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Review

Glial Development: The Crossroads of Regeneration and Repair in the CNS

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Given the complexities of the mammalian CNS, its regeneration is viewed as the holy grail of regenerative medicine. Extraordinary efforts have been made to understand developmental neurogenesis, with the hopes of clinically applying this knowledge. CNS regeneration also involves glia, which comprises at least 50% of the cellular constituency of the brain and is involved in all forms of injury and disease response, recovery, and regeneration. Recent developmental studies have given us unprecedented insight into the processes that regulate the generation of CNS glia. Because restorative processes often parallel those found in development, we will peer through the lens of developmental gliogenesis to gain a clearer understanding of the processes that underlie glial regeneration under pathological conditions. Specifically, this review will focus on key signaling pathways that regulate astrocyte and oligodendrocyte development and describe how these mechanisms are reutilized in these populations during regeneration and repair after CNS injury.

Introduction

A central tenet of regenerative biology is that processes controlling tissue generation during development often control its regeneration: therefore processes regulating developmental gliogenesis in the CNS are likely to provide critical insights into glial repair and its influence on homeostasis in the adult CNS. While injury and pathological states in the adult are comparatively more complex than embryonic and early postnatal development, viewing regeneration through the lens of development lends clarity as well as a starting point for greater insight into the fundamental processes governing glial repair. Therefore, this review will focus on key glial developmental mechanisms that are reused during glial regeneration, how these developmental processes are involved in functional recovery of the CNS, and how they contribute to key neurological disorders. Recently, microglia have been implicated as also playing key roles in CNS regeneration, however, because they have different developmental origins from CNS glia, this review will not cover microglia. In discussing some of these fundamental mechanisms and the crucial cellular interactions involved in glial regeneration, we also hope to demonstrate the potential for future interventions based on identifying putative therapeutic targets. Other excellent review articles have recently considered these topics (Burda and Sofroniew, 2014), and we will refer to them in providing an overview of the field within the limits of the present article.

The ability of an organism to repair and regenerate its injured nervous system often correlates with the organism's longevity and complexity. For example, flies and worms have short lifespans and limited capacity to repair their "CNS," while mice and humans live comparatively much longer and have remarkable ability to repair their damaged CNS. The other side of this equation is that more can go wrong in a CNS with more "moving parts" (cellular elements and complex interactions). Thus, a level of quality control must be in place to ensure that homeostasis is maintained; and the longer you live, the more important this becomes.

In terms of CNS complexity, what key feature separates invertebrates from vertebrates? Besides the existence of many more neuronal subtypes in vertebrates versus invertebrates, glia are clearly a major differentiating element (Freeman and Rowitch, 2013). Invertebrates have a significantly lower proportion of glial cells, with *Caenorhabditis elegans* displaying a ratio of 56 glia to 352 neurons (~1:6 ratio), while the glia-to-neuron ratio in vertebrates ranges from 1:1 to 4:1 (depending who you ask). Coupled with their increasing representation, vertebrates' glial cells also show escalating diversity and functional complexity. Particularly, oligodendrocytes (OLs) and myelin sheaths, which are not present in smaller invertebrates, are necessary and essential adaptations for rapid nerve conduction in axons of larger vertebrates. While aspects of astrocyte function are conserved across species (i.e., glutamate transport), their number and morphological complexity largely increase from mice to humans. Indeed, a single hippocampal astrocyte is estimated to make contacts with ~100,000 synapses (Bushong et al., 2002). This estimate, coupled with recent reports that transplanting human astrocytes into the mouse brain enhances learning and memory, also suggests additional, undiscovered roles for astrocytes in cognition, further reinforcing their central and increasingly complex role in CNS physiology in higher organisms (Han et al., 2013).

This evolutionary evidence, together with the rapid progress over the last two decades in our understanding of glial biology and physiology, demonstrates an essential role for glia in CNS function. Astrocytes and OLs are able to regenerate in response to CNS injury, and glial regeneration and repair are essential for long-term homeostasis and for complete recovery of integrated functions. Given their unique partnerships with neurons and the extremely limited degree of neurogenesis in the adult CNS, this capacity also functions to preserve neuronal populations

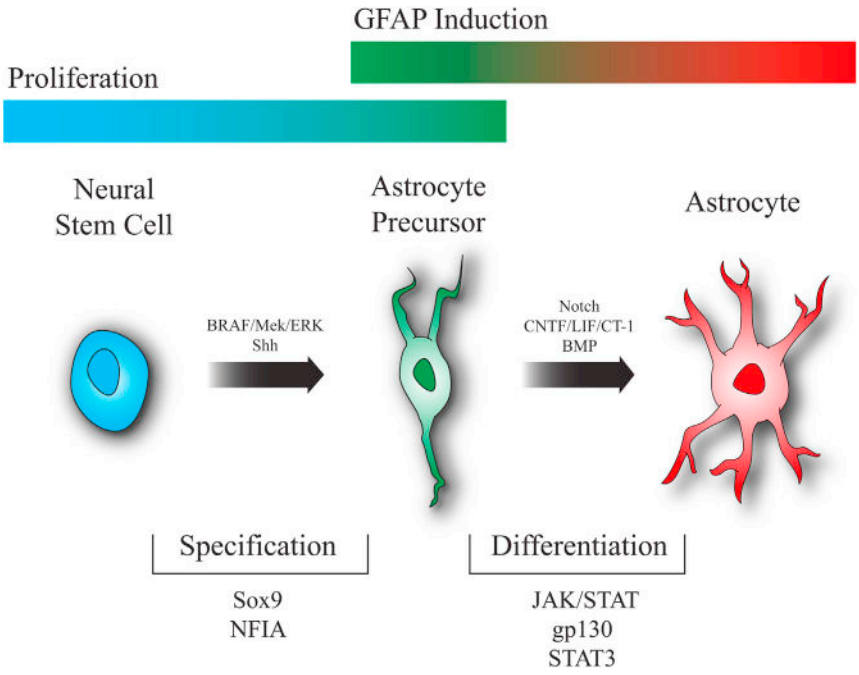

Figure 1. Development of the Astrocyte Lineage

Schematic synopsis of the cellular and molecular processes that oversee the specification and differentiation of the astrocyte lineage. Unlike neuronal- or oligodendrocyte-lineage development, the intermediate stages of astrocyte lineage development remain poorly defined, due in part, to the lack of reliable markers and clearly defined functional endpoints.

postinjury. Furthermore, various types of glial progenitors have the potential to generate neurons under pathological conditions. Thus, glial responses to injury and disease serves two main purposes: (1) repair and preservation of existing cell populations, and (2) regeneration of lost populations, including both neurons and glia.

Astrocyte Development

Generation of astrocytes involves a complex interplay of intrinsic and extrinsic cellular signals that act on neural stem cells (NSCs) and precursor populations to direct their formation. As with the development of any cell lineage, astrocyte differentiation entails a sequential series of events that result in the generation of a mature cell population that actively participates in CNS physiology. Unlike OLs, however, the stages of astrocyte lineage development are poorly defined, lacking stage-specific markers and clearly defined developmental endpoints (Molofsky et al., 2012). Moreover, while astrocytes are a functionally heterogeneous population, the cellular nature of their heterogeneity is just starting to emerge (Chaboub and Deneen, 2012). Many processes associated with astrocyte development have long been shrouded in mystery, but an existing base of knowledge can be used to frame our discussion on reactive astrocytes. The following sections briefly review key aspects of astrocyte development germane to reactive astrocytes and repair (Figure 1).

Specification and Differentiation

During development, neurogenesis precedes gliogenesis. The transition is often used as a model for identifying factors that regulate specification of astrocytes from NSC populations. This developmental interval—the gliogenic switch—is best characterized in the ventral spinal cord, where several recent studies found that transcription factors Sox9 and NFIA comprise a transcriptional cascade that regulates glial specification (Deneen et al., 2006; Kang et al., 2012; Stolt et al., 2003). Subsequently, Sox9/NFIA associate and regulate a set of genes implicated in astrocyte precursor migration and metabolism, key aspects of lineage development (Kang et al., 2012). Interestingly, Shh and Notch signaling have been shown to regulate Sox9 and NFIA, respectively, linking these factors to key developmental pathways active in ventricular zone (VZ) populations (Namihira et al., 2009; Scott et al., 2010). Several studies have implicated both Shh and Notch signaling in astrocyte development and differentiation, although in different regions of the CNS and using different experimental models (Chambers et al., 2001; Garcia et al., 2010).

After specification, astrocyte precursors migrate away from the germinal centers and begin to differentiate. This aspect of astroglial lineage development is defined by the induction of glial fibrillary acidic protein (GFAP), originally identified in reactive astrocytes found in demyelinated multiple sclerosis (MS) plaques (Eng et al., 2000; Gerstl et al., 1970). While GFAP has long been miscast as the definitive marker of astrocytes, identifying the processes that regulate its expression gave crucial insight into the mechanisms regulating astrocyte differentiation. Among key pathways implicated in GFAP regulation, CNTF/LIF/CT-1 cytokine signaling through gp130 and JAK/STAT has been shown in several developmental models to be a key regulator of GFAP and astrocyte differentiation as a whole (Barnabé-Heider et al., 2005; Bonni et al., 1997; Miller and Gauthier, 2007; Sun et al., 2001). Additionally, Notch- and BMP-signaling have been implicated in regulating GFAP-expression and some aspects of astrocyte development, including inhibition of alternative cell fates (Bonaguidi et al., 2005; Grinspan et al., 2000; Namihira et al., 2009; Taylor et al., 2007). Newborn neurons are thought to be the source of these signaling molecules, as separate studies have suggested that CT-1 and Jagged/delta released from neurons promote astrocyte differentiation in vitro (Barnabé-Heider et al., 2005; Namihira et al., 2009). Identifying the in vivo sources of key astrocyte-promoting signaling molecules during development is important for understanding the genesis of reactive astrocytes after CNS injury. Given the complex and heterogeneous cellular response to injury, a knowledge of the normal sources of these key cytokines and signaling molecules can provide insight into paracrine signaling mechanisms that operate after injury (Burda and Sofroniew, 2014).

Proliferative Properties

A distinguishing feature of gliogenesis is the proliferation of precursor populations outside the germinal centers. Both OL progenitor cells (OPCs) and astrocyte precursors (ASPs) display robust proliferative potential postspecification (Ge et al., 2012.; Tien et al., 2012; Fruttiger et al., 1999; Richardson et al., 2011). In the early postnatal cortex, up to 55% of GFAP+ astrocytes are generated after migrating away from the germinal centers (Ge et al., 2012). Similarly, in the developing spinal cord, ASP populations retain proliferative potential postspecification, suggesting the existence of an "intermediate astrocyte precursor" (IAP) that governs the expansion of astrocyte numbers throughout lineage development (Tien et al., 2012). The mechanisms governing ASP or IAP proliferation remain poorly defined, but recent studies implicate BRAF-ERK signaling in the spinal cord (Tien et al., 2012). Interestingly, separate studies in the cortex indicate that MEK1/2, which also signals through ERK, regulates gliogenesis through the CNTF-STAT3 axis (Li et al., 2012). Together, these studies suggest a link between the proliferative and differentiative processes that function in ASPs postspecification. Thus, it will be important to identify additional pathways that couple (or uncouple) ASP proliferation and differentiation and to determine how the existing programs are reused in reactive astrocyte proliferation.

Emerging Heterogeneity

Astrocytes can be broadly classified into two categories: (1) protoplasmic astrocytes that occupy the gray matter, and (2) fibrous astrocytes that occupy the white matter (WM). However, an abundant cell type capable of a variety of physiological functions is likely to comprise a vast, reservoir of subtypes and classes within the adult CNS. Indeed, Cajal (1909) described the presence of several morphologically distinct types of astrocytes in the cerebellum. Recent studies have begun the complicated task of delineating astrocytes' cellular heterogeneity, guided by the principles of developmental patterning. A set of recent studies using genetic and lineage-tracing approaches found that molecularly distinct subtypes of astrocytes originate from separate domains in the developing spinal cord, indicating embryonic patterning as an organizing principle in astrocyte, as well as neuronal, diversity (Hochstim et al., 2008; Tsai et al., 2012). While these patterning principles have yet to be applied to diverse astrocyte populations in the adult brain, a recent study using GFAP- and s100β-reporter mice identified nine morphologically distinct classes of astrocytes distributed in varying constituencies across the adult brain (Emsley and Macklis, 2006). Given the underlying functional heterogeneity of astrocytes and their reactive counterparts, a more comprehensive understanding of their cellular heterogeneity will further resolve their roles after CNS injury.

