8 Transcriptional Regulation and Specification of Neural Stem Cells

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Abstract

With the discovery two decades ago that the adult brain contains neural stem cells (NSCs) capable of producing new neurons, a great deal of research has been undertaken to manipulate these cells to repair the damaged nervous system. Much progress has been made in understanding what regulates adult neural stem cell specification, proliferation and differentiation but much remains to be determined. Lessons can be learned from understanding how embryonic neural stem cells produce the exquisitely complicated organ that is the adult mammalian nervous system. This review will highlight the role of transcriptional regulation of mammalian neural stem cells during embryonic development and compare these to the adult neural stem cell/neural precursor cell (NPC) niches of the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus. Normal physiological NSC/NPC regulation will be explored, as well as their regulation and responses following neural injury and disease. Finally, transcriptional regulation of the endogenous NSC/NPCs will be compared and contrasted with embryonic stem/induced pluripotent stem (ES/iPS) cell-derived NSC/NPCs. Recapitulation of the embryonic sequence of transcriptional events in neural stem cell development into specific neuronal or glial lineages improves directed differentiation of ES/iPS cells and may be useful for activation and specification of endogenous adult neural stem cells for therapeutic purposes.

Keywords

Gliogenesis • Neural stem cell • Neural progenitor cell • Neurogenesis • Transcriptional regulation

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8.1 Introduction

With the discovery two decades ago that the adult brain contains neural stem cells (NSCs) capable of producing new neurons [1, 2], a great deal of research has been undertaken to manipulate these cells to repair the damaged nervous system. Much progress has been made in understanding what regulates adult neural stem cell specification, proliferation and differentiation but much remains to be determined. Lessons can be learned from understanding how embryonic neural stem cells produce the exquisitely complicated organ that is the adult mammalian nervous system.

The nervous system is derived from the embryonic neuroectoderm which generates a self renewing population of neural stem cells (NSCs) that eventually give rise to the majority of cells in the central and peripheral nervous systems. In the simplest pathway, neural specified ectoderm cells, which can be identified by their expression of neural specific markers, such as members of the *Sox* gene family [3] and *Otx2* [4], become the earliest neural stem cells, also known as neuroepithelial cells. These form the neural tube and eventually generate all central nervous system neurons and glial cells (astrocytes and oligodendrocytes, but not microglia, which are derived from the hematopoietic system and migrate into the CNS). Neuroepithelial cells give rise to radial glial cells in the Ventricular Zone (VZ), which are also self-renewing multipotent neural stem cells that can directly generate neurons and glia, as well as generate more restricted intermediate progenitor cells that produce cells of a neuronal or glial lineage, often after a small number of divisions. As the neural tissue expands with development, the ventricular zone shrinks and a new neurogenic site forms, the subventricular zone (SVZ). Stem cells in the SVZ continue to generate neurons, glia and intermediate precursor cells. This structure remains into adulthood, particularly lining the lateral ventricles, as one of two neurogenic niches in the adult brain, with the subgranular zone (SGZ) of the dentate gyrus of the hippocampus being the other. A general overview of different neural stem cell sources and locations is provided in Fig. 8.1.

Neural stem cell maintenance and differentiation decisions are regulated, at least in part, by signal transduction pathways that culminate in transcription factor expression or repression. Expression of these transcriptional cascades is regulated temporally and spatially, with differences in relative expression levels and specific combinations of transcription factors leading to different outcomes. This starts with induction of NSC fate, followed by expansion of NSC numbers, neural cell fate decisions (neurons versus glia – astrocytes and oligodendrocytes) and regionalised specification of specific neuronal cell types. Many of the signals involved in development of the nervous system are recapitulated in some way in adult NSCs or in specification and differentiation of embryonic stem (ES) and induced pluripotent stem (iPS) cells into neural lineages.

This review will highlight the role of transcriptional regulation of mammalian neural stem cells during embryonic development and compare these to the adult neural stem cell/neural precursor cell (NPC) niches of the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus. Normal physiological NSC/NPC regulation will be explored, as well as their regulation and responses following neural injury and disease. Finally, transcriptional regulation of endogenous NSC/NPCs will be compared and contrasted with ES/iPS cell-derived NSC/NPCs. Recapitulation of the embryonic sequence of transcriptional events in neural stem cell development into specific neuronal or glial lineages improves directed differentiation of ES/iPS cells and may be useful for activation and specification of endogenous adult neural stem cells for therapeutic purposes.

8.2 Developmental Regulation During Embryogenesis

8.2.1 Specification of Neuroectoderm Cells and the Neural Lineage

One of the first steps in neural development is the specification of ectodermal cells into neuroectoderm cells that comprise the earliest neural stem

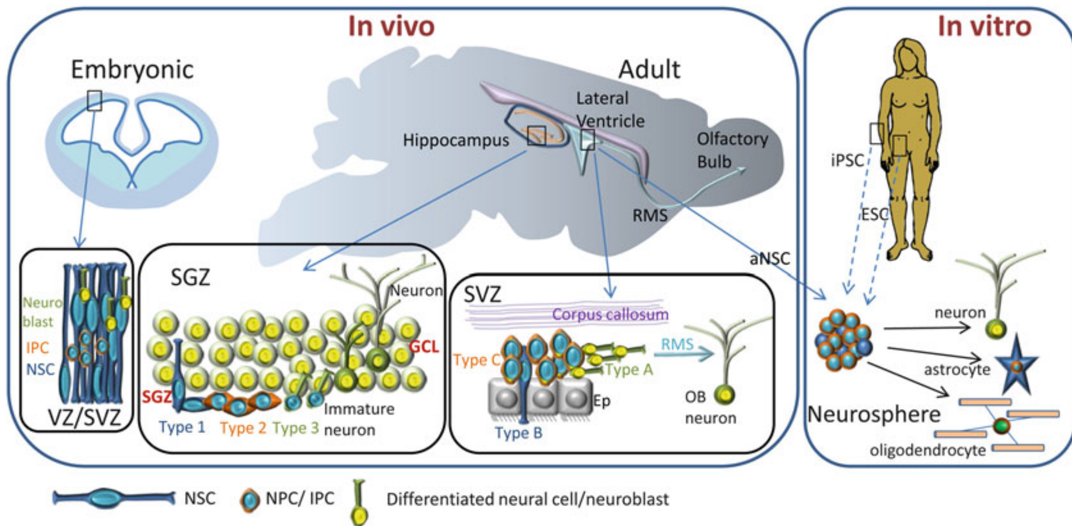

Fig. 8.1 Sources of neural stem cells. In vivo: Neural stem cells (NSCs)/neural progenitor cells (NPCs) are present throughout the nervous system during development, in the ventricular zone (VZ) and in the subventricular zone (SVZ), which contains more restricted intermediate progenitor cells (IPCs). In the adult brain, the SVZ remains as a remnant lining the lateral wall of the lateral ventricles, comprised of Type B neural stem cells, Type C transit amplifying cells (NPCs) and Type A neuroblasts that migrate along the rostral migratory stream (RMS) to differentiate primarily into interneurons in the olfactory bulb. A second adult neurogenic niche is found in the subgranular zone (SGZ) of the dentate gyrus in the hippocampus, which contains Type 1–3 NSC/NPCs that differentiate primarily into neurons in the adjacent granule cell layer (GCL). In vitro: NSC/NPCs are readily cultured, often in the form of neurospheres which, depending on the age and source of the NSC/NPCs, can usually differentiate into all neural cell lineages – neurons, astrocytes and oligodendrocytes. Neurospheres can be grown from embryonic neural tissue, as well as adult SVZ (and in a more restricted fashion from hippocampus). They can also be derived from embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) from a variety of adult tissues, such as skin fibroblasts

cells and are responsible for the formation of almost the entire nervous system. Of course, the nervous system is not a homogeneous organ and overlaid on the simple pathway of neural stem cell differentiation described above is a complex set of spatial regulatory cues that not only determine whether a neural stem cell or precursor cell will become a neuron or a glial cell but whether it will become a spinal cord cell or a brain cell and further, which specific sort of spinal cord or brain cell, e.g. a spinal motor neuron versus a hippocampal granule neuron versus a cortical interneuron. While specification of patterning of the nervous system will not be reviewed in detail, some of the signalling pathways and transcription factors involved in the process are also required for induction of neural stem cells and derivation of specific neural lineages from ES and iPS cells (see Sect. 8.4 and Fig. 8.1) and so will be covered briefly here. More extensive reviews on induction and patterning of the nervous system have been written recently [5–7].

