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Regulation of oligodendrocyte development in the vertebrate CNS

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Abstract

The vertebrate central nervous system (CNS) contains two major classes of macroglial cells, oligodendrocytes and astrocytes. Oligodendrocytes are responsible for the formation of myelin in the central nervous system, while the functions of astrocytes are more diverse and less well established. Recent studies have provided new insights into when, where and how these different classes of cell arise during CNS development. The founder cells of the oligodendrocyte lineage initially arise in distinct regions of the ventricular zone during early development as the result of local signals including sonic hedgehog. In the spinal cord, oligodendrocyte precursors appear to share a developmental lineage with motor neurons, although they may also develop from restricted glial precursors. Immature oligodendrocyte precursors are highly migratory. They migrate from their site of origin to developing white matter tracts using a variety of guidance cues including diffusible chemorepellents. The majority of oligodendrocyte precursor proliferation occurs in developing white matter as a result of the local expression of mitogenic signals. Oligodendrocyte precursor cell proliferation is regulated by a number of distinct growth factors that act at distinct stages in the lineage and whose activity is modulated by synergy with other molecules including chemokines. The final matching of oligodendrocyte and axon number is accomplished through a combination of local regulation of cell proliferation, differentiation and cell death. Not all oligodendrocyte precursors differentiate during development, and the adult CNS contains a significant population of precursors. Understanding the regulation of oligodendrogenesis will facilitate the use of these endogenous precursors to enhance repair in a variety of pathological conditions.

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Abbreviations: PDGF, platelet-derived growth factor; CNP, 2′,3′-cyclic-nucleotide 3′-phosphodiesterase; PLP, proteolipid protein; PDGF-αR, platelet-derived growth factor receptor alpha; Shh, sonic hedgehog; BMP, bone morphogenetic protein; MGE, medial ganglion eminence; LGE, lateral ganglion eminence; TGF, transforming growth factor; O-2A progenitors, oligodendrocyte-type-2 astrocyte progenitors; GRPs, glial restricted precursors; MAG, myelin associated glycoprotein; FGF, fibroblast growth factor; NRG, neuregulin; POA, proligodendroblast antigen; NT3, neurotrophin-3; GC, galactocerebroside; MBP, myelin basic protein; PSA, polysialic acid; NCAM, neural cell adhesion molecule

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1. Introduction

The vertebrate central nervous system (CNS) is composed of three major classes of neural cells; neurons, astrocytes and oligodendrocytes (Peters et al., 1990). All these cell types are originally derived from the neuroepithelial cells of the neural tube and during the last 10 years how such cellular diversity is generated during CNS development has begun to be understood. While neurons are the most characteristic cells of the nervous system and are primarily responsible for information transfer, they are dependent on, interact with and are surrounded by glial cells. Macroglia, astrocytes and oligodendrocytes are derived from the same tissue as the neurons themselves, while microglia, the CNS resident macrophages, are immigrants from the hematopoietic system during very early development.

In the normal adult CNS some general functions of oligodendrocytes are well established. Most oligodendrocytes are located in white matter where their primary role is to form myelin (Bunge, 1968). The myelin sheath is a fatty insulation composed of modified plasma membrane that surrounds axons and promotes the rapid and efficient conduction of electrical impulses along myelinated axons (Bunge, 1968). An individual oligodendrocyte is capable of myelinating up to 60 different axons depending on the specific axon tract and axon diameter. Myelination is essential for the normal functioning of the mature CNS. Disruption of CNS myelin through injury, pathological degeneration (Waxman, 1991), or genetic intervention (Nave, 1995) leads to severe functional deficits and frequently a reduction in life span. Even focal myelin loss, as occurs in demyelinating diseases such as multiple sclerosis, results in a rapid loss of neurologic function (Waxman, 1991).

The functions of astrocytes are less clearly defined. One likely role is the regulation of the composition of the extracellular environment. Astrocytes possess a broad range of neurotransmitter receptors (Kettenmann et al., 1984) and uptake mechanisms and as such are able to clear excess neurotransmitters rapidly. More importantly, astrocytes also express a range of ion channels and are thought to regulate extracellular ion concentrations (Barres et al., 1990a,b; Sontheimer et al., 1992). Indeed, in many regions of the CNS, astrocytes are coupled together with gap junctions (Brightman and Reese, 1969), which provides a large cellular syncytium with which to buffer changes in ionic composition. Recent studies also suggest that astrocytes modulate the formation and efficiency of synaptic connections (Ullian et al., 2001) thereby contributing directly to neuronal function.

The different neural cell types arise in a distinct sequence during development. Classical studies suggested that in any particular region of the CNS, the first cell type to arise are neurons, followed by astrocytes and the last cell type to develop are oligodendrocytes (Altman and Bayer, 1984). Indeed, the necessity for continuous myelination along the entire length of an axon requires that the number of oligodendrocytes that are generated accurately match the number of axons to be myelinated. Not surprisingly therefore most neurons, and thus axons, as well as astrocytes are generated several days prior to the generation of oligodendrocytes (Skoff et al., 1976a,b). Indeed, in most vertebrates, including human, the majority of CNS myelination occurs postnatally and may continue for several years after birth. The generation of the correct number of oligodendrocytes involves several steps. First, oligodendrocyte precursors must be induced from cells of the neuroepithelium. Since these precursors arise a significant distance from the axons they will eventually myelinate, they must actively migrate through the CNS and stop at the correct location. Driven by defined growth factors, oligodendrocyte precursors undergo extensive proliferation, and the majority of this occurs in developing white matter. After a sufficient number of progenitor cells have been generated, oligodendrocyte precursors differentiate into immature oligodendrocytes. Upon differentiation oligodendrocytes coordinately increase their expression of an array of myelin associated molecules and assemble myelin sheaths around the appropriate axons. The ability to identify, isolate and manipulate cells of the oligodendrocyte lineage at specific developmental stages both in vitro and in vivo (Pfeiffer et al., 1993) has provided substantial insights into how many of these processes are controlled in the vertebrate CNS.