Astrocytes in CNS Injury and Repair

With their key role in subserving normal neuronal function by operating as a bridge from neurons to the outside world, a natural extension of astrocyte function after injury would be to reestablish homeostasis in a pathological microenvironment. Reactive astrocytes, the astrocytic response to CNS injury, have been identified in nearly all cases of CNS injury, degeneration, and disease, from multiple sclerosis (MS) and Alzheimer's disease, to glioma, spinal cord injury (SCI), and stroke (Sofroniew and Vinters, 2010). Despite their ubiquity in injury and disease, the properties, functions, and contributions of reactive astrocytes to CNS repair remain somewhat mysterious. Below, we summarize what is known about reactive astrocytes and their contributions to CNS repair and how recent studies have changed long-standing views of astrocyte reactivity.

General Properties

Sites of CNS trauma or disease are populated by reactive astrocytes with three general properties: (1) expression of GFAP, (2) cellular hypertrophy, and (3) cellular proliferation. Thus, reactive astrocytes can be identified by a combination of molecular markers and cell morphology, coupled with accurate localization of injury. These properties are graded, with increasing proliferation and GFAP expression correlated with more severe injury. Their increased proliferation in severe injury disrupts nonoverlapping "tiled" domains of astrocytes and forms densely packed areas containing extensive overlapping of astrocytic processes.

Astrocytes play diverse and crucial roles in normal CNS physiology, regulating synaptogenesis, neurotransmission, metabolic support, blood-brain-barrier (BBB) formation/maintenance, and other functions not yet characterized (Alvarez et al., 2013; Halassa and Haydon, 2010; Matyash and Kettenmann, 2010). Unsurprisingly, injury-induced proliferation, hypertrophy, and tiling disorganization are likely to disrupt these normal functions, and the introduction of new signaling molecules in an injury milieu raises the question of whether reactive astrocytes after an injury are demonstrating a loss of normal functions or the acquisition of new ones (Burda and Sofroniew, 2014). It seems likely that normal functions such as synaptic transmission, metabolic support, and BBB formation would aid in repair. Indeed, several studies have linked these functions to reactive astrocytes and repair (Faulkner et al., 2004; Rothstein et al., 1996; Swanson et al., 2004; Voskuhl et al., 2009). But the emergence of new functions, such as managing the immune response to injury, also contributes to the repair process (Dong and Benveniste, 2001; Farina et al., 2007; John et al., 2003). While the exact functions of reactive astrocytes after injury remain poorly defined, one key question remaining is whether distinct types of injury elicit differential responses from reactive astrocytes and, ultimately, from reactive astrocytes with different repair properties. Recent studies have revealed that stab wounds and ischemia give rise to reactive astrocytes with NSC potential, while degenerative models do not (Shimada et al., 2012; Sirko et al., 2013). These observations hint at complex interplays between type of injury, location, and reactive astrocyte response and function, which are only now being recognized. Decoding these relationships will be essential to understanding how astrocytes respond and contribute to CNS repair.

Good Cop? Bad Cop? Both?

Given the inherent complexity of injury states and the heterogeneous astrocytic response, perhaps a better question at this point is: are reactive astrocytes detrimental or beneficial to CNS repair? The long-standing view of reactive astrocytes is that they are "bad actors" in the repair process. This view derives from the inhibitory effects of glial scarring on axon regeneration after SCI. The glial scar around trauma sites results from reactive astrocyte proliferation and subsequent accumulation of an astrocytic barrier that physically impedes axon

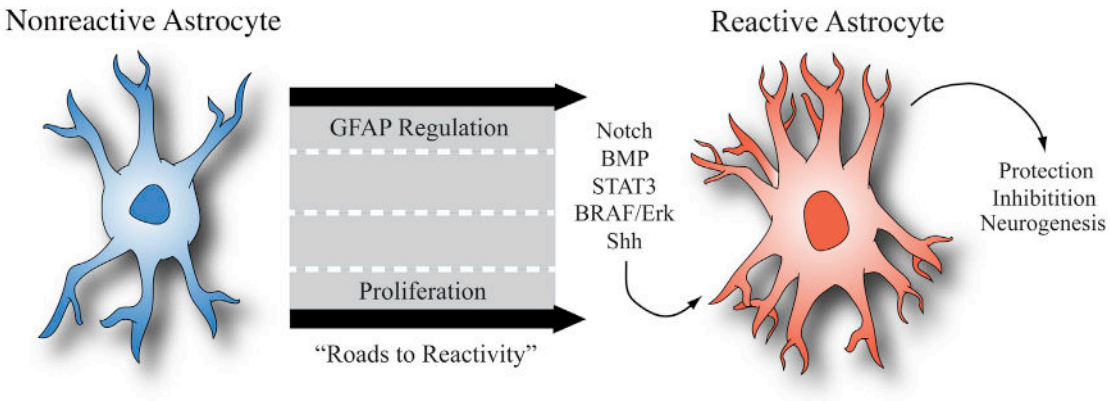

Figure 2. Astrocyte Roads to Reactivity
The two key processes associated with astrocyte development that directly contribute to the reactive astrocyte phenotype are proliferation and GFAP-induction. Molecular regulation of these processes during development is viewed as the road to astrocyte reactivity and understanding how they are recapitulated after injury will serve as a starting point for understanding the nature of reactive astrocytes.

regeneration and releases chondroitin sulfate proteoglycans (CSPGs), which inhibit axon growth (Busch and Silver, 2007; Morgenstern et al., 2002). These observations raise a simple question. If the aftereffects of glial scarring are so bad, why do scars form in the first place? There is general consensus that the reactive astrocyte-glial scar axis functions to "wall off" the damaged area, preventing the spread of inflammatory cells or infectious agents to adjacent healthy tissues, and the axonal inhibitory effects are the cost of this benefit (Rolls et al., 2009). Indeed, ablation or genetic manipulation of reactive astrocytes after SCI increases local inflammation and neuron loss and generally inhibits recovery, indicating that they are essential for repair (Herrmann et al., 2008; Sofroniew, 2009).

The view that reactive astrocytes inhibit CNS repair is evolving, as numerous studies have found that they enhance recovery in a variety of CNS injury models. While neuronal recovery garners much of the attention, reactive astrocytes also contribute to recovery after white matter injury (WMI), being required for remyelination in several lesion models (Franklin et al., 1991; Talbott et al., 2005). In more complex, inflammatory EAE models of WMI, the loss of reactive astrocytes increases inflammation and neuronal loss, although in some cases it also promotes recovery (Brambilla et al., 2009; Voskuhl et al., 2009). Thus, in cases of neuronal or WM repair, despite emerging evidence that reactive astrocytes facilitate the recovery process, their deleterious effects may impair long-term recovery for the benefit of immediate stability. One key area in gaining an understanding of this duality is the nature of astrocyte heterogeneity. Reactive astrocytes are clearly not homogeneous, and given that normal astrocytes play diverse roles in the normal CNS, it is likely that analogous populations of reactive astrocytes exist after injury and during repair. Future studies should aim at decoding these relationships, as more work in this area is clearly needed.

Linking Astrocyte Development to CNS Injury

The developmental processes regulating how astrocytogenesis contributes to CNS repair remain poorly understood. Unlike the restoration of OLs and neurons, the restoration of astrocyte populations is not a major feature of CNS repair. Thus, the developmental processes that regulate astrocytogenesis are not implemented in a manner paralleling development (see Oligodendrocyte Regeneration and Repair in the Adult Brain). It is possible that astrocytes acquire new properties after injury that are not necessarily associated with their normal functions, but are associated with: (1) a new set of regulatory factors, or (2) implementation of the same pathways under vastly different conditions (embryo versus injured adult). Our basic knowledge of astrocyte development has lagged behind that of OLs and neurons, and this significant gap, combined with the preceding points, widens the chasm between our understandings of normal and injury-associated astrocytes.

Despite these limitations, fundamental aspects of lineage development that have been molecularly characterized in normal astrocytes and are associated with reactive and regenerative astrocytes may give insight into their injury-associated responses. These features include GFAP expression and cell proliferation. While the molecular processes regulating these facets of astrocyte development are unlikely to be fully conserved after injury, these developmental criteria provide an entryway into the nature of reactive astrocytes after CNS injury (Figure 2).

Regulation of GFAP: Gateway to Reactive Astrocyte Signaling

For years, GFAP has been used as the definitive marker of normal astrocyte populations. In some ways, this was necessary due to a dearth of reliable astrocyte markers, but in other ways it has hindered the field, as GFAP is not a universal astrocyte marker and relying on it further clouds an already gray area. GFAP has received a lot of bad press lately as the field slowly turns to markers such as Aldh1l1 and Glt1 that are universally expressed in normal astrocyte populations (for complete list, see Molofsky et al., 2012).

Despite these limitations, GFAP upregulation remains a cardinal feature of reactive astrocytes, and logic dictates that the signaling pathways and transcription factors regulating GFAP expression are likely to be associated with reactive astrocytes. This area has received intense investigation, implicating several

key signaling pathways and associated transcriptional regulators including BMP, LIF/CNTF, and Notch, in the regulation of astrocyte differentiation and GFAP expression (see above). Each of these pathways has been linked to reactive astrocytes and, given their broad reach, it is likely that they contribute to aspects of reactive astrocyte physiology and function outside of GFAP regulation. Therefore, one logical extension is that GFAP regulation serves as a gateway for identifying factors that influence reactive astrocytes and their biology. Indeed, several recent studies on these core GFAP regulatory pathways in reactive astrocytes have revealed a broader scope of functions after CNS injury, as well as new insights into the biology of reactive astrocytes.

Notch Signaling. Notch signaling is a central pathway used by astrocytes during development that regulates both the specification of astrocyte precursors from NSCs and their subsequent maturation. Surprisingly, it has only recently been characterized in reactive astrocytes. Notch receptors are upregulated in reactive astrocytes after CNS injury, and inhibition of the Jagged 1 ligand suppresses GFAP and endothelin receptor-B (ET_B-R) expression in reactive astrocytes found in focally demyelinated lesions (Gadea et al., 2008; Morga et al., 2009; Hammond et al., 2014). Furthermore, γ-secretase, a key intracellular regulator of Notch signal transduction, is also upregulated in mouse models of stroke (Arumugam et al., 2006). Interestingly, antisense inhibition of Notch intracellular domain (NICD) expression or treatment with γ-secretase inhibitors improved functional recovery after cerebral artery occlusion (Arumugam et al., 2006). The improved recovery correlated with increased immune invasion of the peri-infarct region and a decrease in proliferating astrocytes. Conditional deletion of Notch1 using GFAP-CreER^{TM} similarly resulted in increased immune invasion and decreased astrocyte proliferation, but did not improve recovery, suggesting that the Notch pathway functions in multiple cell systems present in CNS injury (Shimada et al., 2011).

The above studies suggest that suppressing Notch signaling will decrease the reactive astrocyte "load" and thus improve recovery. However, reactive astrocytes also promote CNS recovery, when combined with different injury modalities, in different brain regions and with different astrocyte constituencies, indicating clearly that the recovery landscape is not a "unified field." The same principles apply to Notch signaling in reactive astrocytes. A recent landmark study using a photothrombic injury model revealed that Notch signaling is required for subventricular zone (SVZ)-induced astrocytogenesis postinjury (Benner et al., 2013). The authors also demonstrated that Notch-regulated, Thbs4-expressing astrocytes comprise a unique subset of SVZ astrocytes that contribute to microvascular repair. The role of Notch signaling in reactive astrocytes is only now emerging; however, it seems likely to be region- and, perhaps even, injury model-specific. This is underscored by recent studies in an LPS WMI model, in which reactive astrocytes suppress remyelination through ET-1 activation of the Notch ligand Jagged 1 (Hammond et al., 2014). At the cellular level, this suppression is mediated by Jagged 1 activation of Notch-signaling in neighboring OPCs, inhibiting their differentiation. These recent advances in our understanding of Notch signaling in reactive astrocytes highlight the underlying complexity and suggest a nuanced role for this key developmental pathway in reactive astrocytes during CNS recovery.

STAT3. IL-6, CNTF, and CT-1 cytokines have all been linked to GFAP expression through activation of STAT3 in astrocytes (Miller and Gauthier, 2007). Because the discovery that activated STAT3 is a key transcriptional regulator of GFAP expression, STAT3 expression has been chronicled in reactive astrocytes in various injury models across several CNS regions, becoming a hallmark of reactive astrocytes (Choi et al., 2003; Justicia et al., 2000; Xia et al., 2002). Its role in reactive astrocytes is best characterized in glial scarring after SCI, where conditional deletion of STAT3 in NSCs or astrocytes significantly impairs functional recovery (Herrmann et al., 2008; Okada et al., 2006). In both these studies, glial scar formation was compromised by decreased proliferation and migration of $STAT3^{-/-}$ astrocytes, resulting in greater inflammation and lesion volume. Mechanistic studies suggest that STAT3 mediates scar formation and recovery by regulating responses to oxidative stress and sequestration of inflammatory cells (Sarafian et al., 2010).