Neural induction of ectodermal cells is thought to be the default state and non-neural tissue is induced by bone morphogenetic proteins (BMPs). Therefore, for the cells to remain neural, BMP signalling needs to be inhibited; this is achieved by expression of BMP antagonists such as chordin and noggin. This induction is also supported by FGF signalling to maintain the neurally induced state. This early neural induction appears to specify anterior neural tissue (destined to become forebrain, midbrain and hindbrain) and involves transcription factors such as *Otx2*, *Lim1* and *FoxA2* [4]. Further refining of anterior/posterior patterning is regulated by gradients of Wnts, with reciprocal gradients of Wnt antagonists such as *Dikkopf*, *Frzb* and *Cerberus* [5]. On top of this spatial patterning, the neural stem cells all undergo a similar sequence of events involving proliferation

and subsequent differentiation, generally into neurons, followed by glial cells. These more general events, in specific contexts, will be the topic of the remainder of this review.

8.2.2 Regulation of NSC Proliferation Versus Differentiation in the Central Nervous System

The first decision a neural stem cell needs to make is whether to proliferate and self renew or whether to differentiate into more mature progeny. Maintaining the balance between total self-renewal, limited self-renewal and then differentiation, as cells progress from multipotent NSCs to multipotent or restricted intermediate neural progenitor cells (NPCs) to mature progeny is under tight transcriptional and temporal control. There are basically three somewhat interrelated functions transcription factors can perform to regulate expansion of NSC populations: (1) regulation of proliferation to expand numbers, (2) regulation of self-renewal i.e. maintenance of multipotent stem cell characteristics and (3) repression of differentiation. Different transcription factors can play multiple roles at different stages of development, depending on levels of expression and combinatorial interactions with other transcription factors and signalling pathways, therefore assigning specific roles for individual transcription factors can be rather complicated. Nonetheless, there has been a plethora of expression analyses, over-expression, deletion and mutation studies to indicate that a number of key transcription factors have a dominant effect on the decision to self-renew, proliferate or differentiate [8].

Notch signalling is one of the most widely studied pathways intimately linked to the balance between expansion of NSCs/NPCs and neural differentiation. The primary effectors of Notch signalling are the transcriptional repressors *Hes1* and *Hes5*, which repress neuronal differentiation and maintain NSCs in an undifferentiated state [9, 10]. While not required for development of neuroepithelial cells (the earliest NSCs), Hes repression of proneural genes is required to maintain neuroepithelial pluripotency as well as radial glial pluripotency and self renewal. This requires signalling through the Notch receptor via the Notch effector C-promoter binding factor 1 (CBF1, also known as RBP/Jκ). Notch signalling is also involved in proliferation of the intermediate NPCs, which are no longer multipotent but largely neurogenic, due to downregulation of CBF1 in these cells [11].

In mammals, neuroepithelial cells are a pseudostratified epithelium forming the neural tube and they undergo symmetric cell division to produce more multipotent neuroepithelial cells (Fig. 8.2). In these cells, transcription factors such as *Hes1* are equally shared between both daughter cells and both remain as neuroepithelial cells. In the absence of Notch activated *Hes1* or *Hes5*, NSCs prematurely differentiate into neurons [9, 12, 13]. *Hes1* and *Hes5* perform all three functions of factors that regulate NSC maintenance, with roles in promoting proliferation, inhibiting differentiation and maintaining multipotency. Later in development, when neuroepithelial cells become radial glial cells, Hes activity remains important for maintenance of radial glial NSC characteristics. Depending on the stage of development radial glial cells can undergo symmetric divisions like neuroepithelial cells or asymmetric divisions, whereby one daughter cell remains a radial glial cell and the other either becomes an intermediate NPC or generates a neuron [14]. In invertebrates, the plane of cleavage during mitosis (vertical or horizontal) dictates segregation of Notch pathway regulatory factors and subsequent Notch pathway activity, leading to one daughter cell retaining activity and remaining a stem cell, with the other losing activity and becoming a more differentiated daughter cell. In mammals the radial glial cells undergo division largely in the vertical plane but such divisions can be symmetric or asymmetric [14] and may have more to do with whether or not cells maintain apical membrane or retain β-catenin containing ventricular end feet [15] than segregation of Notch effectors, which also play a role in subsequent cell fate determination. Further, Notch pathway effectors do not act alone and interact with several other transcription factors that mediate more restricted

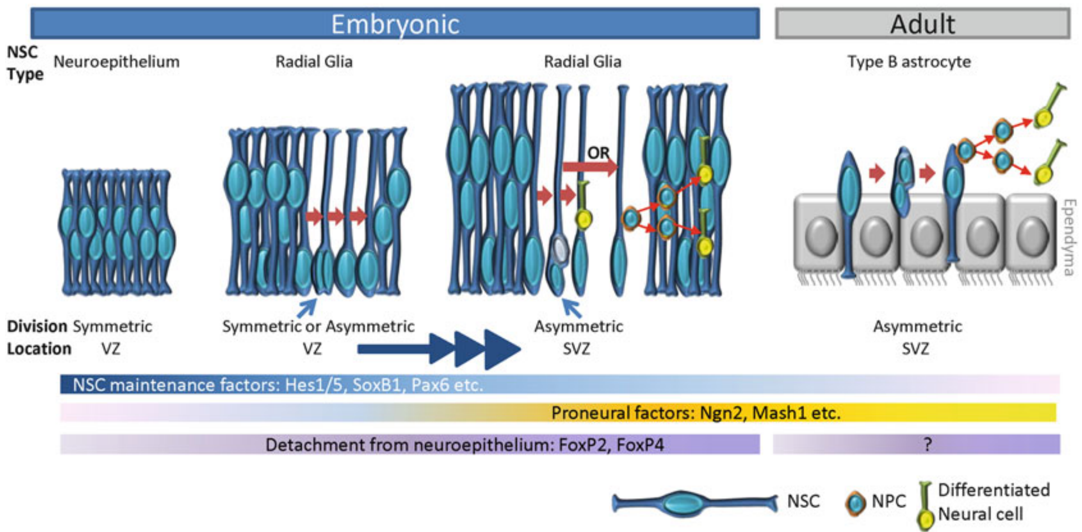

Fig. 8.2 Factors regulating maintenance and differentiation of neural stem cells in vivo. During embryonic development NSCs initially undergo a rapid proliferative phase characterised by symmetric divisions to produce more stem cells. As development progresses NSC division becomes asymmetric, producing one NSC and a neural precursor cell (NPC) or neuron. Transcription factors that maintain the NSCs in a proliferative state include members of the Notch signalling pathway, such as Hes, as well as SoxB1 members (Sox1-3) and Pax6. As expression of these molecules decreases and expression of proneural factors such as neurogenins and Mash1/Ascl increase, NSCs commence differentiation into more mature cell fates. This also requires that the NSCs are able to detach from the basal and pial surfaces to undergo asymmetric division and subsequent differentiation and this requires expression of Forkhead transcription factors such as FoxP2/P4. In the adult SVZ the slowly proliferating NSCs undergo asymmetric division to produce rapidly dividing NPCs (transit amplifying cells). Expression of maintenance and proneural factors plays a similar role in the adult as during development. It is unclear whether FoxP2/P4 continues to play a role

functions in determining whether a NSC self-renews or differentiates.