2. Early development of oligodendrocyte precursors

2.1. Oligodendrocyte precursors arise in restricted regions of the CNS

The majority of mature oligodendrocytes are located in white matter. Although oligodendrocytes were originally thought to differentiate directly from radial glial cells (Choi, 1986; Choi and Kim, 1985), it is now clear the earliest oligodendrocyte precursors arise in discrete regions of the

neural tube (Ono et al., 1995; Pringle and Richardson, 1993; Timsit et al., 1995; Warf et al., 1991). Early oligodendrocyte development has been most extensively studied in caudal regions of the CNS such as the spinal cord and in the optic nerve. In the rat optic nerve, tissue culture studies suggested that the founder cells of the oligodendrocyte lineage originated in the brain or optic chiasm and migrated along the nerve during subsequent development (Small et al., 1987). The source of at least a subset of chick optic nerve oligodendrocytes was subsequently defined as a small foci of cells in the floor of the third ventricle (Ono et al., 1997b). In the spinal cord, oligodendrocyte precursors are located along the entire rostral–caudal extent of the spinal cord as early as neural tube closure (Warf et al., 1991). By contrast, separation of dorsal and ventral regions of the spinal cord during early embryogenesis revealed that oligodendrocyte precursors were present only in ventral regions of the spinal cord (Ono et al., 1995; Warf et al., 1991). Whether the ventral spinal cord is the only source of oligodendrocytes is unresolved (Spassky et al., 1998). A dorsal source of oligodendrocyte precursors in caudal spinal cord regions was supported by initial chick–quail chimera studies in which dorsal portions of the chick neural tube were replaced with equivalent quail tissue and the source of oligodendrocytes determined by species specific labeling (Cameron-Currey and LeDouarin, 1995). Subsequent analyses of similar chimeric spinal cords, however, failed to substantiate these studies or provide evidence for a dorsal source for oligodendrocytes, but rather supported the notion that all spinal cord oligodendrocytes were derived from ventral regions (Pringle et al., 1998). The precise localization of oligodendrocyte precursors to the ventral ventricular zone of the spinal cord and the timing of their appearance has been defined using a variety of approaches. Oligodendrocyte precursors can be recognized in the ventral ventricular zone of the spinal cord by their localized proliferation (Noll and Miller, 1993), expression of growth factor receptors (Pringle and Richardson, 1993), distinct transcription factors (Lu et al., 2000; Zhou et al., 2000) and immunological and molecular profile (Ono et al., 1995; Orentas and Miller, 1996). After the majority of spinal cord neurogenesis is complete, proliferating glial precursors are localized to a distinct region of the ventral ventricular zone dorsal to the floor plate, and a subset of these cells subsequently generates oligodendrocytes (Noll and Miller, 1993). Oligodendrocyte precursors can be identified through the expression of platelet-derived growth factor receptor alpha (PDGF-αR) (Pringle et al., 1992; Pringle and Richardson, 1993), the receptor for their major mitogen PDGF-A (Noble et al., 1988; Richardson et al., 1988) (see Section 2.5). In addition, the expression of several myelin associated components including mRNA for the myelin genes 2′,3′-cyclic-nucleotide 3′-phosphodiesterase (*CNP*) and *DM20*, an isoform of the major myelin proteolipid protein (*PLP*) gene (Timsit et al., 1995) and, in the avian spinal cord, antigens recognized by the monoclonal antibody O4 (Sommer and Schachner, 1981). Ono et al. (1995) and Orentas and Miller (1996) define the discrete ventral ventricular location of oligodendrocyte precursors. More recently, the identification of the particular transcription factors Olig1 (Lu et al., 2000; Lu et al., 2002) and Olig2 (Zhou et al., 2000; Zhou and Anderson, 2002) confirms the restricted origin of oligodendrocyte precursors and provides insights into their initial specification. The ventral ventricular origin of spinal cord oligodendrocytes appears to be a common feature of vertebrate development and has been demonstrated in a broad range of species including *Xenopus* (Maier and Miller, 1995) and human as well as chick, mouse and rat (Ono et al., 1995; Pringle and Richardson, 1993; Warf et al., 1991).

The spinal cord is not the only region where oligodendrocytes arise in restricted locations. In more rostral areas of the CNS the earliest oligodendrocyte precursors appear in defined domains of the ventricular and subventricular zone at particular stages of development (Ono et al., 1997a). For example, a group of cells in the ventricular mantle zone of the ventral diencephalon of the E13 rat express mRNA for the PDGF-αR (Pringle and Richardson, 1993). During subsequent development these cells appear to migrate into the developing thalamus and hypothalamus as well as to more dorsal regions including the developing cerebellum (Pringle and Richardson, 1993). Not all the regions that initially generate oligodendrocyte precursors are ventrally located (Perez Villages et al., 1999). In the chick metencephalon, the earliest arising population of progenitors is adjacent to the floor plate in the ventral metencephalon (Ono et al., 1997a) while a second more dorsal source of oligodendrocytes develop independently (Davies and Miller, 2001). The oligodendrocytes that populate the telencephalon appear to be derived from both the medial and lateral ganglion eminence and later migrate into the cortex (He et al., 2001; Spassky et al., 1998). Whether both regions contribute equally to forebrain oligodendrocytes is not clear. In mutants in which the medial ganglion eminence is converted to the lateral ganglion eminence, there is a significant loss of oligodendrocytes suggesting that the medial ganglion eminence is the major source of oligodendrocytes (Sussel et al., 1999). Oligodendrocytes that populate the telencephalon also arise from alar regions such as the anterior entopeduncular area (Olivier et al., 2001). The exact contribution of each area to overall population of oligodendrocytes in the forebrain remains to be resolved. For example, it is unclear if individual domains generate oligodendrocytes that populate distinct regions of the forebrain or if the different domains give rise to morphologically and biochemically distinct types of oligodendrocytes (see Sections 2.3 and 2.4). A common theme linking the initial genesis of oligodendrocytes in all regions of the CNS is that these cells arise in restricted locations and subsequently migrate widely throughout the CNS to populate presumptive white matter. The restricted origin of oligodendrocyte precursors suggests that localized signals, some of which are known, control their initial appearance.

2.2. The initial appearance of oligodendrocyte precursors is regulated by local signals

In principle, two general mechanisms may account for the ventral origin of oligodendrocyte precursors in the spinal cord. Cells in dorsal regions may lack the intrinsic potential to generate oligodendrocytes or ventrally located signals may instruct neighboring cells to assume an oligodendrocyte fate while dorsal signals inhibit oligodendrocyte induction. Several lines of evidence demonstrate that the localized appearance of oligodendrocyte precursors is a reflection of local signaling. For example, transplant studies indicate that the initial appearance of spinal cord oligodendrocytes is dependent on local influences from the adjacent notochord (Orentas and Miller, 1996; Pringle et al., 1996; Trousse et al., 1995). The notochord, a transient mesodermally derived structure, is located ventral to the developing neural tube and signals from the notochord have been shown to be involved in the formation of the dorsal–ventral axis in the developing CNS (van Straaten et al., 1989). The establishment of dorsal and ventral polarity results in the subsequent specification of distinct populations of neurons found in the ventral spinal cord (Jessell and Dodd, 1990; van Straaten et al., 1988, 1989). Transplantation of an additional notochord adjacent to the dorsal spinal cord resulted in the local induction of ventral neurons (Yamada et al., 1991) and an ectopic cluster of oligodendrocyte precursors in chick and *Xenopus* embryos (Maier and Miller, 1997; Orentas and Miller, 1996). Likewise co-culture of dorsal spinal cord explants with isolated notochord is sufficient to induce motor neurons (Yamada et al., 1991) and oligodendrocytes in the spinal cord tissue (Orentas and Miller, 1996; Poncet et al., 1996; Pringle et al., 1996). The ability of the transplanted notochord to induce oligodendrocytes was restricted to a period during early embryonic chick development, which reflected both a change in the signaling capacity of the notochord and a temporally dependent loss of responsiveness of the dorsal spinal cord cells (Orentas and Miller, 1996). Not only is the notochord competent to induce ectopic oligodendrocytes, but it is essential for the normal ventral appearance of spinal cord oligodendrocytes. In *Xenopus* embryos UV irradiated at the one-cell stage, oligodendrocytes failed to develop in spinal cord regions lacking a notochord (Maier and Miller, 1997). Likewise, oligodendrocytes did not develop in the spinal cord adjacent to the site of notochord ablation at embryonic or larval stages (Maier and Miller, 1997). Similarly, in the short-tailed Danforth mouse, the notochord is discontinuous along the length of the rostral–caudal axis, and while oligodendrocytes developed normally in regions of the spinal cord adjacent to the notochord, they were absent from those regions lacking a notochord (Pringle et al., 1996). Thus, the notochord provides a local signal or signals that result in the subsequent appearance of spinal cord oligodendrocytes.

