neural progenitor cells

Intrinsic transcription factor signalling governs whether a TAP will have a neurogenic or an oligodendrocyte fate. Proneural TAPs have been found to express Mash1, Pax6, Ngn2, and Dlx2 [13-15, 17, 49, 53], and oligodendroglial TAPs express Mash1 and/or Olig2 [53]. Multiple signalling pathways are thus likely to converge on these intrinsic transcriptional regulators in the fast proliferating TAPs to regulate self renewal and lineage progression through control over cell cycle exit and differentiation.

Neuronal versus oligodendrocyte TAP lineage choice

Some TAPs are bipotent. Through fate mapping studies [14, 54], it was found that Mash1-positive TAPs contributed to the majority of all downstream cell lineages originating from the postnatal and adult SVZ. This indicates the importance of Mash1 expression early in cell fate specification in the adult SVZ. Specifically, Mash1-positive cells found throughout the SVZ and RMS can generate either neurons of both the GABAergic and glutamatergic lineages that reside in the olfactory bulb, or oligodendrocyte precursor cells and oligodendrocytes in the white matter [14, 54]. The lineage progression of Mash1-positive cells depends on cell autonomous co-expression and regulation with the neuronal transcription factors Pax6, Ngn2, Dlx2 or the oligodendrocyte transcription factor Olig2 [14-16, 54]. This is reminiscent of both the developing spinal cord [55] and forebrain [52, 56, 57], indicating similar intrinsic regulatory mechanisms exist from development right through into adulthood.

During development Dlx2 signalling negatively regulates Olig2 expression and the generation of oligodendrocytes in the ventral GE in a cell autonomous manner [57]. Mash1 is also involved in this balance during development, acting in a non-cell autonomous manner to limit the number of Dlx2 progenitors through interacting with members of the Notch family, and therefore indirectly regulating Olig2 cell numbers [52, 57]. In contrast to this, Olig2 and Dlx2 do not co-localize in the majority of TAPs in the adult SVZ, suggesting lineage progression towards neuronal or oligodendrocyte fate is already intrinsically specified at the TAP (and even the Type B cell) stage of adult neurogenesis [2, 14, 17, 36, 57]. In agreement with this, Smad4, a transcription factor downstream of BMP signalling, has been found to regulate the neuronal-oligodendrocyte fate choice at the earliest stages of lineage progression from Type B cells, with Smad4 required for Olig2 suppression allowing neurogenic TAPs to be generated in the adult SVZ [36].

Olig2 and Pax6 co-expression in the adult SVZ is
also not normally observed. Olig2 expression in SVZ TAPs is anti-neurogenic, with expression promoting a TAP fate over a neuroblast fate by opposing the action of Pax6. When Olig2 is down-regulated, cells can proceed to a neurogenic lineage [8, 53, 58]. Pax6 and Olig2 have mutually exclusive expression patterns in the developing forebrain, postnatal and adult SVZ. Overexpression of Olig2 is sufficient to convert postnatal cells towards a glial fate [59], while expression of Pax6 specifically in Olig2+ neural progenitor cells leads to decreasing Olig2 protein expression, and converts cell fate from glial to neuronal cell lineage [8]. In vitro studies also show expression of Pax6 in Olig2-GFP cells leads to a downregulation of Olig2 [60]. These studies suggest that Pax6 can repress Olig2, and indeed Pax6 binding sites have been identified upstream of the Olig2 transcription start site [60]. Chromosomal immunoprecipitation (ChiP) analysis from P4 mouse forebrain also demonstrated that Pax6 binds directly to upstream sites in the Olig2 promoter and luciferase assays demonstrated that inhibition of Olig2 transcription and protein translation is directly linked to Pax6 binding to this upstream site [60].

Many other extrinsic factors also control the regulation over the neuronal TAP or oligodendroglial TAP fate, including a number of growth factors and multiple signalling pathways. EGF overexpression can stimulate generation of TAPs of the oligodendrocyte lineage (Mash1+/Olig2+), as can infusion of noggin, a BMP antagonist [29, 36, 61, 62]. Demethylation models also stimulate oligodendrocyte precursor generation from the SVZ [63-65]. So the expression of extrinsic signalling molecules play an important factor in regulating the intrinsic transcriptional programmes involved in the neuro-oligo lineage choice.