The neuroepithelial attachments are maintained by adherens junctions and maintenance versus differentiation is regulated by the coordinated assembly and disassembly of these contacts. Some of the transcriptional regulators involved in this process have recently been identified and involve the progressive expression of two Forkhead transcription factors, *Foxp2* and *Foxp4*. These repress expression of N-cadherin which is critical for maintenance of adherens junctions, leading to detachment of differentiating neurons from the neuroepithelium [16].

A generic overview of NSC proliferation and maintenance versus differentiation is provided in Fig. 8.2.

Members of the SoxB1 family of transcriptional activators (*Sox1*, *Sox2* and *Sox3*) and in particular *Sox2* are among the earliest markers of neural stem cell identity [17]. They act in a partially redundant manner to maintain NSC self renewal capacity, both during development and in adult NSCs [18–20]. Sox2 acts at least in part through the Notch and Sonic hedgehog (Shh) pathways [21, 22] and its transcriptional activation was recently shown to be regulated by a new transcription factor, *Ars2* [23] which is also important for NSC self-renewal. SoxB1 family members that maintain self renewal are in balance with proneural basic helix-loop-helix (bHLH) transcription factors such as neurogenin2 (*Ngn2*) and *Ascl1*/*Mash1*, which promote neurogenesis and there is reciprocal antagonism and regulation of the two opposing roles [18, 24]. Other transcription factors also play critical roles in NSC self renewal, including *Gli2* and *Gli3*, which regulate expression of transcription factors such as *Hes1*, *Hes5* and *Sox2* [25] and BMI-1, a transcriptional repressor that maintains NSC self renewal by

repressing inhibitors of cyclin dependent kinases [26]. *Pax6* also plays a role in balancing NSC self renewal and neurogenesis, particularly in developing cortex [27] with the level of expression being critical in determining which way the balance is tipped [28]. High levels of *Pax6* lead to interactions with proneural transcription factors such as *Ngn1* and *Ascl1* and promotion of neurogenesis at the expense of self-renewal, while an absence of *Pax6* leads to precocious neurogenesis as expression of key cell cycle regulators is decreased and neuronal differentiation is promoted. This highlights that it is not necessarily only the presence or absence of a transcription factor that is important but also the relative levels.

In addition to the transcription factors mentioned above, there are others that also promote NSC proliferation but are not necessarily important for maintenance of a multipotent state, including *Olig2* [29], *Id4* [30] and *Gli1* [31], while others actively repress differentiation, such as Hes-related bHLH transcription factors *HesR1* and *HesR2* [8, 32].

8.2.3 Regulation of Neural Stem Cell Fate

8.2.3.1 Neural Precursor Cell Differentiation

As neural development progresses the symmetric division of radial glial cells decreases to be replaced by asymmetric divisions and production of intermediate progenitor cells (IPCs). During the neurogenic phase these cells largely generate neurons and a glial cell fate is inhibited, while at later embryonic stages an astrocyte fate is promoted at the expense of neuronal fate. The switch from radial glial cell to intermediate progenitor cell involves downregulation of factors important for self-renewal, such as CBF1, *Emx2*, *Pax6* and *Sox2* [11, 33–35], with upregulation of transcriptional regulators such as *Tbr2*, *Svet1*, *Lmo4* and *Cux1-2* [33, 36, 37]. *Tbr2* expression is so specific to cortical intermediate progenitor cells and is switched off in their progeny, unlike many other markers, that it is a particularly good marker for this specific population of cells [33, 38, 39]. However, *Tbr2* is not just a marker, as mis-expression of *Tbr2* in radial glial cells induces intermediate progenitor cell identity, indicating it is important for progenitor cell specification [40]. In the absence of *Tbr2* intermediate neuronal progenitor cells are depleted, stem cell numbers are increased and neurogenesis is decreased [41, 42], at least in part due to repression of *Sox2* [42]. Radial glial and intermediate progenitor cells can also be distinguished by their differential responsiveness to Notch signalling: both cell types respond to Notch receptor activation but signalling via the Notch effector CBF1 is attenuated in the intermediate progenitor cells. Indeed, knockdown of CBF1 can convert stem cells to intermediate progenitor cells [11].

8.2.3.2 Neuronal Differentiation

As differentiation progresses, some transcription factors, such as *Pax6*, that are involved in regulation of neural stem/progenitor proliferation begin to regulate neuronal differentiation [43]. In part they do this by inducing expression of other transcription factors, such as proneural basic helix-loop-helix (bHLH) transcription factors. During this neurogenic period a high level of proneural bHLH expression is required, not only to promote neuronal differentiation but also to inhibit premature astroglial differentiation [44]. Proneural bHLH transcription factors are involved in specifying generic neuronal fate and, depending on the region of the nervous system and co-expression of other transcription factors, also lead to eventual production of specific different neuronal cell types.

Many of the signalling mechanisms involved in neural cell induction discussed above also play a role in neuronal specification, in conjunction with other signal transduction pathways, with the specific environment and developmental age promoting different cell fates. The Wnt signalling pathway is one such example. Activation of the canonical Wnt pathway by overexpression of stabilised β-catenin in early cortical progenitor cells leads to excess proliferation and inhibition of neuronal differentiation [15, 45, 46], while its overexpression at later stages of development induces cell cycle arrest and neuronal differentiation [47]. One of the mechanisms by which Wnt signalling can promote neuronal differentiation

may be by inducing expression of the neurogenic bHLH transcription factors Neurogenin1 and Neurogenin2 (Ngn1/2). Conversely, other signalling pathways inhibit proneural gene expression and consequent neuronal differentiation. For example, FGF2 signalling increases Notch expression and promotes progenitor proliferation rather than neuronal differentiation [48], leading to increased activation of Notch signalling and induction of Hes family transcriptional repressors, which then inhibit expression of proneural genes such as *Ngn1* and *Ngn2* and *Ascl1/Mash1* [24]. Other factors such as growth hormone (GH), also decrease Ngn expression and cortical progenitor neuronal differentiation, but during the neurogenic phase high levels of the intracellular regulator of cytokine signal transduction, suppressor of cytokine signalling-2 (SOCS2), blocks GH/STAT5 signalling and allows normal neurogenesis to proceed [49]. Regulation of Ngn phosphorylation by GSK3 also regulates neurogenic activity. Wnt-mediated repression of GSK3 activity during the early neurogenic phase blocks Ngn phosphorylation, but GSK3 activity leads to phosphorylation and inactivation of Ngn during the late neurogenic/gliogenic phase [50].