Many of the inductive properties of the notochord are due to its production of the signaling molecule sonic hedgehog (Echelard et al., 1993; Roelink et al., 1994). Sonic hedgehog, the vertebrate homologue of the *Drosophila* pattern forming gene *hedgehog*, is localized to the notochord and adjacent floor plate (Roelink et al., 1994). In vitro, sonic hedgehog induces the development of floor plate and different classes of motor neurons in a concentration-dependent manner (Roelink et al., 1994, 1995) through the activation or repression of a series of homeodomain transcription factors (Jessell, 2000). Oligodendrocytes can be induced in vitro at similar concentrations of Shh required for the induction of motor neurons (Orentas et al., 1999; Pringle et al., 1996), suggesting that the development of these two cell types is closely linked (Richardson et al., 1997). In the chick spinal cord, the generation of oligodendrocyte precursors requires continued Shh signaling after the formation of ventral–dorsal polarity and the generation of motor neurons (Orentas et al., 1999). For example, inhibiting Shh signaling immediately prior to the appearance of oligodendrocyte precursors blocks their subsequent appearance, but has little effect on motor neuron pools (Orentas et al., 1999). It seems likely that Shh contributes to the initial commitment of neuroepithelial cells to the oligodendrocyte lineage, possibly through induction of cell type specific transcription factors such as that the *Olig* genes (Lu et al., 2000, Zhou et al., 2000). In addition, recent in vitro studies suggest that the continued dependence of oligodendrocyte precursors on Shh signaling reflects a potent survival rather than proliferative influence on these cells (Davies and Miller, 2001).

In more rostral regions of the CNS, the expression of Shh and the appearance of oligodendrocytes is spatially and temporally closely linked (Davies and Miller, 2001; Nery et al., 2001; Tekki-Kessaris et al., 2001). Furthermore, ectopic expression of Shh leads to concomitant local development of oligodendrocytes (Nery et al., 2001). Whether Shh is essential for the development of all rostral populations of oligodendrocytes is less clear. In cell cultures derived from Shh knockout animals considerable numbers of oligodendrocytes develop, indicating that oligodendrocytes can arise in the absence of Shh signaling (Nery et al., 2001). It seems likely, however, that other members of the hedgehog family can substitute for Shh in its absence and blocking all hedgehog family member signaling with cyclopamine (Incardona et al., 1998) appears to block all oligodendrocyte development (Tekki-Kessaris et al., 2001).

In vitro, the development of oligodendrocyte precursors is inhibited by exposure to members of the TGFβ family (Mabie et al., 1997). Specifically, bone morphogenetic proteins 2 and 4 appear to inhibit the development of oligodendrocytes (Mabie et al., 1997; Mehler et al., 2000). This appears to be in part a reflection of the commitment of cells to astrocyte lineages at the expense of the oligodendrocyte lineage (Mabie et al., 1997; Mehler et al., 2000). Whether BMP signaling contributes to the spatial patterning of oligodendrocyte precursor induction in the developing intact CNS is currently unknown. For example, the failure of oligodendrocyte development in dorsal spinal cord may reflect active

inhibition by BMPs, which is overcome in ventral regions by Shh. If the source of the BMPs was in dorsal tissue adjacent to the spinal cord, this hypothesis would explain why oligodendrocyte develop in isolated explants of dorsal spinal cord over time (Sussman et al., 2000). Additional, as yet uncharacterized, inhibitors of oligodendrocyte precursor development may also exist. Indeed, dorsal spinal cord has been reported to contain an inhibitor of early oligodendrocyte development (Wada et al., 2000) that is functionally distinct from any known BMP (Wada et al., 2000).

2.3. The generation of oligodendrocytes and neurons is closely linked and regulated through transcription factor expression

The finding that oligodendrocytes and distinct populations of neurons arose in similar regions of the neuroepithelium suggested that the development of these cells was closely coupled (Richardson et al., 1997). Several lines of evidence are consistent with this hypothesis. For example, similar concentrations of Shh are required for the induction of both cell types (Pringle et al., 1996) and in vitro the induction of oligodendrocytes is frequently accompanied by the induction of motor neurons (Orentas et al., 1999; Pringle et al., 1996). Lineage analyses in cultures of rat cerebral cortex (Williams et al., 1991) and developing chick spinal cord (Leber et al., 1990; Leber and Sanes, 1991) as well as clonal analyses in cerebral cortical cultures (He et al., 2001) indicate that neurons and oligodendrocytes share a common precursor.

Recent studies on the expression and function of distinct families of transcription factors have provided insights into how neuroepithelial cells in the ventral spinal cord could generate both neurons and oligodendrocytes (Kessaris et al., 2001). The ventricular zone of the ventral spinal cord contains several specific cellular domains identified by different transcription factor expression and generating distinct cell populations (Briscoe et al., 2001; Jessell, 2000). Oligodendrocyte precursors arise during later development from the motor neuron pool that is characterized by expression of the transcription factor Olig2 (Zhou et al., 2001; Zhou and Anderson, 2002). Olig2 is thought to combine with the basic helix–loop–helix transcription factors neurogenin-1 and -2 to generate motor neurons, however, towards the end of spinal cord motor neuron induction, the expression of neurogenins is down-regulated (Zhou et al., 2001). This allows for an alteration in the distribution pattern of a more ventrally expressed transcription factor, Nkx2.2, into the Olig2 domains such that they now overlap. Cells that express both transcription factors subsequently develop into spinal cord oligodendrocytes rather than motor neurons (Zhou et al., 2001) (Fig. 1A). Several lines of evidence support such a model. For example, to ectopically generate oligodendrocytes in other regions of the CNS requires the expression of both Olig2 and either Nkx2.2 or components of the Notch signaling pathway (Zhou et al., 2001). Confirmation of the requirement and roles of the Olig transcription factors in the genesis of oligodendrocytes has come from targeted disruption of these genes. *Olig2* is required for the specification of both motor neurons and oligodendrocytes while *Olig1* is required for the later development of oligodendrocytes particularly in rostral regions of the CNS (Lu et al., 2002). In the absence of both *Olig1* and *Olig2* the cells that would normally give rise to motor neurons and oligodendrocyte generate a specific class of interneurons and surprisingly astrocytes (Zhou and Anderson, 2002). The simple model of a restricted motor neuron oligodendrocyte precursor will, however, require further refinement since in the mouse CNS some early oligodendrocyte precursor cells arise outside the Nkx2.2+ domains of the CNS (Lu et al., 2000; Sun et al., 1998). It may be that there is more than one population of oligodendrocyte precursors that differ in the mechanism by which they become specified (Spassky et al., 2000), or some cells previously characterized as oligodendrocyte precursors are in fact astrocyte precursors.