**Neurogenic TAPs and neuroblast cell fate specification**

In the adult SVZ, Mash1 co-expression with proneural transcription factors Dlx2, Pax6 or Ngn2 in a subset of TAPs lead to a neuronal fate. Dlx2 is expressed in both Dcx- TAPs and Dcx+ neuroblasts throughout the lateral SVZ and RMS [17, 66]. Dlx2 has a dual role in adult neurogenesis, firstly in promoting neurogenesis (in balance with oligodendrogenesis), and secondly in specification of GABAergic subtypes of olfactory bulb granule and periglomerular cells (PGC). *In vivo* work with retroviral vectors has shown that Dlx2 is a potent promoter of neurogenesis in the adult SVZ, is involved in maintaining a fast proliferation rate as well as migration velocity, and is sufficient to instruct progenitors to acquire a GABAergic neuronal fate. [17, 36, 49, 67]. Pax6 also is expressed in both Dcx-TAPs and Dcx+ neuroblasts, in the dorsal SVZ and RMS [17, 66]. It also has a dual role in SVZ neurogenesis, to initially promote a neuronal lineage and then in glutamatergic, and dopaminergic neuronal subtype specification in the olfactory bulb [13, 15, 53]. Pax6 has also been found to be expressed in a small number of Type B stem cells, although its function here is not well understood [13].

Olfactory bulbectomy and cell fate mapping studies have shown that olfactory bulb neuronal subtype specification is established before neuroblasts reach the bulb [17, 53, 68]. Periglomerular subtypes were found to be specified in the RMS, as higher percentages of these cells were labelled when retroviral injections were targeted to the RMS as opposed to the lateral SVZ [53]. A previously unknown heterogeneity thus exists in migrating neuroblasts, and indicates intrinsic regulation over subtype specification is retained in adult progenitors, suggesting subtype specification is not just in response to extrinsic cues that neuroblasts are exposed to when they reach the bulb [13, 17, 53, 69]. Neuronal subtypes in the olfactory bulb include GABAergic granule cells, and periglomerular cells that are calreitinin+, dopaminergic (TH+) and calbindin+ [53, 70]. An intrinsic transcriptional code specifies these different neuronal subtypes.

Specifically, in cells of the glomerular layer, Dlx2 and Pax6 together promote a TH+ dopaminergic fate, in conjunction with the Ets related factor ER81 and homeodomain transcription factor Meis2 [13, 17, 35, 53]. Without Pax6 and Dlx2 expression, TH+ fate is lost and instead neuroblasts acquire a calretinin periglomerular fate, which is further controlled by the zinc finger transcription factor Sp8. Expression of Sp8 is regulated with Pax6, and if Sp8 is downregulated, Pax6 expression is promoted and the subtype fate altered [17, 71]. Dlx2 and Pax6 expression can also promote a calbindin fate in combination with Meis2 [17, 35]. GABAergic interneuron fate in the granule cell layer is regulated by both Sp8 and ER81 [11, 71]. A small amount of glutamatergic neurons are also gen-
erated from the adult SVZ, and reside in the glomerular layer of the olfactory bulb. These are also regulated by Pax6 expression [16]. Specifically, glutamatergic subtypes are defined through a lack of Dlx2, and sequential expression of Ngn2, and T-brain transcription factors Tbr2, Tbr1, and basic helix-loop-helix factors NeuroD1, NeuroD2. These cells express vGluT2 and integrate into the juxtaglomerular layer of the bulb [15, 16].