Both Ngn1/2 and Ascl1/Mash1 induce broad but context-specific neuronal differentiation throughout the nervous system and their role in cortical neuron differentiation and subtype specification will be used here as an example, as cells in these locations will eventually form the hippocampus and SVZ of the adult lateral ventricle, the primary regions of neurogenesis in the adult. In the developing rodent forebrain excitatory (glutamatergic) cortical neurons are generated in columns above the dorsal telencephalic Ngn1/2-expressing VZ/SVZ progenitor cells. The VZ-derived progenitor cells give rise to the excitatory neurons in the lower regions of the cortex (layers 4–6) while intermediate progenitor cells in the SVZ give rise to upper cortical layers (2–4). Cortical interneurons (inhibitory GABAergic) are not generated in the same region as the excitatory neurons, instead they arise from VZ/SVZ of the ventral telencephalon (medial and caudal ganglionic eminences; MGE and CGE respectively) and migrate tangentially to integrate with excitatory neurons in the developing cortex [51]. Ascl1/Mash1 expression is required in the ganglionic eminence progenitor cells to specify general cortical interneuron fate. More detail can be found in recent specific reviews on regulation of telencephalic cell fate [52], cortical projection neuron development [53] and cortical interneuron development [51].

Other regionally expressed transcription factors are required for production of specific neuronal subtype fates, some of which have different roles in different cortical progenitor cell populations and some of which are more specific. The homeobox transcription factors *Cux1* and *Cux2* are expressed by interneuron precursors in the MGE (and CGE for *Cux1*) and are redundantly required for specification of reelin-expressing cortical interneurons (which also express interneuron subtype markers such as calretinin, neuropeptide Y and somatostatin and thus are a heterogeneous population) [54]. However, in the dorsal telencephalon, *Cux2* is expressed in intermediate progenitors in the SVZ and plays a role in regulating their cell cycle exit so that appropriate numbers of upper layer cortical projection neurons are generated [55].

At the early stages of cortical neurogenesis, VZ-derived daughter cells generate the excitatory neurons of the lower cortical layers. These cells and the layer 5/6 neurons they generate express the zinc-finger transcription factor *Fezf2*, which is required for their fate specification as in its absence the cells become upper layer cortical neurons [56]. *Fezf2* induces the post-mitotic co-expression of another zinc-finger transcription factor, *Ctip2*, which is essential for further differentiation and regulates the axonal projections to subcortical targets [56–58]. Further specification of deep cortical layer subtypes arises depending on the combinatorial and relative levels of expression of *Ctip2*, *Sox5* and *Tbr1* [53, 59, 60]. *Tbr1* promotes layer 6 neuron fate and represses layer 5 fate by reducing expression of *Fezf2* and *Ctip2* [61]. *Ctip2* expression is also repressed in upper layer cortical projection neurons by *SatB2*, expression of which is required for their specification [62, 63], while *FezF2* can inhibit *SatB2* expression in lower cortical layers [53].

Later in neurogenesis Pou domain transcription factors such as *Brn1* and *Brn2* are also required for generation of upper layer cortical projection neurons, with a particular effect in double mutants at layer 4, as well as some loss in higher layers [64].

Outside of the cortex different transcription factors are involved in specifying different neuronal types. For example, specification of midbrain dopaminergic neurons involves expression of *Nurr1*, which is regulated by *PitX3* [65] and *FoxA1/A2* [66], while raphe serotinergic neurons are specified by EAGLE [67], *Pet1* [68] and *Lmx1b* [69], which is also required for their maintenance [70].

8.2.3.3 Astrocyte Differentiation

Towards the end of the neurogenic period a gliogenic switch occurs, allowing production of oligodendrocytes (see below) and astrocytes. During the neurogenic phase, gliogenesis is inhibited and this is at least partly achieved by the high expression levels of bHLH transcription factors such as Ngns [71], which suppress gliogenesis by sequestering the gliogenic CBP/p300/Smad transcriptional complex and repressing the JAK/STAT pathway [71, 72]. As development progresses, NPCs become more responsive to signals from gliogenic cytokines, such as BMPs and LIF/CNTF (reviewed in [52]). This is at least in part due to demethylation of STAT3 binding sites in the promoters of astroglial genes such as GFAP and S100β [73–75]. However, compared to the large number of transcription factors and regulatory cascades that have been described for production of neurons and different neuron subtypes during the neurogenic phase, there is a relative paucity of data on transcriptional regulators of astrogliogenesis, and particularly on development of different astroglial types. Some of the transcription factors that have been identified are involved in a more general gliogenic switch (i.e. oligodendrocytes and astrocytes), rather than being specific for astrocytes per se, such as *Sox9* [76], *Olig2* [77] and serum response factor (SRF) [78]. *Sox9* is required for production of spinal cord grey matter astrocytes, while having little effect on white matter astrocytes. Nuclear factor-1A (NF1A) has been shown to regulate initiation of spinal cord gliogenesis [79] and expression of astrocyte-specific markers, such as glial fibrillary acidic protein (GFAP) [80]. It has recently been shown that *Sox9* induces expression of NF1A and together they form a transcriptional cascade that regulates expression of a range of genes involved in astroglial development and particularly those involved in metabolism and migration [81]. In the ventral neural tube astrocyte specification is regulated by the bHLH transcription factor stem cell leukaemia (SCL) [82]. In addition, although *Pax6* regulates neurogenesis, as described above, it is also involved in astrocyte maturation by inhibiting precursor cell proliferation [83].

8.2.3.4 Oligodendrocyte Differentiation

In contrast, the oligodendrocyte lineage is striking in its expression of a well defined set of transcription factors including *Olig1, Olig2, Sox10, Nkx2.2, Mash1/Ascl1* and, upon terminal differentiation, MyRF and *Nkx6.2* [84–86]. Many of these factors have indispensible roles during oligodendrocyte terminal differentiation/myelination, however there is a common theme with many of them also having more subtle roles in regulating oligodendrocyte lineage specification due to their involvement in neural patterning of the developing nervous system.

The process of specification to the oligodendrocyte lineage is strongly linked with the dorso-ventral patterning of the neural tube, where domains are established through gradients of factors such as Shh and BMP and defined through their expression of transcription factors. Within the spinal cord the oligodendrocyte lineage first arises from the pMN domain, which expresses the oligodendrocyte lineage marker *Olig2* as well as *Nkx6.1* and *Nkx6.2*. At later embryonic stages more dorsal regions of the spinal cord give rise to a second wave of oligodendrocyte progenitors which for the most part ultimately replace their earlier ventral counterparts (reviewed in [87]). A similar phenomenon exists in the forebrain, where an earlier wave of oligodendrocyte progenitors from the MGE and enteropeduncular area are largely replaced by a later wave of progenitors that originate from the LGE and CGE [88].

A number of bHLH transcription factors have a role in oligodendrocyte specification, with the pan oligodendrocyte lineage marker Olig2 being the most notable. *Olig2* expression in the pMN domain of the spinal cord inhibits factors that define neighbouring domains, such as *Nkx2.2* and *Irx3*, thus ablation of the *Olig2* gene is associated with an expansion of the p2 domain into what would otherwise be the pMN domain and a resulting loss of motor neuron and oligodendrocyte specification [89, 90]. In contrast, oligodendrocyte specification in the brain is comparatively preserved in the absence of *Olig2*, most likely due to compensation by *Olig1* [89]. This indicates that *Olig2* is not an absolute requirement for specification of the lineage. Similarly, at least in chicken, some oligodendrocyte precursors arise from the Nkx2.2+, Olig2- P3 domain, though these oligodendrocyte progenitors subsequently express *Olig2* [91]. Nevertheless, there is substantial evidence that *Olig2* is important for both oligodendrocyte lineage specification and function in addition to its role in defining the pMN domain. *Olig2* expressing cells of the pMN domain sequentially give rise to motor neurons and oligodendrocytes [89, 90]; this fate decision is largely dictated by the phosphorylation state of the Olig2 protein [92]. A continued role for *Olig2* in maintenance of the lineage has also been recently demonstrated with conditional ablation of the *Olig2* gene in committed oligodendrocyte progenitors diverting them to become astrocytes [93].