2.4. Spinal cord oligodendrocytes also develop from tripotential glial restricted precursors

In apparent contrast to the lineage associations between motor neurons and oligodendrocytes, several recent studies suggest that oligodendrocyte precursors develop from a more immature cell previously restricted to give rise to only glial progeny (Rao et al., 1998). These cells termed glial restricted precursors (GRPs) (Rao and Mayer-Proschel, 1997) are distinct from O-2A progenitor cells in that they give rise to two distinct types of astrocyte as well as oligodendrocytes (Fig. 1B). These cells differ from the previously described O-2A or oligodendrocyte precursor cells in their proliferative response to known growth factors and their requirement for survival factors, as well as their differentiative potential (Rao et al., 1998). It is possible these glial restricted precursors are the proliferating cells seen in the ventricular zone of the spinal cord since they also gave rise to astrocytes as well as oligodendrocytes in subsequent cultures (Noll and Miller, 1993). Transplantation studies demonstrate that GRP cells generate significant numbers of astrocytes when transplanted into the developing or adult brain (Herrera et al., 2001), while oligodendrocyte precursors generate primarily oligodendrocytes and not astrocytes (Espinosa de la Monteros et al., 1993). In contrast to oligodendrocyte precursors that are initially restricted to ventral spinal cord, GRP cells can be isolated from both dorsal and ventral spinal cord during early embryonic development (Gregori et al., 2002) (Fig. 1B). The propensity of dorsal GRP cells to differentiate into oligodendrocytes is, however, significantly less than that of ventrally derived GRP cells (Gregori et al., 2002). The characterization of a glial restricted precursor suggests a model in which an initial step in the commitment of neuroepithelial cells to an oligodendrocyte fate is the segregation of neuron and glial fates. Secondarily,

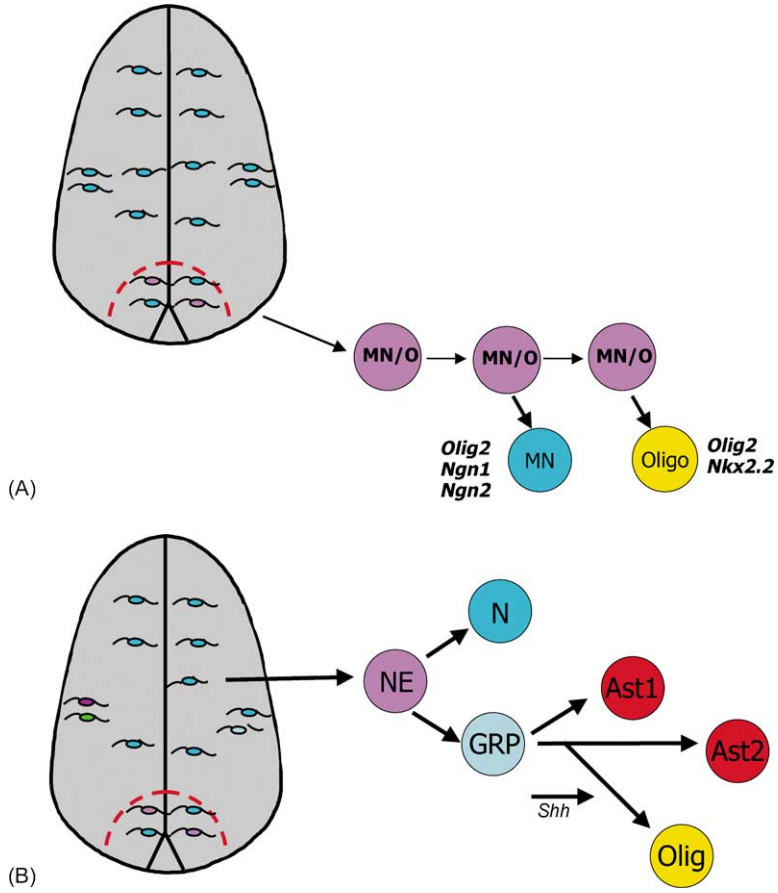

Fig. 1. Two possible models for the initial specification of oligodendrocyte precursors in the developing spinal cord. In (A) neuroepithelial cells in the ventral spinal cord are induced by local signals including sonic hedgehog to become motor neuron/oligodendrocyte precursors (MN/O). Expression of the transcription factors Olig2 and neurogenin in these cells results in motor neuron specification (MN). With time, the expression of neurogenin decreases allowing expression of the transcription factor Nkx2.2 to overlap with Olig2+ cells. Co-expression of Olig2 and Nkx2.2 results in the appearance of oligodendrocyte precursors (Oligo). In (B) neuroepithelial cells throughout the dorso-ventral neuroaxis become specified as either neuronal precursors (N) or glial restricted precursors (GRP). The glial restricted precursors in dorsal and intermediate regions of the spinal cord give rise to predominantly astrocytes (AST) while those in ventral regions are influenced by local Shh to generate oligodendrocytes (Oligo) at the expense of astrocytes. In both, oligodendrocyte precursors are preferentially generated from ventral regions of the spinal cord.

local signals such as Shh acting on a glial restricted precursor lead to the induction of oligodendrocyte precursors.