Ngn2 and NeuroD1 signalling has also been found to be sufficient to direct the differentiation of Mash1 progenitors into calbindin and calretinin expressing neurons, and in the dorsal SVZ NeuroD1 cells were observed to express Dlx2 [15]. Understanding the regulation of neuronal subtype specification is thus complex with more investigation required to clarify all lineage progressions. However, studies to date have shown that although intrinsic regulatory pathways possibly originating from embryonic cues residual in Type B cells and TAPs remain a strong director of cellular fate in the SVZ-olfactory bulb system, there is a degree of lineage plasticity. Experiments that forced overexpression or knockdown of specific genes such as Pax6 or Dlx2 have been shown to alter the expected neuronal subtype [17, 60]. Therefore, intrinsic regulatory pathways can be overridden by other transcriptional signals, possibly originating from extracellular signalling pathways.

**Oligodendroglial TAPs and oligodendrocyte precursor cells**

In addition to olfactory bulb neurons, a small number of both non-myelinating NG2+ oligodendrocyte progenitor cells, and mature myelinating oligodendrocytes are generated from the Type B cells of the normal adult SVZ [72]. When Mash1 is expressed with Olig2 in TAPS of the adult SVZ, an oligodendroglial fate is specified [2, 47, 53, 73]. Olig2 expression is then necessary and sufficient to instruct oligodendrocyte differentiation [74]. Olig2+ oligodendrocyte precursor cells migrate short distances into the corpus callosum, white matter tracts of the striatum and fimbria formix in the normal rodent brain, and differentiate into NG2+ cells and myelinating oligodendrocytes [2, 62].

**The influence of brain injury on progenitor cell lineage regulation**

A wide range of extrinsic signalling changes occur in response to brain injury or during neurodegenerative disease, and these can influence the intrinsic regulation of adult neural progenitor cells [64, 75-77]. In some cases these extrinsic cues even appear to override intrinsic cell lineage genes leading to alterations in proliferation, migration and cell fate switching in progenitors born in the SVZ [64]. Specifically, alterations in transcription factor expression in the adult SVZ has been observed in rodent models of excitotoxic cell loss, stroke and demyelination [64, 66, 75, 77]. Upon striatal lesioning with the excitotoxin quinolinic acid, Mash1, Dlx2 and Pax6 TAPs in the SVZ and anterior SVZ (aSVZ) were found to respond in a heterogeneous manner [66]. A transient decrease was observed in the ipsilateral aSVZ Mash1 and Dlx2 TAP population in the first one-two days post lesion (dpl). This was followed by an increase in the Dlx2 TAP population at 3dpl and the Pax6 TAP population at 3 and 7dpl. Neuroblast numbers were also increased in the aSVZ and rostral migratory stream (RMS), and a subpopulation was redirected into the lesioned striatum. Neuroblasts remaining in the RMS were found to alter their transcriptional profiles, with a higher percentage expressing Dlx2 from 2-7dpl, and Pax6 by 7dpl [5, 66]. This indicates that not only is the lineage profile of the TAP population altered by injury, but lineage sub-types of migratory neuroblast were also altered. Specifically, Dlx2 expression was increased in both populations, suggesting the possibility of endogenous replacement of GABAergic neurons, the cell population specifically targeted by quinolinic acid [66]. Mash1 regulation in adult SVZ progenitors is also altered in the middle cerebral occlusion model (MCAO) of stroke [77], and proliferating Mash1, Pax6 and Emx1 progenitors found in the dentate gyrus of the hippocampus were also found to be altered in a transient ischemia model that kills CA1 layer neurons [78]. When Mash1-lineage cells were continuously labelled from 2-7 days post MCAO using an inducible Mash1-CreER<sup>TM</sup> protocol, an increase in Mash1-lineage cells was observed 7 days later in the ipsilateral SVZ, damaged striatum and corpus callosum. Lineage tracing showed that many Mash1 cells in the damaged striatum became Dcx+ neuroblasts, which were found to differentiate into mature neurons, while other Mash1-lineage cells became oligodendrocytes. Increases in SVZ proliferation post stroke was also found to be mediated through NICD (Notch Intra-Cellular Domain) and Hes1 [77, 79].
Intrinsic regulation of adult SVZ neural progenitor cells