Generation of reactive astrocytes after injury occurs in a cellular milieu comprising several cell types, including immune cells and OLs. Given that reactive astrocytes are generated in a complex pathological cellular environment, it is no surprise that the cytokines regulating STAT3 expression are also found in inflammatory cells in several injury models (Choi et al., 2003; Okada et al., 2004; Sriram et al., 2004). Equally interesting is the cellular interplay of OLs, microglia, and reactive astrocytes orchestrated by STAT3. In a recent study, deletion of STAT3 in astrocytes suppressed remyelination after WMI. Mechanistically, $STAT3^{-/-}$ astrocytes promoted TGFβ-1 expression in microglia, which subsequently suppressed OPC differentiation after injury (Nobuta et al., 2012). This study highlights not only new roles for STAT3 in reactive astrocytes, but also the complexities of paracrine signaling between cellular compartments present in injury. Undoubtedly, future studies will investigate whether similar paracrine mechanisms underlie STAT3 function in reactive astrocytes in other CNS injury and regeneration models, as injury conditions or location may dictate the STAT3-response in reactive astrocytes themselves.

BMP Signaling. The convergence of cellular constituency and signaling complexity after CNS injury—and its influence on regeneration and repair processes—are perhaps best illustrated by the BMP pathway. BMP signaling plays a key role in astrocyte differentiation and is also activated in reactive astrocytes after various CNS injuries, including SCI, ischemia, hypoxia, and WMI (Lewén et al., 1997; Martinez et al., 2001; See and Grinspan, 2009; Setoguchi et al., 2001). Several groups have manipulated BMP signaling in a variety of injury models by administering noggin or BMP ligands, each having a different effect on repair. For example, adding BMP ligand after ischemic injury promoted functional recovery, while several studies indicate that BMP secreted from reactive astrocytes suppresses remyelination in WMI models (Chang et al., 2003; Martinez et al., 2001; Sabo et al., 2011; Wang et al., 2011). The latter findings are supported by several developmental studies, indicating that BMP signaling suppresses normal OPC differentiation (Gomes et al., 2003; See et al., 2004). Thus, BMP signaling in reactive astrocytes during injury response is both detrimental

and beneficial, depending on the type of injury and the cell population being repaired. This duality is best shown in SCI models, where conditional deletions of *BMPR1a* or *BMPR1b* in astrocytes have opposing effects on glial scar formation (Sahni et al., 2010). BMPR1a-cKO demonstrate reduced gliosis, increased lesion volume, and impaired motor recovery, while the BMPR1b-cKO display increased GFAP expression and decreased lesion volume in acute injury, accompanied by reduced scarring in chronic states. The vastly different effects of these receptor subunits on reactive astrocytes in SCI add another layer of regulatory complexity to BMP signaling in CNS injury. Such complexities are likely to be present in other signaling systems that operate in reactive astrocytes or other cell types associated with injury, but have yet to be discovered.

Astrocyte Proliferation: A Path to Regeneration?

The mechanisms regulating astrocyte proliferation during development are poorly understood, partly because a clearly defined postmitotic stage has not been identified during astrocyte maturation. However, the presence of GFAP-expressing astrocytes with proliferative potential in the postnatal cortex parallels the transient amplifying "astrocyte" population in the stem cell niche of the SVZ, allowing us to infer that normal astrocytes harbor latent NSC potential associated with their proliferative response to injury (Kriegstein and Alvarez-Buylla, 2009). Reactive astrocytes demonstrate enhanced production of multipotent NSCs in vitro, suggesting that under proper conditions proliferating reactive astrocytes can acquire NSC-like properties (Robel et al., 2011) and raising the question of whether the mechanisms controlling postinjury astrocyte proliferation similarly regulate dedifferentiation to NSCs and possible neuronal regeneration. Several recent studies are unraveling the processes regulating astrocyte proliferation and their role, if any, in the astrocyte-NSC axis.

BRAF/Mek/ERK Signaling Axis. Recently, Mek and BRAF have been implicated in astrocytogenesis and precursor proliferation during development, respectively (Li et al., 2012; Tien et al., 2012). Given that both Mek and BRAF function through the MAPK-ERK signaling axis, these findings implicate a central signaling pathway in astrocyte generation. While specific expression of activated Mek and BRAF in reactive astrocytes remains limited, activated ERK and MAPK have been detected in reactive astrocytes in various injury models (Carbonell and Mandell, 2003; Mandell et al., 2001; Mandell and VandenBerg, 1999). In ischemia, pharmacological manipulation of p38 MAPK or ERK promotes recovery, although its effect on reactive astrocyte proliferation was never examined (Gadea et al., 2008; Namura et al., 2001). In WMI injury models, activated ERK is present in reactive astrocytes and mediates ET-1-dependent astrocyte proliferation in lesions (Gadea et al., 2008). ERK has also been implicated recently in S1P signaling in reactive astrocytes associated with human MS (Fischer et al., 2011). However, the precise cellular site of action and its influence on the role of MAP-ERK signaling repair remain poorly defined.

More broadly, delineating the upstream and downstream biology surrounding possible BRAF-Mek-ERK signaling in reactive astrocytes is extremely complex. This pathway mediates a myriad of cellular responses in various forms of CNS injury. However, in the context of the astrocyte-NSC axis, EGF signaling plays a major role in NSC formation and functions through the MEK-ERK pathway, which is also implicated in NSC formation (Burrows et al., 1997). This fact, coupled with observed expression of EGFR in reactive astrocytes and EGF in sites of injury, leads to speculation that EGF signaling through the BRAF-Mek-ERK axis in proliferating reactive astrocytes provokes conversion to a NSC-like identity, ultimately stimulating neurogenesis (Planas et al., 1998). Such endogenous repair mechanisms are intriguing and somewhat advantageous, but newborn neurons derived from reactive astrocytes after injury have not been documented in vivo, and cortical transplantation of NSCs derived from reactive astrocytes from ischemia models did not support neurogenesis (Shimada et al., 2012).

Sonic Hedgehog Signaling. The role of Shh in normal astrocytes is complex, as it is required for patterning and therefore indirectly contributes to generating patterned astrocyte subpopulations (Ericson et al., 1997; Hochstim et al., 2008). Consistent with a role in astrocyte development, deletion of smoothened (Smo) results in gliosis in subsets of astrocytes in the cortex and spinal cord, suggesting that Shh signaling suppresses their proliferation and implying stage-specific roles for Shh in astrocyte patterning and differentiation (Garcia et al., 2010; Yu et al., 2013). However, in a stab-wound/freeze CNS injury model, Shh is expressed in reactive astrocytes and pharmacological inhibition via cyclopamine impairs their proliferation (Amankulor et al., 2009). Further evidence of a role for Shh is the expression of the Shh target, Olig2, in reactive astrocytes associated with varied CNS injuries. Analogous to Shh inhibition, conditional deletion of Olig2 in astrocytes results in decreased reactive astrocyte proliferation after injury (Chen et al., 2008). Thus, the role of Shh appears to vary significantly between normal and reactive astrocytes and points again to the differing cellular milieus in development and in injury.

Given the link between astrocyte proliferation and NSC-like states and the effect of Shh as a potent inducer of NSCs and reactive astrocyte proliferation, it seems natural that Shh may regulate aspects of the astrocyte-NSC axis associated with injury. Indeed, these observations were beautifully integrated in a recent study characterizing Shh responses in reactive astrocytes across a spectrum of CNS injury models (Sirko et al., 2013). Sirko et al. (2013) demonstrate that reactive astrocytes acquire NSC-like properties in stab-wound, but not degenerative CNS injury. Shh expression correlates with reactive astrocytes having NSC-like properties, and conditional knockout of Smo in reactive astrocytes decreases their proliferative response and NSC-forming capacity. These observations reinforce the broader point that not all reactive astrocytes are "created equal" and this heterogeneity may be induced by injury states. Alternatively, the role of Shh signaling in patterning and astrocyte diversity may also indicate that subsets of astrocytes are differentially responsive to signaling and act accordingly. Indeed, recent studies in human ESCs found that astrocytes derived from Olig2-expressing neural progenitor cells promote recovery after ischemia, suggesting that Shh signaling may be differentially used in reactive astrocyte populations after injury (Jiang et al., 2013).

While provocative and promising, these findings must be interpreted with tempered optimism, as characterizing the NSC

nature of these reactive astrocytes relies on in vitro analysis. In vitro culture is well known to change the properties of CNS-derived cells, and the Shh-Olig2 axis is especially prone to such deregulation in NSC culture (Gabay et al., 2003). Definitive proof that reactive astrocytes acquire NSC-like properties with neurogenic potential will require complementary conditional lineage tracing analysis, to distinguish the "actual" from the "possible" (Anderson, 2001).

Oligodendrocyte Development

Our knowledge of OL development derives from an extensive range of genetic and biochemical tools—particularly cellular markers and cell-specific gene promoters—that have enabled detailed characterization of OPCs and lineages able to generate OLs during embryonic and postnatal development (Emery, 2010a; Kessaris et al., 2006; Richardson et al., 2006). These tools have also been used to analyze OL turnover and regeneration in adult brain (Fancy et al., 2011a; Franklin and Ffrench-Constant, 2008; McTigue and Tripathi, 2008; Miller and Mi, 2007). The opportunity to identify and fate-map developing OLs in diverse brain regions has revealed cellular factors and intrinsic molecular pathways functionally involved in OL development and regeneration. This analysis has also illuminated and defined cellular interactions between OLs and other neural cells with critical roles in development and pathology. Damaged OLs can be replaced by new cells derived from OPCs that proliferate and differentiate after injury or in disease. Thus, studies elucidating altered development in a perturbed cellular environment will reveal how interactions between intrinsic OPC properties and the injury milieu determine the cells' fate. As many excellent articles have recently reviewed OL development in embryonic and postnatal brain (Emery, 2010b; Liu and Casaccia, 2010; Meijer et al., 2012; Miller, 2002; Mitew et al., 2013; Nishiyama et al., 2009; Richardson et al., 2006), we will focus on some salient aspects of this topic.

Embryonic Development

In the embryo, OLs originate from multiple progenitor cell pools, which populate distinct regions of the developing spinal cord and brain and mature during different time periods. Although a specialized OL domain (pMN domain) was originally thought to exist in the ventral ventricular zone (VZ) of the spinal cord and perhaps in the forebrain (for review, see Rowitch, 2004), recent investigation has demonstrated dorsal—as well as ventral—origins of OLs in both spinal cord and brain (for review, see Richardson et al., 2006). This conclusion is based on analysis of *Nkx6.1* and *Nkx6.2* double mutant mice, in which pMN-derived OPCs are absent from the spinal cord due to impaired *Olig2* activation by *Nkx6*. In these mice, OPCs that express all the proper markers—including the paired box gene *Pax7*—are still produced in the dorsal spinal cord (Cai et al., 2005; Vallstedt et al., 2005). Further Cre-*lox* fate-mapping analysis using *Dbx1* or *Msx* gene promoter elements to control Cre recombinase expression showed that dorsally derived OPCs arise from different domains and generate 10%–50% of dorsal OLs, depending on their origin (Fogarty et al., 2005). Dorsal OPCs are also generated later in development than pMN-derived OPCs (Cai et al., 2005; Fogarty et al., 2005; Vallstedt et al., 2005). Shh signaling activates Olig2 in the pMN domain (Lu et al., 2002), whereas dorsally derived BMPs and Wnts support generation of astrocytes and prevent OL development at earlier embryonic stages (Mekki-Dauriac et al., 2002; Shimizu et al., 2005; Vallstedt et al., 2005). It has also been suggested that FGF signaling is required to specify OLs in the dorsal spinal cord (Vallstedt et al., 2005). In any case, distinct and restricted OPC domains exist in developing spinal cord and are responsible for multiple waves of OPC production influenced by different cellular factors.

In the forebrain, fate-mapping analysis also demonstrated distinct temporal waves of OPC production from separate domains (Kessaris et al., 2006). The main separate domains identified were the medial ganglionic eminence (*Nkx2.1*-derived ventral precursors from ~E12.5), the lateral ganglionic eminence (*Gsh2*-derived; a few days later), and the cortex *Emx1*-derived precursors that produce OPCs predominantly after birth. All precursors migrate vigorously from the VZ to populate distant brain regions, and the population of most ventrally derived precursors disappears after birth (Kessaris et al., 2006).