While such a model might initially seem incompatible with the studies suggesting a common motor neuron/oligodendrocyte lineage discussed above (Section 2.3), both models may be correct. For example, it has been proposed that the oligodendrocytes are a heterogeneous population of cells. Evidence for morphological heterogeneity among oligodendrocytes is well established. Early silver impregnation studies identified four distinct morphologies of myelinating oligodendrocytes, and this was largely confirmed by ultrastructural analyses in a variety of species (Stensaas and Stensaas, 1968; Remahl and Hildebrand, 1990; Bjartmar et al., 1968). Oligodendrocyte morphology is closely correlated with diameter of the axons with which the cell associates (Butt et al., 1997, 1998). Oligodendrocyte types I and II arise late in development and myelinate many internodes on predominantly small diameter axons, while oligodendrocyte types III and IV arise later and myelinate mainly large diameter axons. Such morphological and functional differences between oligodendrocytes are associated with different biochemical characteristics. Oligodendrocytes that myelinate small diameter fibers (types I and II) express higher levels of carbonic anhydrase 11 (CA11) (Butt et al., 1995, 1998), while those myelinating larger axons (types III and IV) express a specific small isoform of the myelin associated glycoprotein (MAG) (Butt et al., 1998). Whether such differences represent the response of homogenous cells to different environments or distinct cell lineages is unclear. Transplant studies demonstrated that presumptive types I and II cells had the capacity to myelinate both small and large diameter axons suggesting that the morphological differences were environmentally induced (Fanarraga et al., 1998). By contrast, developmental studies suggest the different classes of oligodendrocytes may be derived from biochemically distinct precursors (Spassky et al., 2000) that differ in expression of PDGF-αR and PLP/DM20. It may be that the one lineage is derived from the motor neuron

pool and the other from the GRP pool. Alternatively, in the ventral ventricular zone of the spinal cord, an essential intermediate step between the neurogenin positive motor neuron precursor and the Nkx2.2/Olig2 positive oligodendrocyte may be a transient glial restricted phenotype. In the developing cortex, clonal analysis demonstrates that an individual single cell can generate neurons and oligodendrocytes in the absence of astrocytes (He et al., 2001), indicating that if a GRP intermediate is produced it does not have to generate astrocytes, although it may do so under appropriate conditions. Regardless of exact lineage restriction utilized during normal oligodendrogenesis, the identification and isolation of a highly proliferative glial restricted precursor that can generate large numbers of astrocytes and oligodendrocytes in vivo and in vitro (Herrera et al., 2001; Rao et al., 1998) provide a potentially important tool for neural repair.

2.5. Expansion of the oligodendrocyte population is regulated by a variety of growth factors

Following commitment in the ventricular zone oligodendrocyte precursors undergo extensive proliferation. The early phases of this proliferation occur in the ventricular and subventricular zone while the majority of oligodendrocyte proliferation occurs after migration to the developing white matter (Miller et al., 1997). At each phase, a number of growth factors contribute to the proliferation and survival of oligodendrocyte precursors (Fig. 2).

The early generation of oligodendrocyte precursors from neural stem cells in cultures of cerebral cortex (Davis and Temple, 1994) is enhanced by increasing concentrations of fibroblast growth factor-2 (FGF2) (Qian et al., 1997) suggesting this growth factor may contribute to the induction of an oligodendrocyte fate in these cells. In the spinal cord,

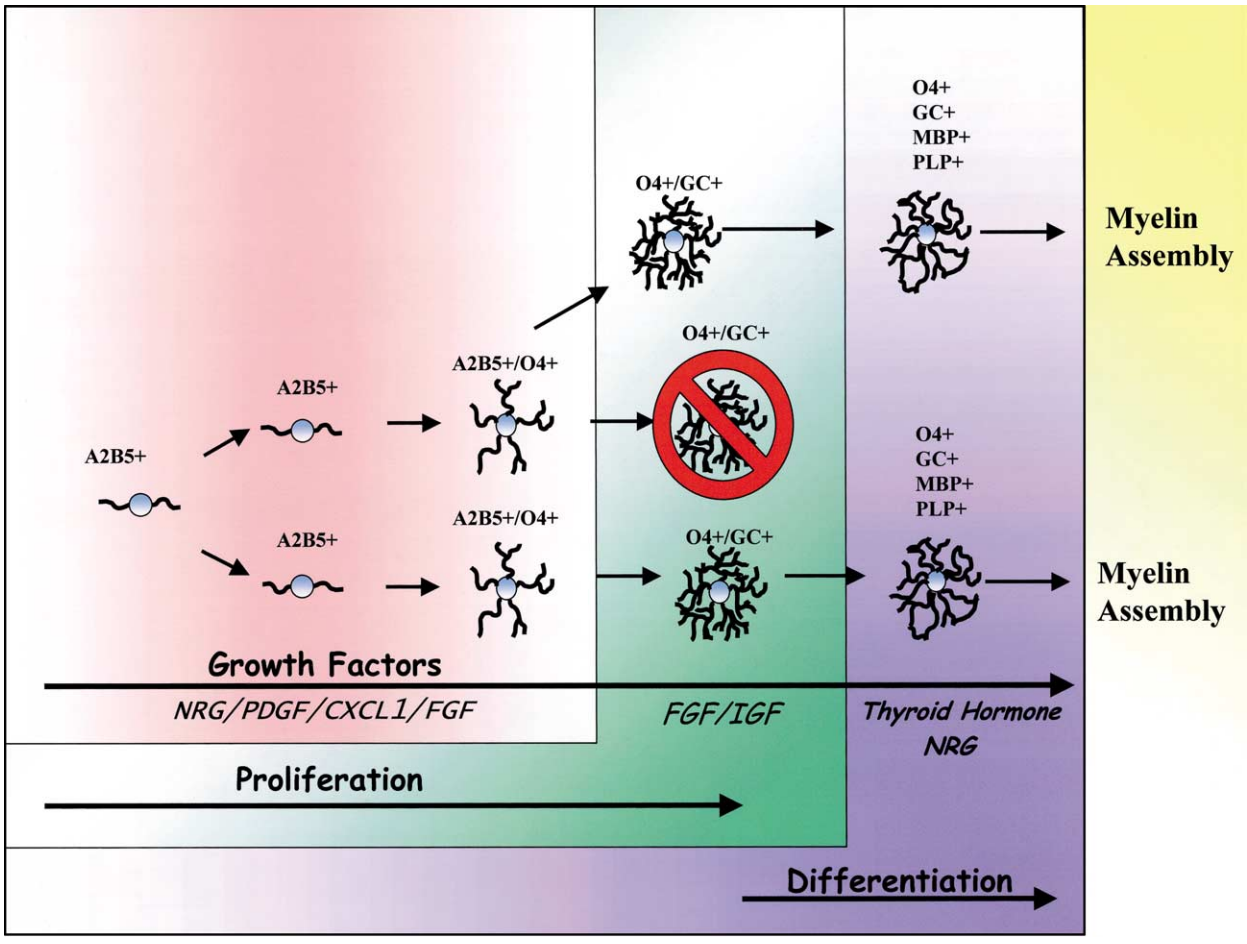

Fig. 2. Schematic representation of some of the major stages in the development of oligodendrocytes and the growth factors known to be important at different stages. Immature oligodendrocytes develop in distinct domains of the ventricular zone of the neural tube and rapidly acquire expression of cell surface antigens recognized by the monoclonal antibody A2B5. These cells are bipolar and highly migratory. Several growth factors act on these cells including PDGF, bFGF NRG NT3 and the chemokine CXCL1. As the cells mature they acquire expression of antigens recognized by the monoclonal antibody O4 and lose proliferative responses to PDGF. Differentiation of oligodendrocyte precursors is accompanied by expression of galactocerebroside a major glycolipid in myelin. Newly generated oligodendrocytes are highly susceptible to cell death. Maturation of oligodendrocytes is accompanied by increased expression of myelin components including major myelin proteins such as myelin basic protein and proteolipid protein followed by assembly of the myelin sheath.