The bHLH transcription factor *Ascl1/Mash1* also has a role in specification of a number of oligodendrocyte progenitor pools. Within the ventral telencephalon, *Ascl1/Mash1* promotes oligodendrocyte specification by restricting the expression of *Dlx1&2* which otherwise promote interneuron specification at the expense of the specification of Olig2+ oligodendrocyte progenitors [94, 95]. Somewhat contrastingly, within the spinal cord *Ascl1/Mash1* appears to mark a pool of neuronal/oligodendrocyte progenitors; ablation of *Ascl1/Mash1* increases their commitment to the glial lineages [96]. It should be noted that although *Ascl1/Mash1* is not required for the generation of the oligodendrocyte lineage in totality, it is required for oligodendrocyte terminal differentiation [97].

Several Nkx factors have roles in the specification process. *Nkx6.1* and *Nkx6.2* have a strong role in promoting oligodendrogenesis in ventral regions via their inhibition of *Nkx2.2* (thus allowing for the expression of *Olig2* and definition of the pMN domain [98, 99]). However, *Nkx6.1* and *Nkx6.2* are not required for the more dorsally derived oligodendrocytes in the spinal cord and within the hindbrain even act to limit specification to the oligodendrocyte lineage [99]. *Nkx2.2* also has a mixed role in oligodendrocyte specification; although within the ventral spinal cord it initially inhibits *Olig2* expression and oligodendrocyte specification, ultimately *Nkx2.2* and *Olig2* are co-expressed in the lineage and *Nkx2.2* has important roles in oligodendrocyte terminal differentiation [91, 99, 100].

In addition to the above factors, which are largely implicated in the patterning of the developing nervous system, roles for several other transcription factors have been identified in oligodendrocyte specification. In vitro, SoxE proteins *Sox8*, *Sox9* and *Sox10* can direct neural precursor cells towards the oligodendrocyte lineage, at least in part by regulation of Suppressor of Fused (Sufu) expression [101]. The delta-notch system is also important in regulating oligodendrocyte differentiation [102] and also appears to promote specification to the lineage in the developing zebrafish nervous system [103]. Although not strictly required for the initial specification of the oligodendrocyte lineage, REST has an important role in inhibiting neuronal gene expression once the lineage is specified, thus allowing the maintenance of oligodendrocyte identity [104].

8.3 Adult Neural Stem Cells

8.3.1 Endogenous Neural Stem Cells

Although the bulk of neurogenesis and gliogenesis occurs during embryonic and early postnatal development, NSCs/NPCs continue to produce neural cells in the adult brain. Interestingly, unlike during development, the vast majority of adult-derived cells are fated to a neuronal lineage, with a much

smaller percent differentiating into astrocytes and oligodendrocytes in the normal adult brain. The two primary regions that contain adult NSCs/NPCs are the subventricular zone (SVZ) lining the lateral walls of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus (Fig. 8.2). The SVZ produces NPCs that form neuroblasts which migrate along the rostral migratory stream and become neurons in the olfactory bulb; while the NPCs in the SGZ become neurons of the granular cell layer of the dentate gyrus in the hippocampus. In addition, precursor cells (primarily oligodendrocyte precursor cells – OPCs) are scattered throughout the parenchyma and primarily generate cells of glial lineage [105, 106].

Both intrinsic and extrinsic factors regulate neurogenesis and, as in the embryo, transcription factors are involved in proliferation, migration and differentiation of new neurons and glial cells in the adult. As described below, some of the transcriptional regulation that defines embryonic NSC/NPC self-renewal versus differentiation are retained in the adult, either performing the same function as in the embryo or with a new/altered function in the adult (Fig. 8.3 and Table 8.1). However, in general, the diversity of cell types (and particularly neuronal subtypes) that can be spontaneously generated by adult NPCs is substantially limited compared to embryonic cells. This currently limits the ability of endogenous NSCs to replace specific neuronal types in different regions in the CNS. To induce appropriate neuronal specification of adult neural stem cells, a good understanding of the events that lead to appropriate specification during embryonic development is needed, so that NPCs can be manipulated in the adult to achieve the desired outcome.

8.3.1.1 Hippocampal Neurogenesis

There is a progression of development of neural progenitor cells in the hippocampus. Initially, there are radial and horizontal NPCs (type 1) that transition to intermediate progenitors (type-2a, 2b and 3) and on to immature granule neurons. Finally, the new neurons become dentate granular neurons and make large mossy fibre projections with CA3 pyramidal neurons [242]. Within each of these transitions there are specific transcription factors that are expressed (reviewed in [243]). Many of these recapitulate their function in embryonic neural development.

Multiple transcription factors are involved in proliferation and maintenance of the precursor pool within the SGZ. As in embryonic development, *Sox2* is a marker of NSCs in the SVZ and SGZ and following *Sox2* deletion there is a loss of neurogenesis [19, 244, 245]. Thyroid hormone has recently been shown to act as a neurogenic switch in the SVZ by repressing expression of *Sox2* [218]. *Pax6* and the CCAAT/enhancer binding protein β (C/EBPβ) are involved in the proliferation of type-1 NPCS along with *Sox2*, which is a mediator of Notch signalling also involved in maintaining the precursor pool via Shh in adult SGZ [22, 192, 205]. The transcriptional repressor gene *Hes1* is also activated by Notch signalling leading to repression of proneural gene expression and maintenance of NPCs [144] while expression of *Hes5* distinguishes the cells as type-1 NPCs [152]. The orphan nuclear receptor Tlx can activate the Wnt/β-catenin pathway and is important for proliferation and maintenance of adult NPCs in both the SGZ and SVZ and has been shown to form a molecular network with SOX2 [109]. Recently, another factor, REST/NRSF (repressor element 1 silencing transcription/neuron restrictive silencer factor), has been shown to maintain NPC pools and direct stage-specific differentiation [246], while the forkhead transcription factors (FoxOs) have role in the long term maintenance of progenitors [133].

Neuronal fate specification occurs through the expression of *NeuroD1*, *Sox3*, *Sox 4*, *Sox11* and *Prox1* [39, 200, 201, 221, 223]. *NeuroD1* is activated by the Wnt/β-catenin pathway, which is necessary for survival and maturation of NPCs in both the SGZ and SVZ [108, 173]. The bHLH transcription factors also control fate commitment. *Ngn2*, *Tbr2* and *Ascl1*/*Mash1* are expressed in Type 1/2a NPCs that will become glutamatergic neurons in the hippocampus [162, 178, 247], while over-expression of *Ascl1*/*Mash1* produces oligodendrocytes [163]. Synaptic integration of new born neurons is controlled by Kruppel like factor 9 (*Klf9*) and CREB. Furthermore, both transcription factors are involved in survival and late phase neuronal maturation [119, 120, 248].

8.3.1.2 SVZ Neurogenesis

Similar to the SGZ, there is a progression of NPC development in the SVZ. Astrocytes in the SVZ (Type B cells) are the primary precursors of highly proliferative transit-amplifying Type C cells which will generate neuroblasts (Type A cells) destined for the olfactory bulb via migration along the rostral migratory stream (RMS) [249–251]. The zinc-finger protein ARS2 (arsenite-resistant protein 2) controls the multipotent progenitor state of NSCs through activation of *SOX2* [107]. c-Myb is required for maintenance of the neural stem cell niche, promoting expression of *Sox2* and *Pax6* and subsequent proliferation [252].