Postnatal Development

In the postnatal brain, the SVZ is the major source of OPCs and OLs (Aguirre et al., 2007; Menn et al., 2006; Nait Oumesmar et al., 1999). Located around the tips of the lateral ventricles, this region is mostly derived from the embryonic lateral ganglionic eminence and lateral cortex. Pioneering work using retroviral labeling of dividing cells in the SVZ showed that cells in this brain region are able to generate both OLs and astrocytes (Levison and Goldman, 1993), and more recent analysis of postnatal and adult brains demonstrated that proliferative OPCs in the SVZ express NG2 and Olig2, as well as other OPC and progenitor markers including PDGFPα and Mash1 (Aguirre et al., 2004, 2007; Menn et al., 2006). In the adult SVZ, OPCs express a type C cell phenotype and derive from type B stem cells (Aguirre et al., 2004). During postnatal development, OPCs migrate from the SVZ into WM regions, where they stop dividing and differentiate into mature myelinating OLs (Aguirre et al., 2007; Gonzalez-Perez et al., 2009; Levison and Goldman, 1993; Menn et al., 2006). The accessibility of the postnatal SVZ and its ease of manipulation have facilitated the analysis and identification of cellular factors and molecular pathways regulating OPC proliferation, migration, and differentiation. This highly gliogenic region of the postnatal/adult brain has been intensively studied in animal models of injury and pathology to define pathways that could be used for OL regeneration.

Oligodendrocyte Regeneration in the Developing Brain

Animal Models of Developmental Injury and Pathology

This section will focus on examples of pathological insults in the immature brain to illustrate the differential responses of distinct OPC populations and to relate these responses to regeneration and repair. We limit our discussion to models of injury and pathology that have contributed to defining cellular and molecular pathways involved in OL and myelin regeneration and repair during development. OPCs' ability to react to injury may be greater in the young adult brain (Ruckh et al., 2012), and these early mechanisms are potentially applicable to the less favorable environment of the pathological adult brain (van Wijngaarden and Franklin, 2013). Furthermore, interventions targeting specific

progenitor cells and molecular pathways may be more successful during a period of ongoing developmental programs that would permit a higher degree of neural plasticity. Identification of signaling systems activated after brain injury or during the course of neurological disorders can guide strategies that lead to more robust amplification of the OPC pool and to enhanced repopulation, regeneration, and functional recovery of the injured brain.

Perinatal Hypoxia and Ischemia

Animal models of neurodevelopmental disorders and neonatal brain injury attempt to reproduce different aspects of the pathologies found in humans. However, these animal models should satisfy the following criteria: (1) the model must accurately reflect the histopathological spectrum of a specific injury to the developing brain, (2) the model should display a phenotype that correlates with developmental changes observed in humans, and (3) the model should display abnormal functional outcomes also observed in human pathology.

Cerebral WMI and brain gray matter atrophy are the most frequent brain insults in preterm infants and major causes of disability in survivors. WM abnormalities in preterm infants persist throughout adolescence and young adulthood (Hack et al., 2002). Chronic periventricular white matter injuries (PWMIs) comprise a broad spectrum, including the most severe form—focal cystic necrotic lesions (periventricular leukomalacia [PVL])—or diffuse hypomyelination (diffuse white matter injury [DWMI]). PWMI is directly associated with adverse outcomes such as cerebral palsy, cognitive delay, and learning disabilities (Hack et al., 2002). Although other animal models have been extensively utilized (Back and Rosenberg, 2014; Salmaso et al., 2014), the two primary animal models of premature brain injury represent hypoxia/ischemia (HI) (Rice et al., 1981) and chronic perinatal hypoxia (HX) (for review, see Back and Rosenberg, 2014; Scafidi et al., 2009; Vaccarino and Ment, 2004). Both models result in neuropathological changes resembling those seen in premature human infants, including severe hypomyelination and decreased gray matter volume (Salmaso et al., 2014).

Glial cell types susceptible to insult in chronic PWMI have been identified by their expression of cell-specific markers. OLs are particularly vulnerable to PWMI, but microglial activation and astrogliosis are also observed, along with axonal injury. In chronic PWMI, the maturation of late OPCs/pre-OLs is believed to arrest at a premyelinating stage, contributing to myelination failure in PWMI (Back et al., 2002). Indeed, maximal PWMI susceptibility in preterm infants and perinatal rodents corresponds to developmental stages characterized by a sizable and susceptible population of late OPCs (Back, 2006). In perinatal HX, analysis of different cell populations in the OL lineage also indicated occurrence of delayed OL maturation, along with specific abnormalities in myelin ultrastructure, even when overall myelination levels appeared normal (Jablonska et al., 2012; Scafidi et al., 2014). Consistent with this finding, WM changes showed recovery in some prematurely born adolescents or young adults, but physiological and behavioral abnormalities of WM function still occurred (Nagy et al., 2003; Fjell et al., 2011). Thus, early intervention is critical for OL regeneration after PWMI and requires identification of unique specific cell populations in the brains of premature infants to promote WM recovery after neonatal injury.

Sources of OPCs

Paralleling the effects on OPC differentiation and delayed OL maturation described above, HI- or HX-induced WMI also produced regenerative responses. Several studies demonstrated enhanced SVZ progenitor cell proliferation and migration after insult to the perinatal brain—an event resulting in significant expansion of neuronal and glial progenitor pools. Increased SVZ cell proliferation was observed within 2 days after HI and within 6 days of chronic perinatal HX and persisted for several weeks (Fagel et al., 2006; Felling et al., 2006). HX-induced proliferation of NG2-/Olig2-expressing OPCs occurs in the SVZ within the first few days after insult and depends on activation of the Cdk4 pathway (Jablonska et al., 2012). Hypoxic rearing doubled the number of $Blbp^{+}Glast^{+}GFAP^{+}$ cells in mouse SVZ during the first week of recovery (Fagel et al., 2006), and a similar proliferative response occurred after perinatal HI (Ong et al., 2005; Plane et al., 2004). After HI, SVZ precursor cells display multipotency in vitro and generate more neurons and OLs in vivo (Yang and Levison, 2006; Zaidi et al., 2004). These cellular dynamics suggest that the early postnatal SVZ is a potential source of OPCs as well as other progenitor cell populations for repair. Studies of the SVZ have shown that OPC proliferation is key to repair and that identifying regions with this potential is essential for targeting specific progenitor cell populations and signaling pathways involved in OL regeneration.

Another major source of OPCs is the parenchyma, including the WM itself. OPCs in the parenchyma express the same cellular markers (NG2, PDGFRα, Olig2) as their SVZ counterpart (Aguirre et al., 2007; Jablonska et al., 2012; Scafidi et al., 2014). Fate-mapping analysis showed PDGFRα-expressing OPCs to be a major source of newly generated OLs in the WM following HX (Scafidi et al., 2014).

OPC Proliferation Drives Oligodendrocyte Regeneration

The studies discussed above indicate that proliferation of immature progenitor cell populations is necessary for glial regeneration. Therefore, we will briefly describe some molecular mechanisms that regulate OPC proliferation after neonatal brain injury.

Significant OL death in the brain occurs within the first 2 weeks after perinatal HX, resulting in transient hypomyelination (Jablonska et al., 2012). OPCs in the parenchyma—particularly in subcortical WM—actively divide and regenerate OLs after HX (Jablonska et al., 2012; Scafidi et al., 2014). Immunocytochemical and fate-mapping analysis demonstrated that NG2+PDGFRα+ OPCs proliferate within a week after HX and generate new OLs for the following 3–4 weeks (Jablonska et al., 2012; Scafidi et al., 2014). Unlike the SVZ, OPC proliferation in WM depends on Cdk2 activation and formation of the Cdk2/CyclinE complex, a major regulator of G1-S transition in the OPC cell cycle in both developing and adult brains (Jablonska et al., 2012; Belachew et al., 2002). The proliferative response of endogenous OPCs to HX is crucial for expanding this progenitor pool and for regenerating a normal number of OLs, restoring normal myelin protein levels (Jablonska et al., 2012; Scafidi et al., 2014). Conversely, blockage of signaling pathways (e.g., EGF/EGF-receptors) that promote OPC expansion after HX impairs OL regeneration and functional recovery (Scafidi et al., 2014).

What molecular mechanisms delay or prevent timely OL maturation from OPCs after HX? Do these mechanisms involve

intrinsic molecular pathways that regulate OL proliferation under normal physiological conditions? At least two pathways of functional importance in OL development play essential roles in OL regeneration: $p27^{Kip1}$ and Wnt signaling. Importantly, alterations in molecular elements of these pathways have been noted in animal models of premature brain injury, as well as in postmortem brain tissue of infants who died of hypoxic/ischemic encephalopathy (Jablonska et al., 2012; Scafidi et al., 2014).

Many studies have contributed to identifying $p27^{Kip1}$ as an important regulator of OL differentiation (Casaccia-Bonnefil et al., 1997): $p27^{Kip1}$ knockout mice display fewer OLs, and signals that prevent OL maturation also increase $p27^{Kip1}$ levels in OPCs (Casaccia-Bonnefil et al., 1997; Ghiani et al., 1999). $p27^{Kip1}$ levels are significantly reduced in the OL lineage of mice exposed to HX and in human postmortem tissue, and the effects of HX on OL development are enhanced in $p27^{Kip1}$ null mice (Jablonska et al., 2012). HX regulates $p27^{Kip1}$ via at least two mechanisms: (1) by reducing expression of FoxO transcription factors, which are required to maintain normal $p27^{Kip1}$ levels, and (2) by enhancing activity of the $p27^{Kip1}$-degrading enzyme Skp2, which causes ubiquitination of the cyclin kinase inhibitor (Jablonska et al., 2012).

Wnt-β-catenin plays an important role in OL development, as downregulation of this signaling pathway is required for OL maturation (Fancy et al., 2009). Transcription factors (e.g., Sox17) and cellular signals that promote OPC differentiation and myelination suppress Wnt-β-catenin signaling (Chew et al., 2011). Axin2, one of the negative regulators of Wnt-β-catenin, is expressed at higher levels in OPCs than in OLs and induces β-catenin degradation (Fancy et al., 2011a). HX destabilizes Axin2, but treatment with a small molecule inhibitor of the enzyme tankyrase prevents this effect and promotes new OL generation and timely myelination (Fancy et al., 2011a). The findings discussed above on $p27^{Kip1}$ and on Wnt-β-catenin not only demonstrate clear links between OL development and regeneration/repair, but also show that manipulation of molecular pathways regulating OL maturation under normal physiological conditions may hold important therapeutic implications for promoting regeneration of these cells and preventing hypomyelination after neonatal brain injury.

Growth and Trophic Factors: Therapeutic Insights

A multitude of growth and trophic factors regulate OL development, especially OPC proliferation, migration, and differentiation (Bansal, 2002; Baron et al., 2005; Miller, 2002). Similarly, OL survival and myelin maintenance depend on growth and trophic factors (Casaccia-Bonnefil, 2000; Nave and Trapp, 2008). An important question, which may have significant therapeutic implications, is whether these factors' availability is altered in the pathological immature brain after neonatal injury. If changes in the overall levels of specific growth factors induced by injury mimic those seen during normal development that would indicate reactivation of endogenous developmental programs aimed at OL recovery. Several studies have harnessed our developmental knowledge of these factors for therapeutic interventions aimed at OL regeneration.

Fibroblast growth factor 2 (FGF2), epidermal growth factor (EGF), and leukemia inhibitory factor (LIF) are upregulated in the SVZ after hypoxic insult (Covey and Levison, 2007; Ganat et al., 2002; Scafidi et al., 2014). These factors promote OL generation from OPCs, as well as OL maturation and survival during normal development. Experimental analysis indicates that these factors cause: (1) expansion of the SVZ progenitor pools observed after HX, and (2) generation of new OLs from these progenitors (Covey and Levison, 2007; Ganat et al., 2002; Scafidi et al., 2014). Similarly, insulin-like growth factor-1 (IGF-1) plays a crucial role in promoting oligodendrogenesis and myelination in early brain development (Carson et al., 1993; Ye et al., 2002). IGF-1 treatment after neonatal brain injury recapitulates some developmental effects of this growth factor and promotes OL regeneration. IGF-1 administration prevented immature OL death, enhanced myelination after HI and protected OPCs in the SVZ and WM regions (Lin et al., 2005; Zhong et al., 2009).

We recently observed upregulation of endogenous EGF in WM and the SVZ after perinatal HX and showed that EGFR overexpression in the OL lineage enhances OL regeneration and promotes functional recovery in WM (Scafidi et al., 2014). Consistent with these findings and with EGF's effects on OL during normal development, noninvasive intranasal EGF delivery during a critical developmental time window immediately after HX causes significant expansion of the OPC pool in WM and promotes OL regeneration and functional/behavioral recovery (Scafidi et al., 2014). Although EGF appears to act via various mechanisms, a major effect is to prevent HX-induced Notch activation in OL lineage cells, inhibiting OPC differentiation and contributing to the delay in OL maturation observed after HX (Scafidi et al., 2014). This EGF-Notch interaction occurs in the SVZ during normal development and regulates the size of the OPC pool in this neurogenic region (Scafidi et al., 2014). To summarize, EGF prevents the delay in OL maturation caused by HX by generating a significant number of new OLs and inhibiting signaling pathways that arrest OPC maturation.