initial development of oligodendrocyte precursors is dependent upon several factors including neuregulin-1 (Vartanian et al., 1999). In spinal cord explant cultures of neuregulin-1 knockout animals oligodendrocytes and their precursors fail to develop (Vartanian et al., 1999). These cells can be induced, however, by addition of recombinant NRG directly to the culture indicating the requirement for NRG signaling at the time that oligodendrocyte precursors first arise (Vartanian et al., 1999). The receptors that mediate this signaling are unknown. In other cell types NRG signaling is mediated by members of ErbB receptors (Lemke, 1996) and while some of these receptors such as ErbB2 are critical at later stages of oligodendrocyte development (Park et al., 2001), it does not appear to be critical for early oligodendrocyte precursor development.

Once committed to the oligodendrocyte lineage, precursors express cell surface antigens recognized by the monoclonal antibody A2B5 (Raff, 1989; Raff et al., 1984). In vitro these cells have the capacity to give rise to both oligodendrocytes and astrocytes and have thus been termed oligodendrocyte-type-2 astrocyte (O-2A) progenitor cells (Raff et al., 1984). These cells constitutively differentiate into oligodendrocytes but require environmental signals in order to give rise to astrocytes (Hughes et al., 1988; Lillien et al., 1990). Whether O-2A progenitors manifest this type of phenotypic plasticity in the normal CNS is currently unclear (Espinosa de la Monteros et al., 1993). Over time oligodendrocyte precursors mature and begin to express cell surface antigens recognized by the monoclonal antibody O4, which includes galactosulfatide and a novel POA antigen (Bansal and Pfeiffer, 1992; Pfeiffer et al., 1993). Late precursors or proligodendrocytes are multiprocessed, less motile and no longer retain the capacity to give rise to type-2 astrocytes (Fok-Seang and Miller, 1994; Pfeiffer et al., 1993). Immature and late oligodendrocyte precursors or proligodendrocytes differ in their proliferative responses to a variety of different mitogens (Fok-Seang and Miller, 1994; Gard and Pfeiffer, 1990).

One of the best-characterized mitogens for oligodendrocyte precursors is platelet-derived growth factor A (PDGF-A) (Noble et al., 1988; Richardson et al., 1988), and immature oligodendrocyte precursors express the PDGF-αR (Pringle et al., 1992). Not only is PDGF a powerful mitogen for oligodendrocytes, it is also a significant survival factor. In the intact CNS, PDGF-A is ubiquitously distributed, being synthesized by both astrocyte and neuronal populations (Yeh et al., 1991). Over expression of PDGF-A results in a dramatic increase in the number of spinal cord oligodendrocyte precursors (Calver et al., 1998), while in PDGF-A knockouts the number of oligodendrocyte precursors is dramatically reduced (Fruttiger et al., 1999). The proliferative response of immature oligodendrocytes to PDGF is modulated by synergistic interactions with other molecules. The chemokine CXCL1 enhances the proliferation of oligodendrocyte precursors to PDGF (Robinson et al., 1998; Wu et al., 2000) in a concentration-dependent manner as well as regulating the migration of immature precursor cells (Tsai et al., 2000) (see Section 2.8). Immature oligodendrocyte precursors also proliferate in response to basic FGF (bFGF), which appears to be widely distributed in the embryonic CNS. The expression of PDGF-αRs on immature oligodendrocyte precursors is up-regulated by bFGF (McKinnon et al., 1991) and in combination with PDGF, bFGF promotes extended proliferation of oligodendrocyte precursors (Bogler et al., 1990; McKinnon et al., 1990). The differentiation of late precursors or proligodendrocytes (Pfeiffer et al., 1993) that continue to proliferate in response to bFGF (Fok-Seang and Miller, 1994; Gard and Pfeiffer, 1993) is also blocked by bFGF (Gard and Pfeiffer, 1993; Mayer et al., 1993). Further, although it has been proposed that bFGF causes mature oligodendrocytes to revert to a more immature phenotype (Grinspan et al., 1993), subsequent studies indicate that rather than a reversion, bFGF exposure results in the induction of a novel cell phenotype (Bansal and Pfeiffer, 1997), which may reflect a functionally distinct cell population. Several forms of bFGF receptors are present on cells of the oligodendrocyte lineage and their expression is developmentally regulated (Bansal et al., 1996). The expression of FGF-receptor 1 increases as cells mature through the lineage; FGF-receptor 2 is expressed predominantly in differentiated oligodendrocytes while FGF-receptor 3 is predominantly expressed in proligodendrocytes (Bansal et al., 1996). The differential expression of distinct FGF receptors is likely to mediate the different responses of oligodendrocyte lineage cells to growth factor stimulation during progression through the lineage (Bansal et al., 1996). Several other growth and trophic factors regulate the development of oligodendrocytes in vitro. The neurotrophin-3 (NT3) is mitogenic for purified optic nerve (Barres et al., 1994b) but not spinal cord oligodendrocytes of the same age (Robinson and Miller, 1996). Retinoic acid and its derivatives appear to inhibit progression of immature oligodendrocyte through the lineage (Noll and Miller, 1994), while enhancing their differentiation at more mature stages (Barres and Raff, 1993). In general, the differentiation of oligodendrocyte precursors is characterized by a withdrawal from the cell cycle and expression of the major myelin glycolipid glactocerebroside (GC) (Raff et al., 1978). Oligodendrocytes exhibit a multiprocessed phenotype and their maturation results in the coordinated elevated expression of a number of major myelin components such as myelin basic protein (MBP) and proteolipid protein (PLP) (Campagnoni, 1995; Lemke, 1988).