New neurons migrating from the RMS to the olfactory bulb primarily become GABAergic granule neurons that provide lateral inhibition between mitral and tufted cells. A minority of the new neurons become periglomerular neurons that are involved in lateral inhibition between glomeruli, and a small number of these cells are dopaminergic.

Transcriptional regulation of transient amplifying cell fate is the result of *Olig2* expression, and direction of neuronal fate is via *Pax6* and *Dlx2* [126]. These transcription factors also induce a dopaminergic periglomurular phenotype in adult mice [127, 182, 193]. Recently, it was shown that the transition from amplifying cell to neuroblast requires the down-regulation of *Sox9* by miR-124 [253]. In addition, bHLH transcription factors also control specific neuronal type commitment. Type C cells fated to become GABAergic interneurons in the olfactory bulb express *Ascl1/Mash1* [162]. *Ngn2* and *Tbr2* are expressed in dorsal SVZ progenitors that become glutamatergic juxtaglomerular neurons [179], while *Sp8* is required for parvalbumin-expressing interneurons in the olfactory bulb [226].

8.3.1.3 Transcriptional Regulation of NSCs/NPCs After Injury and Disease

Neurogenesis and gliogenesis are known to be initiated following brain injuries, such as ischemia, seizures, traumatic injury and neurodegenerative diseases [254–256]. However, these new neurons and glia do not usually effectively replenish those that were lost. Recent studies have begun to examine the fate and transcriptional regulation of NPCs following these insults with the aim of promoting cell replacement and functional repair. Table 8.1 provides a comparative summary of transcription factor expression in NPCs following injury and in the normal brain.

Ischemia

Focal ischemic stroke is the most common type of stroke, which results in a contained area of necrotic tissue and a surrounding area known as the penumbra. Focal ischemia promotes SVZ neural progenitor proliferation and neurogenesis [254, 257–259]. However, following cerebral ischemia, repressors to neurogenesis are expressed, such as *Olig2* [184]. Subsequently, gliogenic cells are primarily induced from the adult SVZ [260]. The majority of the SVZ neuroblasts in the damaged striatum express the transcription factor *Sp8* and do not express the transcription factors of the primarily damaged medium spiny neurons [227], suggesting that after brain injury the NPCs do not change their intrinsic differentiation potential. However, following ischemia, pro-neuronal transcription factors are expressed in primate progenitors in the SGZ, including *Emx2*, *Pax6* and *Ngn2* [130]. Recently it has been shown that following 30 and 60 days after stroke, *Ascl1/Mash1* expressing cells in the ischemic striatum gave rise to GABAergic neurons and mature oligodendrocytes [165].

Injury and Seizures

Both blunt and acute injuries to the brain and spinal cord trigger neurogenesis in both the SVZ and SGZ; however it is still unclear if the neurogenesis is stable and productive [261–264]. Following injury to the spinal cord *Sox11b* promotes neuronal determination of endogenous stem cells in adult zebrafish [225]. However, following a stab wound to the brain in mice, *Olig2* has been implicated in repressing neurogenesis. Interestingly, *Olig2* is expressed in glial progenitors that precede the appearance of reactive astrocytes, suggesting that NPCs have a minor role in the repair process [184, 185]. Conversely, following quinolinic acid induced striatal cell loss there is compensatory replacement of neurons from the SVZ, primarily from an increase in NPC

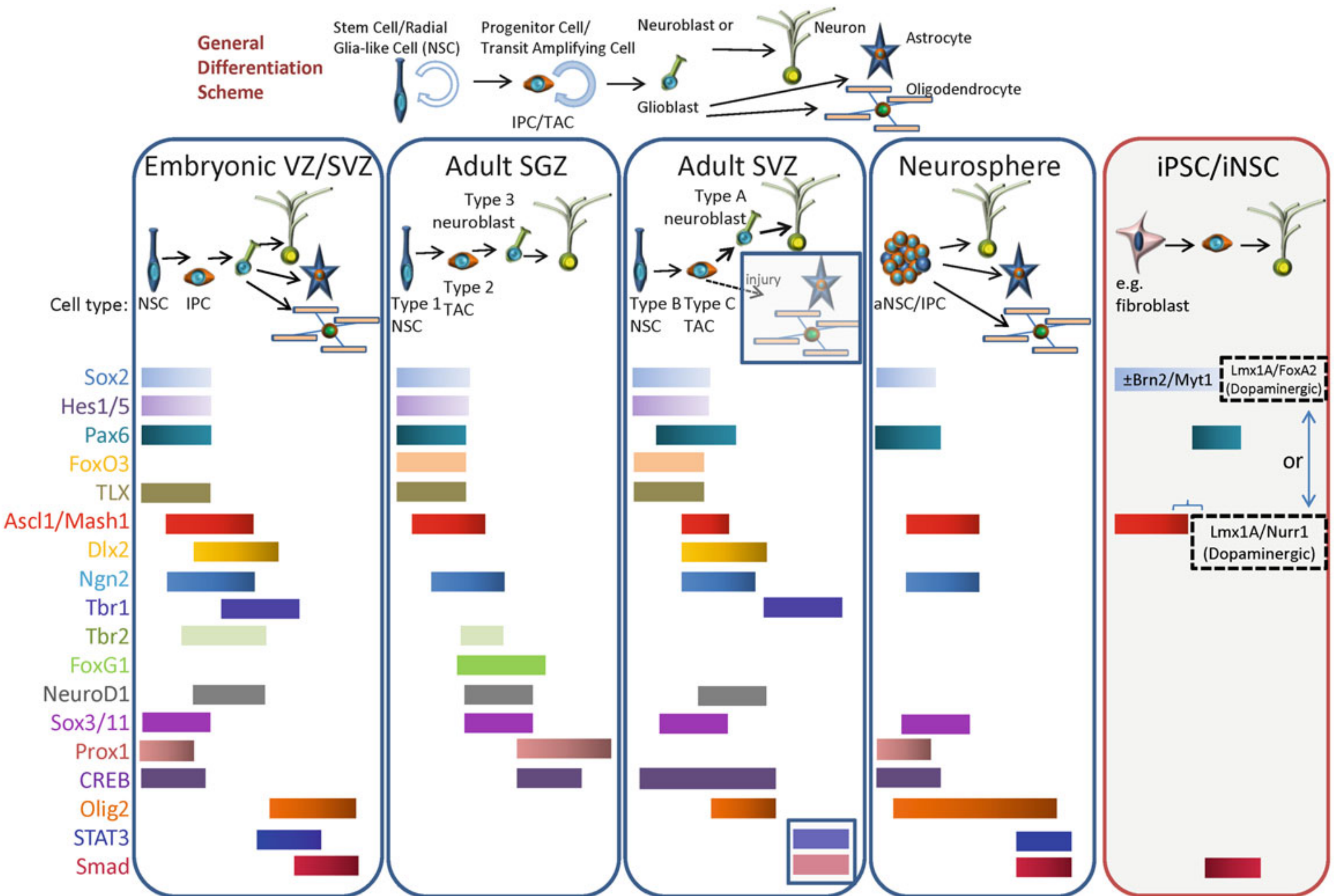
General Differentiation Scheme
Stem Cell/Radial Glia-like Cell (NSC)
Progenitor Cell/ Transit Amplifying Cell
IPC/TAC
Neuroblast or
Glioblast
Neuron
Astrocyte
Oligodendrocyte
Embryonic VZ/SVZ
Adult SGZ
Adult SVZ
Neurosphere
iPSC/iNSC
Cell type:
NSC
IPC
Type 3 neuroblast
Type 1 NSC
Type 2 TAC
Type A neuroblast
Type B NSC
Type C TAC
injury
aNSC/IPC
e.g. fibroblast
±Brn2/Myt1
Lmx1A/FoxA2 (Dopaminergic)
or
Lmx1A/Nurr1 (Dopaminergic)
Sox2
Hes1/5
Pax6
FoxO3
TLX
Ascl1/Mash1
Dlx2
Ngn2
Tbr1
Tbr2
FoxG1
NeuroD1
Sox3/11
Prox1
CREB
Olig2
STAT3
Smad