A similar therapeutic intervention developed in an animal model of intraventricular hemorrhage (IVH) mimics a major cause of WMI in preterm infants. The intervention was based on the well-established idea that thyroid hormone (TH) signaling—involving TH receptor α (TRα) and TRβ—strongly promotes OL maturation and myelination. It was hypothesized that IVH would decrease TH levels and reduce TH signaling. Interestingly, in both preterm brain tissue and rabbits with IVH, levels of TH-activating enzyme deiodinase-2 were reduced, whereas TH-deactivating enzyme deiodinase-3 increased (Vose et al., 2013). Treating IVH pups with TH accelerated OPC proliferation and maturation into OLs, enhanced myelination, and restored neurological function (Vose et al., 2013).

Together, the EGF and the TH treatment paradigms demonstrate that targeting specific factors required during normal development for OPC proliferation, survival, and differentiation might represent a viable therapeutic strategy in pathologies associated with premature brain injury. The studies also uncover the existence of rather specific time windows of intervention that closely follow the injury and likely permit enhancing plasticity processes to occur in the developing WM. Importantly, a study in human neonatal tissue demonstrated that neurogenesis ceases after 18 months, but OPCs are detected in the SVZ after this age (Sanai et al., 2011), strongly indicating that gliogenesis

continues and highlighting the potential for regeneration at later developmental stages of the postnatal brain.

A different approach was undertaken in rodent models of HI to target iron, an essential trophic factor for OL development and survival. Iron plays a crucial role in oxygen consumption and ATP production in all cells, but OLs are the major brain cells that stain for iron, indicating higher levels (Todorich et al., 2009). Iron deficiency causes hypomyelination and neurological abnormalities, which can be reversed by intracranial injection of apotransferrin (aTf) at early developmental stages (Badaracco et al., 2008). The use of aTf to restore physiological levels of iron transport has been explored in neonatal WMI after HI, as HI increases iron release in WM regions (Guardia Clausi et al., 2012). Intranasal administration of aTf immediately after HI promoted neuroprotection of the neonatal mouse brain by reducing WM damage, astrogliosis, and OL death. The treatment also enhanced OPC proliferation in the SVZ and corpus callosum and promoted OPC differentiation. Overall, this noninvasive treatment acting on a signal with a crucial role in normal development also promoted functional recovery. The results obtained with aTf also suggest that future studies could investigate the use of combined treatments (e.g., EGF+aTf) delivered at different times after neonatal injury.

Transcription Factors and Epigenetic Regulation

Despite extensive characterization of transcriptional regulation of OPC development/differentiation, the reuse of these processes after neonatal HX or HI remains poorly defined. Myt1 and NFIA, two transcription factors with important roles in OL development, were recently studied in animal models of neonatal HX and in PVL tissue. Myelin transcription factor 1 (Myt1) is a zinc finger DNA-binding protein expressed at higher levels in OPCs than in mature OLs (Armstrong et al., 1995). Based on its expression pattern, regulation, and functional analysis, Myt1 is thought to modulate OPC transition from a proliferative to a terminally differentiated state that requires high levels of myelin gene transcription (Armstrong et al., 1995; Nielsen et al., 2004). Interestingly, in normally developing human brains, many Myt1-expressing glial cells are found between gestational weeks 19 and 26 but decrease by 1 year of age (Hirayama et al., 2003). In PVL brains, a large increase in Myt1-expressing cells is observed around necrotic foci and in regions displaying higher levels of myelin protein immunoreactivity (Hirayama et al., 2003), strongly suggesting their role in human OL pathology/regeneration.

A similar pattern of developmental regulation was observed for NFIA in OLs. During mouse embryonic development, NFIA is expressed in OPCs but not in differentiated OLs; its overexpression prevents OPC differentiation by directly repressing myelin gene expression (Fancy et al., 2012). Notably, in HIE lesions, NFIA is expressed in OPCs, but not in PLP-expressing cells (Fancy et al., 2012), indicating that NFIA dysregulation may contribute to the delayed OPC maturation and hypomyelination found in HIE, by repressing myelin gene expression. Indeed, misexpression of NFIA suppressed remyelination in an adult LPS model, suggesting a conserved function after WMI.

Epigenetic mechanisms, including DNA and histone methylation and acetylation, represent a different level of developmental regulation of the OPC-OL transition. In normal brain, timely OPC differentiation and myelination require histone deacetylation (HDAC) during a critical developmental time window (Shen et al., 2005), and HDAC activity regulates the regenerative potential of OPCs during development (Shen et al., 2008). Some hypothesize that epigenetic mechanisms—including acetylation/deacetylation and methylation—are involved in neurodegenerative diseases and stroke as regulators of the extent of injury (López-Otín et al., 2013; Schweizer et al., 2013). Altered gene expression caused by ischemia is an important contributor to neuronal or glial damage, and HDAC inhibitors have attracted significant attention as potential neuroprotective agents (Kumral et al., 2009, 2013). Although the role of HDAC and HDAC inhibitors has been specifically investigated only in regeneration and remyelination of adult OLs (see below), particular alterations in HIF-mediated gene transcription have been observed in neonatal HI (Kumral et al., 2009; Singh et al., 2012). Thus, it will be important to define changes in DNA methylation and acetylation following HX or HI, as these changes will strongly influence the expression of genes involved in OL regeneration and WM recovery in the neonatal brain. Finally, as significant sex differences have been observed in the extent of premature brain injury—males being more susceptible than females—sex differences in histone modifications (Tsai et al., 2009) might account at least partially for differential vulnerability seen in WM of male and female infants.

Future studies will further investigate the links between specific growth factor signaling pathways and differing levels of transcriptional regulators after developmental injury and during regeneration. Understanding these signaling axes will be crucial to generating new therapeutic approaches based on molecular mechanisms regulating normal glial development.

Oligodendrocyte Regeneration and Repair in the Adult Brain

The hope for OL replacement in various myelin disorders and in adult WMI rests on the established finding that the adult brain contains populations of undifferentiated OPCs able to divide and regenerate myelinating OLs. Recent reviews have extensively discussed the cellular and molecular properties of these "activated" OPCs and their developmental potential in the context of demyelination/remyelination of adult brain (Franklin and Gallo, 2014; Zuo and Nishiyama, 2013; Fancy et al., 2011b). Our discussion will focus on the signaling pathways shared between development and remyelination and whether these represent true recapitulation of developmental programs. Many developmental signals and associated molecular pathways have been identified as either negative or positive regulators of OL regeneration, and studies have investigated how those mechanisms interact with cellular changes that occur in the pathological microenvironment of the adult brain. This section will focus on OL regeneration and remyelination in animal models of demyelination, particularly models of MS.

Animal Models of Injury and Pathology of the Adult White Matter

Recent reviews have comprehensively and elegantly discussed all available animal models of MS and demyelinating diseases (Franklin and Ffrench Constant, 2008; Ransohoff,

Table 1. Models of Adult Demyelination/Remyelination

Model	Type	Mechanism/Description
Cuprizone	Toxin	- Orally administered copper chealator; inhibits copper-dependent mitochondrial enzymes monoamine oxidase and cytochrome oxidase - Causes selective cell death of oligodendrocytes resulting in widespread CNS white matter demyelination
Lysolecithin	Toxin	- Focally injected membrane solubilizing agent - Induces demyelination in focal lesions that cause local cell death of predominantly oligodendrocyte in the surrounding tissue
Ethidium Bromide	Toxin	- Focally injected DNA-intercalating agent - Similar to lysolecithin: Focal lesions are caused by the non-specific cell death of all cell types in the surrounding tissue
Experimental Autoimmune Encephalomyelitis (EAE)	Immune Mediated	- Injectable antigen induced encephalomyelitis (purified myelin, myelin proteins - MBP, PLP, MOG and spinal cord homogenate) - Causes an autoimmune inflammatory response resulting in more pronounced white matter vs. gray matter deymyelination
Theiler's Murine Encephalomyelitis (TME)	Immune Mediated	- Injectable virus (single-stranded RNA cardiovirus) induced encephalomyelitis - Causes an autoimmune inflammatory response affecting all cells of the CNS and results in demyelination, predominantly in the spinal cord
Murine Hepatitis	Immune Mediated	- Injectable virus (positive-strand RNA coronavirus) induced encephalomyelitis - Similar to the TME virus: causes an autoimmune inflammatory response affecting all cells of the CNS and results in widespread demyelination
Diphtheria Toxin (DT) Receptor Targeting	Genetic	- Two inducible Cre-mediated strategies for the selective ablation of oligodendrocytes in adult animals: 1) DT injections administered to transgenic mice that express DT receptor in oligodendrocytes of the CNS, 2) Transgenic mice that express DT receptor in oligodendrocytes of the CNS where no DT administration is necessary. Upon Cre recombination DT-A mediated cell death of oligodendrocytes occurs. - Selective elimination of oligodendrocytes results in widespread CNS demyelination

2012). These animal models (summarized in Table 1) have been used extensively for revealing the endogenous remyelination potential of the central nervous system as a possible therapeutic approach to functional recovery. For example, the presence of OPCs in MS lesions is well established (Chang et al., 2002; Wolswijk, 1998), so understanding their origin and response to demyelinating insults is fundamentally important to developing new cell-based strategies for remyelination. OPC activation (i.e., changes in morphology, proliferation, migration, and expression of specific genes) and recruitment occur in all animal models of adult brain demyelination, including experimental autoimmune encephalomyelitis (EAE) and cuprizone- and lysolecithin (LPC)-induced demyelination (Aguirre et al., 2007; Cate et al., 2010; Messersmith et al., 2000; Nait-Oumesmar et al., 1999; Picard-Riera et al., 2002). These changes also occur in "activated" OPCs in MS tissue, probably induced by signals present in lesions (Nait-Oumesmar et al., 2007).

Enhancers of Oligodendrocyte Development and Regeneration

Several intrinsic and extrinsic regulators of OL development have been identified as enhancers of regeneration (Figure 3), opening up new opportunities to design molecularly targeted approaches aimed at enhancing remyelination.

Growth Factors. During normal development, OPC proliferation and cell-cycle progression are positively regulated by two

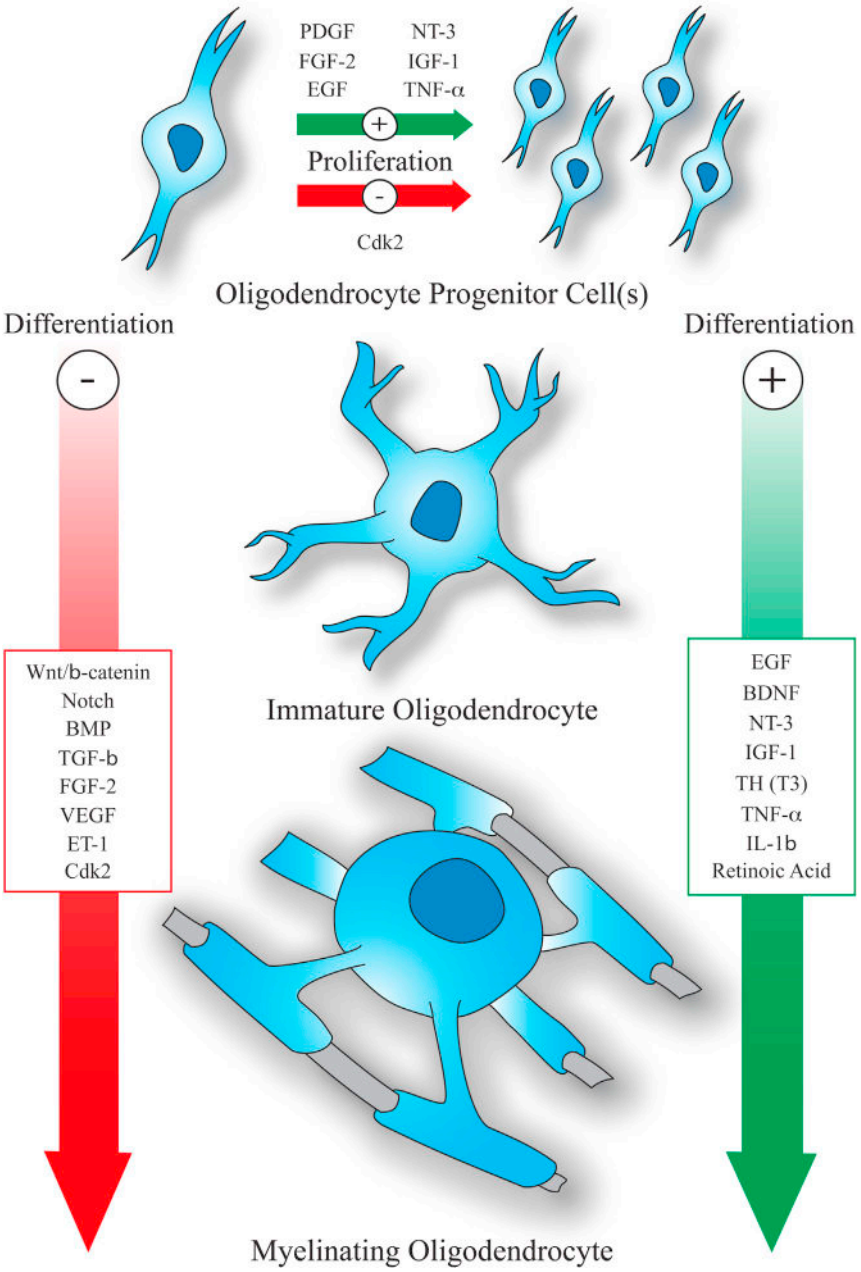

Figure 3. Positive and Negative Regulators of Oligodendrocyte Development and Regeneration