2.6. Myelination of developing white matter is dependent on oligodendrocyte precursor migration

In the adult CNS, oligodendrocytes are widely distributed, while in early development their precursors arise in highly restricted ventricular domains (see Section 2.1). The spatial separation between the location of origin of oligoden-

drocyte precursors and their final destination means that normal myelination is dependent on the long distance migration of oligodendrocyte precursors. Although the migratory capacity of oligodendrocyte precursors has been clear for several years, the molecular mechanisms mediating this migration are only now becoming understood. The earliest indications that oligodendrocyte precursors were capable of long distance migration came from transplantation studies (Lachapelle et al., 1984, 1994). Transplantation of fragments of normal CNS tissue into host animals lacking myelin proteins resulted in the substantial dispersal of normal oligodendrocytes throughout the host CNS (Lachapelle et al., 1984) some of which may have occurred by trafficking through the ventricular system. Similar analyses using purified cell populations demonstrated that the capacity for long distance cell migration through the neurophil of the CNS is predominantly a characteristic of immature oligodendrocyte precursors and is lost as the cells mature (Warrington et al., 1992, 1993). Likewise, retrospective analyses of the oligodendrocyte precursors that migrated into the cerebellum indicated they were highly immature (Goyne et al., 1994). Together these observations suggested that the migration of immature oligodendrocyte precursors was an essential component for normal myelination in the vertebrate CNS.

The extent of oligodendrocyte precursor migration during CNS development has been highlighted by analyses of the optic nerve (Small et al., 1987; Ono et al., 1997b; Sugimoto et al., 2001) and spinal cord (Warf et al., 1991; Ono et al., 1995). The oligodendrocytes that populate the optic nerve migrate into the nerve from the brain during late embryonic and early postnatal stages (Fig. 3). This migration was first documented using cell culture (Small et al., 1987). For example, cell cultures derived from brain or chiasmal regions of the optic nerve acquired the capacity to generate oligodendrocytes several days before cultures isolated from retinal regions of the nerve (Small et al., 1987). The source of optic nerve oligodendrocytes and their dispersal along the nerve was directly visualized by labeling the cells at their origin in the floor of the third ventricle in developing chick embryos (Ono et al., 1997b). In contrast to rat, mouse and human, where oligodendrocytes and myelin are restricted to the optic nerve, oligodendrocytes migrate into specific regions of the chick (Ono et al., 1998) and rabbit retina (ffrench-Constant et al., 1988) where they myelinate the proximal region of retinal ganglion cell axons. In the spinal cord similar approaches have been used to document the migration of oligodendrocyte precursors from ventral to dorsal regions. Isolated cultures of ventral spinal cord generated oligodendrocytes from the time of neural tube closure (E12), while isolated cultures of dorsal spinal cord did not acquire the capacity to generate oligodendrocytes in a physiological time frame until E16 (Warf et al., 1991). The acquisition of the capacity to generate oligodendrocytes in dorsal spinal cord correlated directly with the arrival of ventrally-derived precursors (Ono et al., 1995). Direct evidence of the ventral to

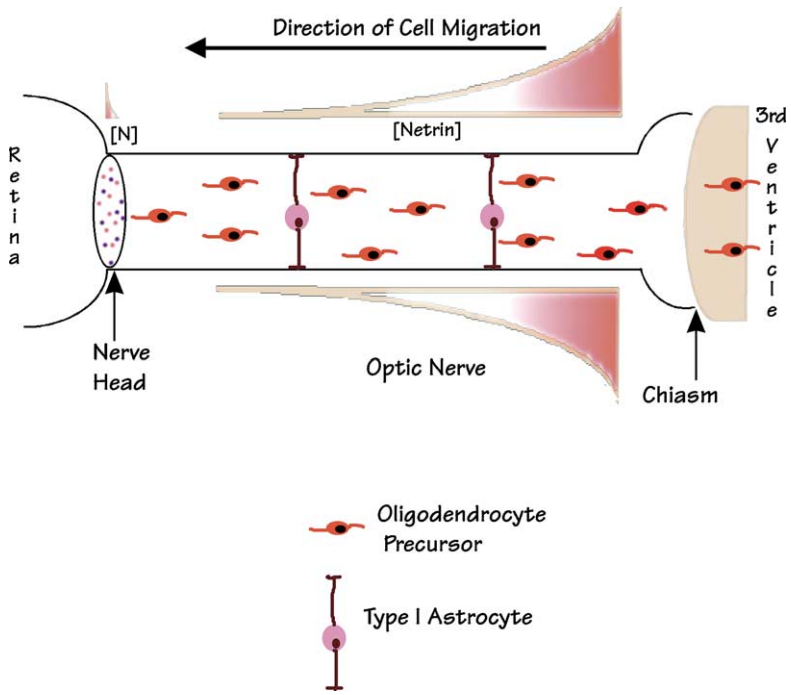

Fig. 3. Model for the migration of oligodendrocyte precursors along the optic nerve. Oligodendrocyte precursors originate in the floor of the third ventricle and subsequently migrate along the length of the nerve. The migration of the cells is directed by chemorepellent signals including netrin originating from the region of the optic chiasm. In some species oligodendrocyte precursors are kept out of retinal regions by a barrier to migration at the optic nerve head. The cellular substrates and molecular mechanisms mediating the migration of oligodendrocyte precursors along the nerve may involve interactions with axons and extracellular matrix molecules. Type I astrocytes develop from cells along the length of the nerve and are not as highly migratory.

dorsal migration of spinal cord oligodendrocyte precursors has been provided by cell tracking experiments using in vitro preparation of rat spinal cord (Warf et al., 1991).

In more rostral regions of the CNS the migration of oligodendrocytes precursors is also pronounced. During development of the cerebral cortex, immature oligodendrocyte precursor cells have been suggested to migrate from the lateral ganglion eminence (LGE) as well as the medial ganglion eminence (MGE) into the developing forebrain (He et al., 2001; Spassky et al., 1998). At later stages of development glial precursor cells, including oligodendrocytes, migrate from the subventricular zone in radial and tangential directions towards the pial surface (Kakita and Goldman, 1999) to populate all regions of the cortex.

The natures of the cellular substrates utilized and the molecular mechanism mediating oligodendrocyte precursor migration are not well understood. In the optic nerve many of the migrating oligodendrocyte precursors are closely associated with retinal ganglion cell axons and it has been suggested that this migration is axophilic (Ono et al., 1997b). Migration along pre-existing axon tracts would also provide a pathway for the ventral to dorsal migration in the spinal cord where migrating cells would utilize the earlier developed circumferential axon tracts. Not all oligodendrocyte precursor migration is dependent upon axons, however. In the rat optic nerve, removal of the retinal ganglion cell axons through eye enucleation or disruption of the neural retina in the postnatal animal (Ueda et al., 1999) failed to completely block the population of the nerve by oligodendrocytes, although the number of cells was greatly reduced (Ueda et al., 1999). It may be, however, that significant numbers of oligodendrocyte precursors had populated the nerve prior to the perturbation (Small et al., 1987) or residual cues remained after the removal of the axons. Cell surface components such as adhesion molecules (Wang et al., 1994; Payne and Lemmon, 1993) and extracellular matrix receptors also have been proposed to play a role in regulating migration (Kiernan and ffrench-Constant, 1993; Kiernan et al., 1996; Garcion et al., 2001). In explant studies, removal of NCAM associated polysialic acid (PSA) inhibits the dispersal of oligodendrocyte precursors (Wang et al., 1994, 1996). However, in the developing chick optic nerve removal of NCAM associated PSA does not play a pivotal role in regulating precursor migration (Ono et al., 1997b). Oligodendrocyte precursors also express an array of integrin receptors that may play important role in regulation of both migration and cell differentiation (Milner and ffrench-Constant, 1994; Garcion et al., 2001). Since differentiated oligodendrocytes are not migratory, it is not surprising that control of differentiation and migration would be closely linked.