Fig. 8.3 Comparative expression and function of transcription factors from different sources in vivo and in vitro. A range of the more broadly characterised transcription factors known to play a role in NSC/NPC maintenance, differentiation and subsequent maturation are compared across the embryonic VZ/SVZ, adult SGZ, adult SVZ and neurospheres (embryonic or adult brain derived). Cells from each of these sources display a version of a general differentiation scheme which is summarised above, whereby a proliferative neural stem cell (NSC) produces a more proliferative neural progenitor cell, also known as a transit amplifying cell (TAC) or intermediate progenitor cell (IPC) depending on the source of cell. These then differentiate into neuroblasts or glioblasts which then further differentiate into mature neurons or astrocytes and oligodendrocytes respectively. Many of these factors play a similar role in the different types of brain derived stem cells, with some differences, particularly in the hippocampal SGZ cells. In addition, while adult SVZ cells primarily produce neurons under normal physiological conditions, they can also produce glial cells following neural injury or disease. While many factors are known that regulate brain-derived NSC/NPCs, this is sharply contrasted with the current state of knowledge regarding transcription factors regulating neural development of induced pluripotent stem cells (iPSCs) or induced neural stem cells (iNSCs). While the transcription factors that can induce a neural cell fate on these cells have been elucidated, knowledge of factors that regulate their subsequent differentiation is much more limited. Most attention has been focussed on production of dopaminergic neurons for replacement of cells lost in Parkinson’s disease, however specification of other neural fates, including glial cells, is currently limited to modification of culture conditions

Table 8.1 Comparative list of transcription factors in neural stem cell from different sources, ages and injury/disease conditions

Transcription factor	Embryonic NSCs	Adult SGZ neurogenesis	Adult SVZ & neurospheres	Injury/disease-induced neurogenesis	ESCs/iPSCs/ iNSCs
Ars2	[107]		[107]		
β-catenin	[15, 45, 46]	[108]	[109, 110]	Ischemia – [111]	[112]
Bmi-1	[26]		[26, 113, 114]		
C/EBPβ	[115]	[116]	[117]		
CREB	[118]	[119]	[120–123]	HD – [124]	[125]
Cux2	[36, 54, 55]				
Dlx2	[95]		[126, 127]	Striatal loss – [128]	
E2F1		[129]	[129]		
Emx2	[34]		[34]	Ischemia – [130]	
Fezf2	[53, 56, 61, 131]		[132]		
Forkhead (Fox)	[16, 66, 133–136]	[133]	[137]	PD – [138]	[139]
Gli1-3	[25, 31, 140]	[141]	[142]		[143]
Hes1	[9, 10]	[144]	[145, 146]	HI and general injury/disease [147–150]	[151]
Hes5	[9, 10]	[152]		PD – [153]	
HesR1-2	[8, 32]				
Id2/4	[30, 154–156]		[110, 156–158]		
Lmx1	[69]			PD – [159]	[139, 159–161]
Mash1 (Asch1)	[18, 24, 94, 95]	[162, 163]	[162, 164]	Ischemia – [165]; AD – [166, 167]; PD – [159]	[168, 169]
Mll1			[170]		
mPer2		[171]			
NeuroD1	[172]	[39, 108, 173–175]	[173, 174, 176]	HD – [177]	[168, 169]
Ngn2	[18, 24]	[175, 178]	[164, 179]	Ischemia – [130]; Seizure – [178]	
NPAS3		[180]			
Nurr1	[65]			PD – [138, 159]	[139, 159, 181]

Olig2	[29, [89–93]		[29, 126, 182, 183]	Ischemia & brain injury – [184, 185]; AD – [166, 167]	
p63	[186, 187]		[188]		
p73	[186, 189]	[190, 191]	[186, 189, 191]		
Pax6	[27, 28]	[39, 192]	[126, 179, 182, 193]	Ischemia – [130]; Striatal loss – [128]	[194–197]
Prox1	[198, 199]	[200, 201]			
Querkopf			[202]		
RBPJkappa	[11, 144, 203, 204]	[152, 205]	[144, 204, 206]		
Smad	[71, 207–210]		[211, 212]	HD – [124]	[196, 213–217]
Sox2	[17]	[22, 107, 205]	[107, 218, 219]	HD – [124]	[220]
Sox3	[17, 221]	[221]	[221]		[221]
Sox11	[222]	[223, 224]		SCI – [225]	
Sp8			[226]	Ischemia – [227]	
STAT3	[71, 208, 209]	[228]	[212, 229–231]		
Tbr2	[33, 40, 41]	[42]	[41, 176, 179]		
Tlx	[232]	[109, 233–236]	[237–239]	Ischemia – [240]	
Zic2		[241]			

HD Huntington's disease, *PD* Parkinson's disease, *SCI* spinal cord injury, *AD* Alzheimer's disease *HI* hypoxia/ischemia

proliferation and neuroblast formation induced by the expression of *Dlx2* and *Pax6* [128]. Similarly, neurogenesis is increased in the SGZ and SVZ after seizures [265–267]. However, the survival of the new born neurons is low as most undergo apoptotic cell death in proportion to the severity of the seizure [268]. In the SGZ, proliferating NPCs show a transient expression of the transcription factor *Ngn2* [178].

Neurodegenerative Disorders

Alzheimer's disease (AD) results in the degeneration of basal forebrain cholinergic neurons in the cortex and hippocampus from the deposition of neurofibrillary tangles and amyloid-β plaques [269]. The neuropathological hallmark of AD is the amyloid-β plaques; however small oligomeric amyloid-β appears to be the noxious component. Neurogenesis can be both increased and decreased in AD, depending on the transgenic model used (reviewed in [270]. Early in the disease, oligomeric amyloid-β may transiently promote the generation of immature neurons from NPCs. However, reduced concentrations of multiple neurotrophic factors and higher levels of FGF2 seem to induce a developmental arrest of newly generated neurons. Further, there is a down-regulation of *Olig2* and over-expression of *Ascl1/Mash1* caused by amyloid-β that switches the cell fate to death [166, 167].

Parkinson's disease (PD) is the outcome of the loss of dopaminergic neurons in the substantia nigra of the midbrain (reviewed in [271]). In transgenic mouse models, there is a decrease in newly generated neurons in both the dentate gyrus and olfactory bulb [153, 272]. Alterations in neurogenesis have been linked to a decrease in *Notch1* and *Hes5* expression [153]. Neurogenesis research in PD has focused on generating replacement dopaminergic neurons, primarily with the use of transplanted ES/iPS cells (see below). Recent studies have elucidated the transcription factors necessary to produce dopaminergic neurons. The combination of *Ascl1/Mash1*, *Nurr1* and *Lmx1a* result in the generation of functional dopaminergic neurons from mouse and human fibroblasts [159]. Other studies have shown that *Foxa2* in combination with *Nurr1* can also induce the production of nigral (A9)-type midbrain neurons from NPCs [138].