Schematic synopsis of the major developmental phases of oligodendrocyte maturation—i.e., proliferation, cell-cycle exit/differentiation and myelination—after demyelination of the adult brain. Green arrows refer to enhancers of these processes under pathological conditions, whereas red arrows refer to inhibitory pathways. Preventing or suppressing the inhibitory effects of specific pathways, as well as leveraging on enhancers promotes oligodendrocyte maturation and myelination and might define future cell-based therapeutic approaches to demyelinating diseases.

potent mitogenic factors—platelet-derived growth factor (PDGF) and fibroblast growth factor 2 (FGF2)—that act either individually or cooperatively through PDGFRα and FGFR1 to generate mature OLs (Calver et al., 1998; Fortin et al., 2005; McKinnon et al., 1990; Miller, 2002). Expression of the ligand PDGF-A is upregulated in reactive astrocytes of demyelinated lesions (Armstrong et al., 2002: Messersmith et al., 2000), and both FGF2 and FGFRs are upregulated in areas of acute or chronic cuprizone-induced demyelination (Messersmith et al., 2000). PDGF and FGF2 control differential responses in the OL lineage after demyelination (Murtie et al., 2005). Consistent with a role of PDGF in proliferation, OPC amplification and subsequent repopulation of demyelinated lesions are impaired in a heterozygote PDGFRα$^{+/-}$ or in a GFAP-driven PDGF-A null mouse (Murtie et al., 2005). Conversely, FGF2 acts to inhibit remyelination through FGFR1 (see below).

Stimulation of epidermal growth factor (EGF) signaling is an example of successfully leveraging a developmental mechanism to promote regeneration in the adult brain. EGF exerts multiple effects on the OL lineage, both OPCs and mature OLs (Aguirre et al., 2007; Scafidi et al., 2014). Selective EGFR overexpression in OL lineage cells promotes OPC proliferation and migration, enhancing the extent of functional remyelination of the corpus callosum after LPC-induced demyelination (Aguirre et al., 2007). Consistent with these findings, EGF infusion into the lateral ventricle (Gonzalez-Perez et al., 2009) or intranasal HB-EGF administration (Cantarella et al., 2008) promoted OPC recruitment from SVZ to demyelinated lesions. Furthermore, viral-mediated EGFR overexpression in WM OPCs increased proliferation and maintained an undifferentiated phenotype (Ivkovic et al., 2008). Other growth factors are also involved in regulating OPC number under physiological or pathological conditions: for example, analysis of null mouse strains demonstrated that brain-derived neurotrophic factor (BDNF) is required to regulate the number of OPCs during normal development and during remyelination (Vondran et al., 2010; VonDran et al., 2011). Together, these studies demonstrate that, similar to the perinatal brain, specific GFs activate endogenous pools of OPCs that can be redirected from proliferative areas to injury sites to promote recovery in adults. The OPC response to demyelination and to cellular factors present in a lesion is integrated by numerous cell-cycle regulatory proteins, including Cdk2 and p27^{Kip1}, which regulate the number of OPCs recruited to a lesion (Caillava et al., 2011; Crockett et al., 2005).

Developmental studies and analyses in animal models of demyelination have also identified factors that positively regulate OPC differentiation and maturation of myelinating OLs under normal physiological and pathological conditions. During normal development, OL maturation is enhanced by ciliary neurotrophic factor (CNTF) (Stankoff et al., 2002), which also exhibits a strong promyelinating effect after demyelination (Albrecht et al., 2003). Growth factor BDNF also promotes OPC differentiation and myelin protein expression after cuprizone-induced demyelination, demonstrating that this factor modulates diverse phases of the OL lineage (VonDran et al., 2011). Similarly, the neurotrophin NT-3 produced a broad range of developmental and regenerative effects in OLs—promoting OPC proliferation and supporting survival of mature OLs through TrkC receptors and MAPK phosphorylation (Cohen et al., 1996). Notably, direct NT-3 injection into the corpus callosum promoted oligodendrogenesis and remyelination in a model of LPC-induced demyelination (Jean et al., 2003).

Insulin-like growth factor 1 (IGF-1) was identified early on as a necessary factor for OL differentiation and myelination in vitro and in vivo (Mozell and McMorris, 1991; Werther et al., 1998). In vivo studies demonstrated that IGF-1 ablation causes reduced brain size and hypomyelination (Beck et al., 1995; Ye et al., 2002). The IGF type 1 receptor (IGF-1R) is continuously expressed throughout the entire OL lineage, and IGF-1 appears to act at multiple developmental stages, promoting OPC proliferation, OL survival, and myelin synthesis (Barres et al., 1993; Ye and D'Ercole, 1999; Zeger et al., 2007). Consistent with its multiple developmental roles, IGF-1 significantly attenuates the damage induced by a demyelinating insult. In a transgenic mouse strain expressing higher IGF-1 levels in the brain, the cellular effects of cuprizone-induced demyelination on OL death were significantly reduced, although significant demyelination was seen. Furthermore, the remyelination rate was much higher than in wild-type (WT) controls (Mason et al., 2000). Consistent with these findings, IGF-1 decreased lesion severity and clinical abnormalities in the EAE mouse model (Yao et al., 1995). These results indicate that IGF-1 may improve recovery from a demyelinating insult by selectively enhancing OPC differentiation and supporting survival of the more mature OL population. However, the experimental paradigm of enhanced IGF-1 expression might be crucial, as increasing local IGF-1 mRNA levels by adenoviral vector failed to promote remyelination (O'Leary et al., 2002).

How does IGF-1 promote OL survival and differentiation? Analysis of signaling in OLs demonstrated IGF-1 to be a potent activator of the PI3K/Akt and mTOR pathway (Min et al., 2012). Exposure to IGF-1 maintains Akt signaling in differentiating OPCs (Ness et al., 2002), consistent with the idea that IGF-1 signaling through PI3K/Akt and mTOR is functionally linked to OPC differentiation into mature OLs. Recent research identified mTOR as a critical signaling kinase in OL differentiation and myelination and showed its effects occurring through the mTORC1 and mTORC2 signaling complexes (Tyler et al., 2009).

The preceding discussion of growth factors in demyelination and remyelination points to the need for in vivo studies in various animal models of pathology, each model designed to define specific cellular and developmental effects of individual growth factors on OL regeneration. The discussion also suggests that sustained expression of various factors during distinct phases of injury and recovery from a myelin insult might be used to coordinate and integrate multiple cellular mechanisms that lead to successful functional remyelination. Furthermore, analysis of glial regeneration and repair should be extended to other cellular factors that modulate glial development. For example, hepatocyte growth factor (HGF) has been identified as a positive regulator of oligodendrocyte proliferation and migration and an inhibitor of differentiation (Yan and Rivkees, 2002: Ohya et al., 2007; Mela and Goldman, 2013). The role of HGF in remyelination has not been explored, but it might promote early phases of OPC expansion and repopulation of demyelinated lesions.

Hormones. Several lines of evidence indicate that specific hormonal states regulate OL numbers, developmental myelination, and myelin repair. Sexual dimorphism exists in rodent subcortical WM, where females display a higher proportion of unmyelinated axons (Kim and Juraska, 1997) and higher OL turnover (Cerghet et al., 2006). MS occurs more frequently in females and undergoes remission during pregnancy (Confavreux et al., 1998), although the hormonal causes are poorly understood. Interestingly, pregnant mice demonstrate an increase in newly generated OLs and in the number of myelinated axons in corpus callosum (Gregg et al., 2007), and pregnant mice show enhanced ability to remyelinate after LPC-induced focal demyelination (Gregg et al., 2007). And prolactin has been identified as a major regulator of OL plasticity and WM repair during pregnancy, inducing OPC proliferation and enhancing OL regeneration in vivo (Gregg et al., 2007).

Thyroid hormone (triiodothyronine [T3]) is the best-studied hormone for its effects on OL development. T3 regulates the timing of OPC differentiation (Barres et al., 1994) and promotes morphological maturation via a metabolic switch in OPCs that supports myelin synthesis in mature OLs (Baas et al., 1997; Younes-Rapozo et al., 2006). Specific cellular changes induced by T3 have been extensively analyzed in purified cultured OPCs or in reaggregating cultures (Baas et al., 1997; Jones et al., 2003; Matthieu et al., 1992). In vivo, hypothyroidism causes delayed and poor deposition of myelin during development (Ferreira et al., 2004; Ibarrola and Rodríguez-Peña, 1997), while hyperthyroidism accelerates myelination (Marta et al., 1998). Prolonged neonatal hypothyroidism decreases the number of myelinated axons in adult rats, although most of the myelinated axons display normal thickness of the myelin sheath. Two animal models of myelin pathology demonstrated the beneficial effects of T3 on OL regeneration and remyelination. In the cuprizone model, systemic T3 injection in rats significantly enhanced remyelination by increasing the ratio of mature OLs to OPCs (Franco et al., 2008). In the EAE model, T3 treatment yielded myelin sheath and axonal protection and enhanced nerve conduction (Dell'Acqua et al., 2012). These cellular and physiological studies support previous molecular analyses demonstrating that T3 thyroid receptors can directly activate *MBP* and *PLP* gene promoters in mature OLs (Farsetti et al., 1991; Bogazzi et al., 1994).

The analysis of hormones in vivo reveals that both prolactin and T3 promote WM plasticity during development and in regeneration, implicating these hormones as potential therapeutic agents for targeting axons and OLs in demyelinating diseases.

Inflammatory Cytokines and Chemokines. Among the influences on OL development and regeneration, cytokines and chemokines have been studied as factors predominantly upregulated after demyelination. Tumor necrosis factor-α (TNFα) is an inflammatory cytokine able to induce a broad range of cellular responses, including cell proliferation and cell death, mediated by the activation of two distinct receptors—TNFR1 (p55) and TNFR2 (p75) (Dopp et al., 1997; Raine et al., 1998; Tchélingérian et al., 1995). In the brain, TNFα is synthesized and released by astrocytes and microglia (Liu et al., 1998). This cytokine was shown to negatively regulate OPC number and differentiation, as well as OL survival in developing cultured cells (Cammer and Zhang, 1999). In keeping with these findings, studies in the EAE model showed that genetic ablation or blockade of TNFα signaling attenuated myelin pathology (Hövelmeyer et al., 2005). However, analysis of TNFα and TNFR1 and TNFR2 mutant mice in a different model of demyelination also revealed a role for this cytokine in OL regeneration and remyelination. Cuprizone-induced demyelination substantially increased TNFα and TNFR2 in lesions, and genetic ablation of the cytokine caused significant reduction in OL apoptosis, delayed demyelination, and ultimately enhanced remyelination (Arnett et al., 2001). TNFR2 was identified as the primary receptor mediating the influence of TNFα on remyelination, which was attributed to potent effects on OPC proliferation and to generation of new OLs during demyelination/remyelination (Arnett et al., 2001).

The mechanism of OL regeneration and its modulation by TNFR2 appear complex. More recent analysis demonstrated that TNFR2 also regulates expression of the chemokine CXCL12, which acts on the CXCR4 receptor to modulate remyelination. Interestingly, genetic ablation of TNFR2 causes significant downregulation of CXCL12 expression in cuprizone-induced lesions and decreases the number of CXCR4-expressing OPCs (Patel et al., 2012). Cellular analysis, combined with rescue experiments, demonstrated that TNFR2 activation in astrocytes induces CXCL12 expression in demyelinated corpus callosum, in turn promoting OPC proliferation and differentiation. Consistent with this hypothesis, loss of CXCR4 signaling decreased OPC maturation and prevented remyelination after cuprizone-induced demyelination (Patel et al., 2010). As CXCL12 also regulates normal OL development—in particular OPC proliferation, migration, and differentiation (Dziembowska et al., 2005; Patel et al., 2012)—the findings described above indicate that reactivation of CXCL12 signaling has similar effects on OL regeneration and remyelination.