In addition to alterations in neurogenic transcription factors after striatal injury, in a cortical lesion model Trb2+ progenitors born in the SVZ have been observed to be recruited through the white matter towards the injured cortical area, and differentiate along a glutamatergic lineage [16]. Demyelination models in rodent indicate that Olig2+ oligodendrocyte progenitor cells, and intriguingly, neuronal fated cells from the SVZ are recruited to lesioned white matter where they contribute to repair [2, 63, 64, 73, 80]. In human post-mortem multiple sclerosis tissue where demyelination is accompanied by axonal damage and neuronal loss, increased numbers of Dlx2+ and PSA-NCAM+ cells have been found in SVZ areas contiguous to white matter demyelination [81]. Further, in a rodent model of demyelination, GAD65-GFP and Dcx-GFP Pax6 expressing progenitors from the SVZ were redirected from the RMS and tracked to the lesioned white matter, where their lineage was redirected from a neuronal to an oligodendrocyte fate [64]. This was shown to be in response to an increase in the BMP antagonist chordin following demyelination. These results indicate that intrinsic TAP and neuroblast regulation through Mash1, Dlx2 and Pax6 is altered following different forms of brain injury. It also demonstrates that the lineage pathways intrinsic within SVZ progenitor cells can be overridden by external cues that are induced upon brain injury.

Intrinsic fate determinant genes can also be used to direct cell type specific repair by cells that are not derived from the SVZ through reprogramming cell fate. Reactive astrocytes are a hallmark of many brain injury paradigms, and these cells share some characteristics with neural stem cells and radial glia. These include the ability to proliferate, and express the markers Nestin, Vimentin and BDLP, suggesting the possibility of a dedifferentiated state [82]. In vitro, forced expression of Gln2 into adult cortical NG2+ and GFAP+ cells has been shown to drive functional glutamatergic neural network formation [83]. In addition, forced expression of Dlx2 into adult cortical astroglia and reactive astrocytes isolated from the adult injured cerebral cortex is able to reprogram the cells into GABAergic neurons [84]. This indicates that intrinsic gene reprogramming by a single proneural transcription factor is possible from glial cells located away from normal neurogenic brain regions [83, 84]. In vivo, a transient increase in Olig2 has been found in the brain parenchyma after a number of types of brain injury including cortical stab wound, the MCAO model of stroke and in a chronic demyelinating model of amyloid plaque deposition [85]. Olig2 expression is thought to be involved in both limiting endogenous repair after injury through suppression of neurogenesis, and the generation of new oligodendrocyte precursor cells in the grey matter after injury [8, 86]. When parenchymal Olig2 levels were antagonised after a cortical stab wound injury in adult mice, using a retrovirus encoding a dominant negative form of the gene, a small but significant number of neuroblasts appeared from infected cells [8], with some Dcx+ neuroblasts also expressing Pax6. Increasing levels of neurogenesis was also observed upon transduction with a Pax6-encoding retrovirus, suggesting the balance between neuronal and glial fates may be regulated by these two transcription factors following injury [8]. Similar results were found when Olig2 was antagonised, or Pax6 overexpressed in the damaged striatum after MCAO [87]. Furthermore, neuroblasts generated from infected cells in this model were capable of generating single action potentials and receive synaptic input, even though mature phenotypes were never seen [87].

Conclusion

Although many extrinsic factors can affect the regulation of adult neurogenesis, strong intrinsic signals remain from development. Proneural transcription factor regulation over cell cycle exit, lineage commitment and neuronal sub-type specification has been identified in all the cell types of the adult SVZ. Newly identified heterogeneity has been discovered in Type B stem cells, TAPs and neuroblasts throughout the SVZ-RMS-olfactory bulb system, through examining their transcription factor profiles. This allows insights into the underlying intrinsic regulatory mechanisms within these cells. The balance between proneural and oligodendroglial transcriptional interactions underlying neural progenitor fate choice is important to elucidate, especially if stem cell therapies are to be attempted following brain injury. Newfound plasticity in lineage commitment demonstrated after injury, and in knock-down and overexpression experiments, indicates that these intrinsic regulatory mechanisms can also be overridden. Fur-
Intrinsic regulation of adult SVZ neural progenitor cells

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Intrinsic regulation of adult SVZ neural progenitor cells

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