Other neurodegenerative diseases such as Huntington's disease have shown a decrease in neurogenesis. NPC proliferation is decreased in Huntington's disease in both the SGZ and SVZ, with some reports of reduced numbers of newly born neurons (reviewed in [270]. In a rat model of Huntington's disease, SGZ progenitor cell proliferation is decreased due to an increase in *Sox2*-positive quiescent stem cells and a decrease in CREB signalling [124]. Interestingly, during progressive striatal degeneration, new neurons are produced; however there is low survival and little replacement of lost striatal neurons. Furthermore, neither SVZ-derived nor intrastriatal generated neurons have the potential to differentiate into striatal projection neurons as they lack the transcription factors necessary for such specification [273].

Models of myelin injury have shown an increased production of oligodendrocytes from the SVZ. Oligodendrocyte production is increased following lysolecithin-induced focal demyelination [274, 275]. In a model of inflammatory demyelination, experimental autoimmune encephalomyelitis (EAE), an increase in proliferation of cells in the SVZ, their migration to lesion sites and their expression of oligodendrocyte and astrocyte markers was reported [276], while upregulation of chordin in the SVZ following lysolecithin-induced demyelination changes the GAD65 and Dcx positive progenitors from neuronal to glial fates, producing more oligodendrocytes in the corpus callosum [193]. In the cuprizone-induced demyelination model, infusion of noggin into the lateral ventricles inhibits BMP signalling and increases the numbers of oligodendroglia in the SVZ [277] and the number of oligodendrocytes in the corpus callosum [278]. Also in the cuprizone model, overexpression of *Zfp488*, an oligodendrocyte-specific zinc finger transcription repressor, promotes oligodendrocyte production in the SVZ [279]. This increased specification to the oligodendrocyte lineage following injury is associated with expression of *Olig2* [274, 279] and *Sox10* [279].

Other disease models show that exogenous factors have an influence on NPC intrinsic transcription that occurs following injury or pathology to the brain. Recently it was shown that the cytokine TWEAK which is induced by cerebral ischemia and other brain disorders activates NF-kappaB and reduces progenitor proliferation in the SVZ. Concurrently, TWEAK lowers the expression of *Hes1*, thereby inducing neuronal differentiation [147]. Pathological brains can have an increase in oxidized redox state, which can alter NPC fate; oxidative conditions up-regulate the histone deacetylase *Sirt1* (sirtuin 1). *Sirt1* binds to a co-repressor complex of *Hes1* and inhibits the pro-neuronal *Ascl1/Mash1*, in so doing, directing the NPCs toward glial differentiation [148, 149].

8.4 Derivation of Neural Stem/Precursor Cells from ES and iPS Cells

8.4.1 Transcriptional Networks Involved in the Differentiation or Reprogramming of Human Pluripotent and Somatic Cells Down Neural Stem/Precursor Cells Lineages

Human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) express a cohort of transcription factors that maintain self-renewal and repress differentiation [280–282]. In order to induce differentiation in pluripotent stem cells, it first requires the down-regulation of the pluripotent transcriptional network followed by the up-regulation of lineage specific transcription factors. By mimicking the extrinsic signalling factors used during development hESCs and iPSCs can be pushed out of self-renewal and their differentiation biased towards a range of cell types including those of the nervous system [194, 283]. The differentiation down a neuroectoderm lineage has been shown to utilise the extrinsic factor Noggin, which is found to be critical during neurogenesis across species [284, 285]. The addition of the BMP antagonist Noggin biases human pluripotent stem cells towards a neuroectoderm cell lineage, resulting in early neural stem cells that no longer express the pluripotency-inducing transcription factor OCT4, but now express the transcription factor PAX6 [194, 195]. More recently the dual inhibition of BMP signalling by noggin and inhibition of Activin/Nodal signalling by the small molecule SB431542 was shown to be an efficient and rapid method for generating PAX6+ neural stem cells [196]. Examination of human fetal development shows that PAX6 is expressed at the earliest stages of neuroectoderm commitment [197]. Not only is it a marker of the human neural plate but forced expression of PAX6 in human embryonic stem cells drives their differentiation towards a neural fate, demonstrating that it is a determinant of neuroectoderm cell fate [197]. Further to this, knockdown of PAX6 prevents neuroectoderm differentiation. Interestingly however, in mouse ES cells forced expression of PAX6 is more involved in the progression of neuroectoderm towards radial glia rather than specification of neural lineages and highlights a potential species difference between human and mouse [286].

8.4.2 Direct Specification of Neural Lineages

Over the last several years, through transgenic manipulation of cells, other transcriptional determinants of cell fate have been uncovered for the nervous system. Rapid progress in this field has been fuelled by the discovery that somatic cells can be reprogrammed back into a pluripotent state through the forced expression of a defined set of pluripotent transcription factors [282, 287, 288].

The direct conversion of human and mouse fibroblasts into neurons has been achieved through use of various combinations of transcription factors. A screen of 19 neural tissue specific genes identified three critical factors, *Ascl1/Mash1*, *Brn2* (also called *Pou3f2*), described above for their roles in neural stem cells during development, and *Myt1l* [168]. Forced expression of these factors in mouse or human fibroblasts results in a rapid and efficient conversion into neurons in vitro

[168, 169]. NeuroD1 was further shown to enhance the maturation and functional characteristics in the reprogramming of human fibroblasts. However, a combination of 4 other transcription factors, *Oct4, Sox2, Klf4*, and *cMyc* have also been shown to directly convert mouse and human fibroblasts directly into NSCs [289, 290] and it has also been reported that *Sox2* alone is sufficient to directly convert mouse and human fibroblasts into neural stem cells which were self renewing, multipotent and non-tumorigenic [220].

Further progress in this field of reprogramming has demonstrated that neurons with distinct functional neurotransmitter phenotypes can also be achieved. Most work has focussed on specification of dopaminergic neurons for replacement in Parkinson's disease. The direct conversion of human fibroblasts into dopaminergic neurons has been obtained by using the same three transcription factors involved in neural specification *Ascl1/Mash1*, *Brn2* and *Myt1l*, along with the addition of *Lmx1a* and *FoxA2* to promote neurons with a dopaminergic phenotype [139]. These two additional transcription factors had previously been demonstrated to be critical for mesencephalic dopaminergic differentiation from ES cells and present during embryonic development of these neurons [181]. Interestingly an alternate set of transcription factors, *Ascl1/Mash1*, *Nurr1* and *Lmx1a* was also shown to be capable of directly converting human and mouse fibroblasts into functional dopaminergic neurons without going through a progenitor cell stage [159].

Transcriptional determinants involved in the specification of neural progenitor cell types from hESCs have also been investigated. GLI1 has been shown to be a determinant of floor plate specification when expressed in PAX6 positive neural stem cells derived from hESC [291]. Furthermore, neural differentiation of hESC under ventralising conditions, along with the forced expression of *Lmx1a* revealed it to be a determinant of mesencephlalic dopaminergic cell fate [160].

Overall, these studies highlight some of the transcriptional determinants that are critical during the development of the nervous system that can be capitalised upon to direct human cells along desired neural lineages. However, direct differentiation of other neural lineages from hESC/iPSCs, such as motor neurons and oligodendrocytes has not yet been achieved and still relies on manipulation of the extrinsic culture environment, with variable efficiency, such as use of retinoic acid (RA) and sonic hedgehog (Shh) to enhance differentiation along the motor neuron lineage (reviewed in [292].

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