Another cellular mechanism of action was attributed to the proregenerative effects of yet another cytokine—Interleukin-1β (IL-1β). This cytokine was shown to promote OL differentiation after acute demyelination, as IL-1β$^{-/-}$ mice failed to properly remyelinate despite an OL depletion rate similar to that of wild-type (WT) mice (Mason et al., 2001). The cytokine's effects were indirect and were attributed to delayed OPC differentiation due to lack of IGF-1 produced by astrocytes and microglia (Mason et al., 2001). These findings show cytokines acting at multiple levels—both directly and indirectly—to regulate OL regeneration and remyelination, and cellular interactions between OPCs, astrocytes, and microglia modulate all phases of remyelination. These mechanisms are likely important for cell-based therapies, as recent studies of NSCs engrafted after demyelination revealed a requirement for CXCL12 and CXCR4 signaling in NSC migration and proliferation giving rise to OLs (Carbajal et al., 2010).

Transcription Factors. Converting OPCs to a regenerative phenotype is thought to involve enhanced expression and activity of several transcription factors playing important roles in OL development. A number of studies indicate that multiple transcription factor networks probably regulate OPCs' response to demyelination, modulating OL regeneration. During development, Olig1, Olig2, and Nkx2.2 are crucial in OL specification and maturation (Lu et al., 2002; Soula et al., 2001), and expression of transcription factors that regulate OL fates—including Olig2 and Nkx2.2—is enhanced in adult OPCs after demyelination (Fancy et al., 2004). This upregulation is generally observed during acute phases of demyelination and during early remyelination, indicating that OPC transition to a regenerative phenotype probably involves recapitulation of developmental programs. Although some transcription factors may play roles in both development and repair of glia, others—like Olig1—appear to be primarily involved in repair. Given that remyelination is less efficient in Olig1$^{-/-}$ mice, Olig1 is regarded as crucial in myelin repair in the adult brain, although this factor is redundant in OL development (Arnett et al., 2004). Indeed, Olig1 displays nuclear localization in early remyelinating lesions in animal models of demyelination and in MS tissue, but is mostly cytosolic in normal WM (Ligon et al., 2006). A similar expression pattern is observed for transcription factor Myt1, which appears to modulate OPC proliferation and contribute to the timing of differentiation (Nielsen et al., 2004; Vana et al., 2007).

Two other transcription factors—Ascl1/Mash1 and Sox17—belong to distinct families and play differing roles in OL development and regeneration. The proneural gene *Ascl1/Mash1* was newly identified as a regulator of embryonic and postnatal oligodendrogenesis (Parras et al., 2004, 2007). In the embryonic CNS, Ascl1 is expressed in ventral forebrain and cooperates with Olig2 to specify OPCs (Parras et al., 2007). In the postnatal SVZ, Ascl1 is expressed in progenitors of both OL and neuronal lineages (Parras et al., 2004; Nakatani et al., 2013) and positively regulates OPC specification as well as the balance between proliferation and differentiation. In the animal model of lysolecithin-induced focal demyelination, Ascl1 activity is upregulated during OL regeneration, and Ascl1 is required for proper remyelination from OPCs (Nakatani et al., 2013). Importantly, Ascl1 expression is also enhanced in MS chronic active lesions (Nakatani et al., 2013).

Another group of transcription factors are induced by injury, inhibit OPC proliferation, and increase cell differentiation, but have complex effects on various neural cell lineages. In the OL lineage, expression of Sox17 RNA and protein peaks at P15 and precedes myelin gene expression (Sohn et al., 2006). Unlike Ascl1, Sox17 does not appear to be involved in OPC specification but rather in cell-cycle exit and initiation of differentiation (Sohn et al., 2006). Developmental studies in cultured cells and transgenic mice in vivo demonstrated that Sox17 promotes OPC differentiation by inhibiting the Wnt/β-catenin pathway (Chew et al., 2011; Ming et al., 2013). Extensive analysis of Sox17 expression and regulation in animal models of

demyelination demonstrated that, during remyelination, Sox17 expression is highest in newly generated OLs, suggesting a role for this transcription factor in OL regeneration (Moll et al., 2013). In MS tissue, Sox17 is highly expressed in chronic active lesions (Moll et al., 2013). Finally, selective overexpression of Sox17 in the OL lineage strongly attenuated the effects of LPC-induced demyelination by promoting OPC differentiation and OL survival (Ming et al., 2013), indicating that sustained activation of Sox17 promotes OL regeneration and myelin repair.

Retinoic acid receptor signaling strongly induces neuronal differentiation during embryonic development and in adult NSCs (Bain et al., 1996; Goncalves et al., 2005). In addition, retinoid X receptor gamma (RXR-gamma) (Huang et al., 2011) positively regulates OL differentiation during myelination and remyelination. Nuclear translocation of RXR-gamma was noted during OPC differentiation and OL regeneration and, importantly, predominantly nuclear RXR-gamma was detected in OPCs in MS tissue within active lesions, periplaque WM, and remyelinated plaques. Thus, its presence in the nucleus was consistent with cellular activity and repair capacity in MS. The finding that systemic administration of 9-*cis* retinoic acid after demyelination promoted axonal remyelination (Huang et al., 2011) demonstrates that activating this pathway is a potentially effective treatment for demyelinating lesions.

The findings described above indicate that several intrinsic regulators of OL development are important in regeneration and myelin repair. While direct targeting of transcription factors may represent a challenge in regenerative therapies, elucidating the signaling pathways regulated by these factors will open new avenues for molecularly targeted approaches to myelin repair. Furthermore, identifying the transcription factors that promote an OL phenotype under physiological and pathological conditions will enhance the efficiency of OL generation in cell-based therapies involving NSCs or induced pluripotent stem cells (iPSCs).

Other Signaling Pathways. The morphogen Sonic Hedgehog (Shh) is another example of reactivation of a developmental signal during OL regeneration (Ferent et al., 2013). Shh is required for OPC specification during embryonic development (Orentas et al., 1999; Spassky et al., 2001) and regulates OL production in adult cortex and corpus callosum (Yung et al., 2002). In LPC-induced focal demyelination, Shh transcripts and protein were upregulated in OL lineage cells within the lesion in a time-dependent fashion; furthermore, increased transcription of Shh target genes showed significant reactivation of the Shh pathway. Gain- and loss-of-function analyses demonstrated that Shh signaling plays a positive role in OL regeneration and myelin repair, enhancing OPC proliferation and differentiation as well as OL survival. Yet, activation of Shh signaling decreased astrogliosis and macrophage infiltration (Ferent et al., 2013), indicating that some of these beneficial effects may be indirect.

Reactivation of signaling pathways that stimulate OPC migration also occurs after demyelination. Netrin-1 positively regulates OPC migration in the postnatal optic nerve (Spassky et al., 2002), and a recent study demonstrated involvement of Netrin-1 in promoting migration of OPCs out of the adult SVZ after LPC-induced demyelination (Cayre et al., 2013). Netrin-1 was strongly upregulated in the SVZ after demyelination and was identified as the signal involved in local angiogenesis and progenitor cell migration, likely by activation of deleted in colorectal cancer (DCC) and neogenin receptors (Cayre et al., 2013). Demyelination induced vascular remodeling in the SVZ, and VEGF-mediated progenitor cell recruitment occurred with specific association between reactive blood vessels and OPCs (Cayre et al., 2013).

Metalloproteinase inhibitors may also play positive roles in OL regeneration in response to injury. Recent analysis demonstrated that myelin injury upregulates tissue inhibitor of metalloproteinase (TIMP-1) in reactive astrocytes, regulating secretion of matrix metalloproteinases from these cells (Nygårdas and Hinkkanen, 2002). Analysis in TIMP-1 null mice showed that oligodendrogenesis and compact myelin formation are significantly impaired, at least partly due to a reduced number of OPCs (Moore et al., 2011). In EAE, TIMP-1 expression is associated with astrocytes in demyelinated lesions, and remyelination is impaired in TIMP-1 null mice (Crocker et al., 2006). In clinical studies, robust TIMP-1 expression was found in acute demyelinating diseases that display some degree of remyelination (Ichiyama et al., 2006), while cerebrospinal TIMP-1 levels are not modified in MS (Avolio et al.,, 2003).

Inhibitors of OL Development and Regeneration

Mechanisms underlying the failure of remyelination in WM lesions include depletion of the endogenous OPC pool, limited migration of endogenous OPCs in a pathological environment, loss of axonal signals that support OPC-derived remyelination, and presence of inhibitors (likely produced by both astrocytes and infiltrating microglia) preventing their complete differentiation (Chong and Chan, 2010; Mason et al., 2004; Miron et al., 2013). Many of these inhibitors also negatively regulate normal OPC development (Figure 3).

A fundamental phase in OL development consists of OPC proliferation and the generation of sufficient OLs. Proteins that regulate cell-cycle progression and cell-cycle exit in OPCs—i.e., ultimately, the number of OPCs—have been intensely analyzed for their roles in development and repair. During normal development, type 2 cyclin-dependent kinase (Cdk2) is necessary for OPC proliferation but does not affect differentiation (Belachew et al., 2002). However, after demyelination, loss of Cdk2 accelerates CNS remyelination by altering OPC cycle exit and enhancing differentiation, indicating Cdk2 to be an inhibitor of OL maturation in pathology (Caillava et al., 2011). Recruitment of progenitors to a demyelinated lesion in spinal cord is negatively regulated by Cdk2 inhibitor $p27^{Kip1}$, as more OPCs were found in the lesion of $p27^{Kip1}$ null mice than in WT controls, and these cells differentiated into mature OLs (Crockett et al., 2005). The other Cdk inhibitor, $p57^{Kip2}$, appears to have a different role, as it prevents OL differentiation and remyelination in the EAE model (Kremer et al., 2009). This is consistent with the finding that suppressing $p57^{Kip2}$ expression promotes oligodendrogenesis from NSCs (Jadasz et al., 2012). Together, these findings indicate that failure to remyelinate may be due, at least partly, to cell-cycle regulators that inhibit OL maturation from OPCs.

Studies of cellular factors identified inhibitors that should, ideally, be eliminated from a demyelinated lesion to promote regeneration of mature OLs. These inhibitors—BMP, FGF2,

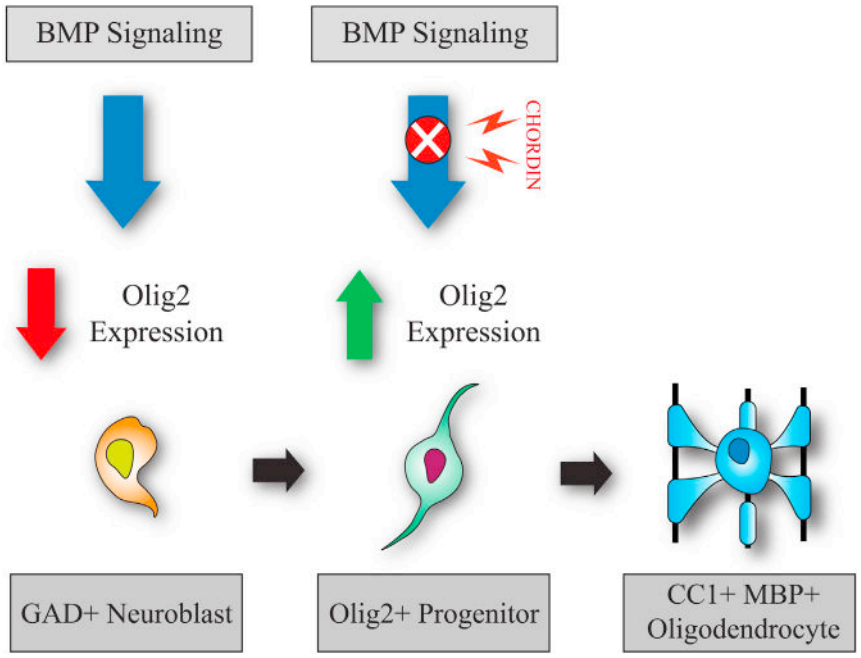

Figure 4. Oligodendrocyte Regeneration through Lineage Plasticity of GAD-Expressing Neuroblasts

Demyelination of the adult white matter (corpus callosum) causes fate plasticity in GAD-expressing (GAD+) neuroblasts of the subventricular zone (SVZ). Under normal physiological conditions, Olig2 expression is repressed by BMP signaling in GAD+ neuroblasts. Demyelination causes upregulation in the levels of the BMP antagonist chordin in the SVZ, which prevents BMP signaling and results in induction of Olig2 expression in GAD+ cells. These cells migrate out of the SVZ into the corpus callosum, where they generate mature, myelinating oligodendrocytes (see Jablonska et al., 2010).

Notch, and Wnt signaling—act similarly in preventing oligodendrogenesis during normal development. During development, BMP signaling suppresses oligodendrogenesis, promoting neurogenesis (Colak et al., 2008) and astrogliogenesis (Gomes et al., 2003; Samanta et al., 2007; See et al., 2007; See and Grinspan, 2009). BMPs negatively control OPC specification and lineage commitment, as well as OPC maturation into myelinating OLs (See et al., 2007). These effects likely involve induction of inhibitor of differentiation (Id) expression and inhibition of Olig activity (Samanta and Kessler, 2004; Chen and Panchision, 2007). BMP expression is enhanced in several animal models of CNS injury (Ara et al., 2008; Chen et al., 2005; Hampton et al., 2007; Matsuura et al., 2008) and—consistent with the complex developmental functions of BMPs—this can exert opposite effects on neural cell regeneration after injury. In animal models of demyelination, the expression of BMP-4, BMP-6, and BMP-7 is upregulated (Ara et al., 2008; Fuller et al., 2007; Sabo et al., 2011) and BMPs likely released by neurons and astrocytes inhibit remyelination and impair recovery (See and Grinspan, 2009). Infusing the BMP antagonist Noggin into demyelinated lesions increased the density of mature OLs during remyelination of the CC (Sabo et al., 2011). The BMP antagonist chordin was identified as a SVZ signal that promotes oligodendrogenesis from GAD65- and Dcx-expressing neuroblasts of the adult SVZ (Figure 4), indicating that niche-dependent mechanisms regulate lineage plasticity of progenitors in the adult brain (Jablonska et al., 2010). In contrast to the role of FGF2 (or FGFR1) in normal development, their genetic ablation under pathological conditions dramatically enhanced OL regeneration by promoting OPC differentiation (Armstrong et al., 2002; Zhou et al., 2012), indicating that this growth factor actually inhibits OPC maturation in a demyelinated lesion. Thus, manipulation of BMP and FGF in a demyelinated lesion environment illustrates how the extent of remyelination from endogenous OPCs can be enhanced by differentially modulating activity of specific developmental signals.

Notch signaling was also identified as a developmentally regulated inhibitor of OPC maturation, as downregulation of this pathway is required for OL differentiation and myelination (Hu et al., 2003; Wang et al., 1998). Suppressors of Notch signaling enhance OPC maturation during normal development (Aguirre et al., 2010; Hu et al., 2003; Wang et al., 1998). Interestingly, Notch signaling in adult brain is reactivated after demyelination of the CC (Hammond et al., 2014; Zhang et al., 2009), and Jagged 1 upregulation found in MS chronic lesions (John et al., 2002) suggests that activated Notch contributes to preventing endogenous OPC maturation and remyelination. The question is: which endogenous signals activate Notch after demyelination, and how is Notch activated in OPCs? Our recent study using a transgenic Notch-reporter mouse showed that the peptide Endothelin-1 (ET-1) is a major regulator of Notch after focal LPC-induced demyelination (Hammond et al., 2014). ET-1 is upregulated in mouse and MS reactive astrocytes and induces Jagged 1 expression in these cells, which in turn activates Notch and delays OL maturation after demyelination. These findings suggest that ET-1 is one of many signals that regulate Notch in a demyelinated lesion and in MS and that various cellular factors in pathological WM might converge on the inhibitory Notch "hub" in developing and adult brain.

OL differentiation and activation of the myelination program are both essential in timely myelination. Like Notch, LINGO-1—another inhibitor of OL differentiation and myelination—is a modulator of cell-cell interactions that precisely regulate the timing of myelination (Mi et al., 2005). LINGO-1 is a transmembrane protein selectively expressed in the CNS, specifically in axons and OPCs (Mi et al., 2005). LINGO-1 is a component of the Nogo receptor complex and its expression is developmentally regulated (Mi et al., 2004). Studies in cultured cells and knockout mice demonstrated that downregulation of LINGO-1 promotes OL differentiation and myelination during development (Mi et al., 2005). Importantly, LINGO-1 is upregulated in a variety of animal models of CNS pathology, including the EAE model of MS in which functional blockage of LINGO-1 enhances OL regeneration and remyelination and promotes functional

recovery (Mi et al., 2007). Two other molecules expressed in neurons directly regulate OPC development, myelination, and remyelination: Semaphorin 3A and 3F (Sema 3A and 3F) exert opposite effects—chemorepulsive and chemoattractive, respectively—on OPC migration (Okada et al., 2007; Syed et al., 2011; Xiang et al., 2012). Both Sema 3A and 3F are upregulated in demyelinated lesions and in MS but appear to play different functional roles in OPC-derived remyelination. Loss- and gain-of-function analysis demonstrated that Sema 3A is needed for OPC recruitment and repopulation of the demyelinated lesion, whereas Sema 3F promotes both OPC recruitment and remyelination (Syed et al., 2011). Together, these findings indicate that population of the adult WM, as well as OL differentiation during myelination and remyelination, are finely regulated by multiple interactions between OPCs and neurons.

Genome-wide screening has been extensively used to identify novel regulators of OPC development, and a screen performed in remyelinating rodent lesions found ~50 transcription factors regulated during regeneration (Fancy et al., 2009). These included the Wnt pathway mediator Tcf4, indicating that activation of this pathway may be involved in delaying myelin recovery. Subsequent gain- and loss-of-function analysis demonstrated that the canonical Wnt pathway negatively regulates OL differentiation during developmental myelination and remyelination (Fancy et al., 2009). The effects of Wnt are mediated by BMPs (Feigenson et al., 2011). But how do OPCs and OLs eventually overcome this pathway's inhibitory effects when remyelination does occur? Recent analysis identified transcription factor Sox17 as a suppressor of Wnt/β-catenin, consistent with its role as a positive regulator of OL maturation and regeneration during normal development (Chew et al., 2011). Sox17 was first identified as a transcription factor that promotes OPC cycle exit and induces differentiation. After demyelination, Sox17 levels are highest in newly generated OLs and active MS lesions (Moll et al., 2013) and its selective overexpression in the OL lineage promotes remyelination (Ming et al., 2013). These findings, along with enhanced remyelination induced by Axin 2 targeting (Fancy et al., 2011b), indicate the Wnt/β-catenin pathway as a strong therapeutic target in adult myelin regeneration.

Another type of inhibitor of OL maturation is directly linked to a specific role in OL survival. Death receptor 6 (DR6), a member of the TNF receptor (TNFR) superfamily, is expressed at high levels in immature OLs but downregulated in myelinating cells (Mi et al., 2011). Enhanced DR6 expression causes caspase 3 (casp3) activation and cell death, whereas attenuation of DR6 function promotes OL maturation, myelination, and casp3 downregulation (Mi et al., 2011). In two different animal models of demyelination, genetic ablation of DR6 enhanced remyelination, and treatment with a DR6 antagonist antibody had the same effect (Mi et al., 2011). These findings reveal not only a crucial role for DR6 in OL development, regeneration, and in remyelination, but also a cellular mechanism that could be targeted in MS to promote remyelination and inhibit the autoimmune component of the disease.

Epigenetic Regulation

Epigenetic mechanisms also regulate OL regeneration and remyelination in adult WM. After demyelination of young brains, HDACs are efficiently recruited to promoter regions of differentiation inhibitors to promote remyelination; however, this process is impaired in old animals, whose accumulated transcriptional inhibitors prevent myelin gene expression and efficient remyelination (Shen et al., 2008). Treating young animals with HDAC-inhibitor valproic acid reproduces the defect observed in adults (Shen et al., 2008), indicating that the age-dependent decrease in remyelination efficiency is—at least in part—due to epigenetic modulation of OL differentiation potential. Importantly, the OL-specific transcription factor TCF7L2/TCF4—a bipartite coeffector of β-catenin—was also shown to mediate cross talk between HDAC1/2 and the Wnt signaling pathway to regulate OL differentiation (Ye et al., 2009). Similar to mice lacking HADC1 and 2, TCF7L2 null mutants displayed impaired remyelination (Ye et al., 2009). Together, these results indicate that HDACs represent important molecular targets for promoting remyelination under pathological conditions.

Conclusions and Future Directions

The rapid and significant progress in understanding astrocyte and OL development and pathology continues to raise important questions about the role of these cells in human neurological disorders and brain injury. These glial cells clearly play crucial roles in virtually all brain pathologies and defining their role in brain disease will also provide information about the function of astrocytes and OLs in normal brain development. Continuing to define the cellular, molecular, and physiological properties of glial populations is essential to gain a true understanding of relationships between neural development and regeneration.

A first critical issue in future studies on the roles of astrocyte and OL progenitors in disorders of the developing and adult brain is the lack of specific molecular tools that enable the heterogeneity of these cell populations to be resolved. Once glial populations of different brain regions are identified and isolated, advanced molecular and genetic techniques can be applied to discover crucial genes that regulate their functional properties under normal and pathological conditions. Lineage reporters combined with gene expression profiling, and chromatin immunoprecipitation (ChIP)-on-ChIP, chromatin immunoprecipitation sequencing (ChIP-seq), and RNA sequencing (RNA-seq) assays can be also used to isolate genes preferentially expressed in glial cell subtypes and to define sets of developmentally regulated glial genes. Genome-wide screening in specific identified glial progenitor cell subpopulations will help identify spatiotemporally restricted expression patterns of transcription factors, as well as other molecular regulators of glial development (Fu et al., 2009) and regeneration (Fancy et al., 2009). Such studies are essential entry points for the isolation and subsequent characterization of these factors and regulators in the developing and injured CNS. These approaches will also help to determine how genetic defects affect glial lineages and the impact of altered glial development on normal brain function. Protein products of genes involved in neurodevelopmental disorders (Pacey and Doering, 2007) or in adult neurological diseases (Rempe and Nedergaard, 2010) may be expressed in glial progenitor cells and impair specific signaling pathways. Future research will reveal how specific glial defects contribute to these and other brain disorders and to brain injury.

A second critical issue for future research is glial progenitor fate plasticity, particularly the identification in vivo of

microenvironmental factors that favor or restrict fate plasticity in glia within the intact CNS. Understanding this phenomenon and its underlying mechanisms is important for manipulating not only the fate of endogenous glial progenitor cells but also the fate of progenitors grafted into the pathological brain. Recent studies have identified new roles for the vasculature and endothelial cells' response to injury in modulating glial progenitor cell proliferation, migration, and differentiation (Cayre et al., 2013; Goldman and Chen, 2011). Therefore, signaling pathways that regulate glial progenitor-vasculature interactions might also represent attractive targets for enhancing glial regeneration under pathological conditions.

Another topic for future study is the progressive changes in cellular and molecular properties experienced by glial progenitor cells during CNS development and aging. For example, the remyelinating potential of OPCs decreases from early postnatal development to adulthood (Sim et al., 2002) and astrocytes outside the classic neurogenic areas undergo progressive lineage restriction and lose their neurogenic potential (Berninger, 2010; Bi et al., 2011; Laywell et al., 2000). It is crucial to continue characterizing the molecular and cellular mechanisms that regulate timely generation and lineage progression of different glial types in the developing CNS, to define: (1) the determinants of developmental time windows for neurogenesis, gliogenesis, and proper functional maturation of the brain, and (2) the potential for extending these time windows for regenerative purposes.

Finally, advances in iPS and ES cell technology hold great promise for cell-replacement therapies across a spectrum of tissues and associated pathologies. Several groups have established protocols to derive astrocytes and OLs, providing a foundation for translational applications. The likely application of this technology in glial repair is in WMI and OL replacement, as myelin sheath restoration is the clear focus of these therapeutic interventions. For astrocytes, the goal is less clear, as their complex roles in injury (protective versus inhibitory), injury conditions, and cellular heterogeneity make modeling of these conditions very difficult. Future in vivo studies aimed at understanding how different forms of injury differentially harness the reactive astrocyte response are essential for developing iPS or ES approaches to generating protective and regenerative astrocytes for cell-based therapies.

Resolving the issues in brain pathology discussed above will be critical to further elucidate relationships between glial cell populations in rodent models and their human counterparts, providing a better perspective on how to harness knowledge of glial development for therapeutic purposes. In addition, new techniques applied in parallel to human and animal brains—in particular noninvasive neuroimaging (e.g., fMRI, DTI, in vivo spectroscopy), as well as molecular analysis of postmortem tissue or surgical specimens—will determine how findings in animal models of disease relate to human conditions. The generation of more sophisticated animal models that incorporate the genetic heterogeneity seen in humans (Niu et al., 2014) will also promote better translation of animal research to clinical conditions. Thus, studies of glial cells and their responses to injury and pathology present a unique opportunity to interface studies in animal models of disease with neurodevelopmental disorders and diseases of the adult human brain.

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