2.7. Guidance of glial precursor migration

The migration of oligodendrocyte precursors throughout the developing CNS is likely to be mediated by specific directional and substrate cues. The immigration of oligodendrocyte precursors into the optic nerve seen in culture and labeling studies (Ono et al., 1997b; Small et al., 1987) might simply have reflected the random movement of cells originating from a focal source within the brain. Likewise, the population of the dorsal spinal cord with ventrally-derived precursors might occur by non-directional dispersal (Ono et al., 1995). Such a mechanism is unlikely. It would likely be very slow in dispersing cells and fail to accommodate the finding that different tracts of the spinal cord become populated with oligodendrocytes at defined times in development. The motility of immature oligodendrocyte precursors is promoted by PDGF, the same growth factor that promotes their proliferation and survival (Armstrong et al., 1990, 1991). In chemotaxis chambers oligodendrocyte precursors migrate towards higher concentrations of PDGF indicating this growth factor has chemotactic properties. In vivo PDGF appears to be ubiquitously distributed throughout the CNS, being made by populations of astrocytes and neurons (Yeh et al., 1991) and so is unlikely to guide glial migration. Recent studies suggest, however, that the migration of oligodendrocyte precursors is guided by specific cues (Sugimoto et al., 2001). For example, labeling of cells in a section of optic nerve demonstrated that the majority of the cell migration was unidirectional from the chiasm to the retina (Sugimoto et al., 2001). This observation implied that the migration of cells along the nerve is guided by directional cues in the environment. Tissue culture studies indicated that the directional cues were located in the optic chiasm. Without the optic chiasm the migration of glial precursors was bidirectional with similar numbers of cells moving short distances in both directions along the nerve. By contrast, in the presence of the chiasm, glia cells in the optic nerve exhibited preferential migration away from the chiasm and toward the retina indicating that guided glia migration was influenced by chemorepellent factors produced by the optic chiasm (Sugimoto et al., 2001). Localization studies identified netrin-1 and semaphorin-3a as potential chiasm-derived chemorepellent signals and, consistent with this hypothesis, in vitro functional analyses confirmed that both netrin-1 and semaphorin-3a were chemorepellent for optic nerve glial precursors (Sugimoto et al., 2001). It seems likely that the different chemorepellents act on different cell populations, with netrin being chemorepulsive for oligodendrocyte precursors and semaphorin-3a repulsive for astrocyte precursors in the optic nerve, although this hypothesis awaits further confirmation. One question raised by these studies is how ubiquitous guided glial precursor migration is throughout the developing CNS? Studies in the spinal cord indicate that the dispersal of oligodendrocyte precursors from the ventral ventricular zone is in part mediated by localized expression of netrin-1 consistent with a common mechanism (Tsai and Miller, 2001). Analyses of the migration paths of glial precursors in other regions of the developing CNS, however, suggest the situation may be more complex (Kakita and Goldman, 1999). For example, in striatum, glia precursors take two pathways that are almost perpendicular

to each other. These discrete patterns of migration may reflect utilization of alternative cellular substrates of migration such as radial glial fibers or axon tracts (Meintanis, 2001; Ono et al., 1997b) rather than secreted guidance cues.

2.8. Stop signals for migrating glia

One striking characteristic of the rodent optic system is the spatial restriction of myelination of retinal ganglion cell axons to the optic nerve, while more proximal portions of the same cell axons in the retina are unmyelinated. Myelin is distributed evenly along the optic nerve but stops abruptly at the lamina cribosa of the optic nerve head in a number of species, because this region acts as a barrier for the migration of oligodendrocyte precursors (ffrench-Constant et al., 1988). The mechanisms that inhibit the migration of oligodendrocyte precursors at the optic nerve head may involve localized expression of the ECM molecules such as tenascin-C in conjunction with other signals (Bartsch et al., 1994; Kiernan et al., 1996). During development, netrin-1 is transiently expressed at the optic nerve head (Deiner, 1997) and it may be that this localized expression of netrin serves as a repulsive cue to stop the migration of oligodendrocyte precursors into the retina. Another candidate stop signal for migrating oligodendrocyte precursors is the chemokine CXCL1, which appears to regulate spatial and temporal patterning of spinal cord myelination through inhibiting cell motility as well as promoting cell proliferation (Tsai et al., 2000). The cellular source of these stop signals is in part astrocytes and other glia. However, since the majority of oligodendrocyte precursors in presumptive white matter will differentiate into oligodendrocytes that will myelinate axons, it seems likely that as yet uncharacterized axonal signals will regulate many of the final steps in the development of mature oligodendrocytes.

3. Control of oligodendrocyte differentiation and maturation

3.1. Control of oligodendrocyte precursor number

In order to produce the appropriate number of oligodendrocytes in any particular region of the CNS the generation of oligodendrocyte precursors must be regulated. Several mechanisms contribute to the control of oligodendrocyte precursor numbers. The proliferation of oligodendrocyte precursors is regulated in part by the availability of mitogen. Increasing amounts of PDGF either in vitro or in vivo increase precursor proliferation and precursor number (Fruttiger et al., 2001). Some of the increase in precursor number may also reflect increased precursor survival in the presence of elevated levels of PDGF since PDGF is a strong survival factor for cells of the oligodendrocyte lineage (Barres et al., 1992). The proliferation of oligodendrocyte precursors is also inhibited by environmental signals. Conditioned medium from cultured oligodendrocytes inhibits the proliferation of oligodendrocyte precursors, and this effect may be mediated in part by TGFβ (Louis et al., 1992; McKinnon et al., 1993). Local signals also appear to regulate oligodendrocyte precursor proliferation (Nakatsujji and Miller, 2001; Zhang and Miller, 1996). In cultures of embryonic rat spinal cord oligodendrocyte lineage cells reach a steady-state density independent of the initial number of precursors and the presence of mitogens. This normalization of cell number, which reflects a feedback inhibition of precursor proliferation at high density, is cell type specific and does not appear to be mediated through the release of a soluble factor (Zhang and Miller, 1996). The signaling pathways mediating density-dependent inhibition of oligodendrocyte proliferation are unknown. The concept that cell proliferation may be regulated in a density-dependent fashion is not new (Wieser et al., 1990), and some of the cellular mechanisms responsible for the decreases in oligodendrocyte precursor proliferation are beginning to be defined. Increasing cell density of oligodendrocyte precursors, as in other cell types (Hengst and Reed, 1996; Kato et al., 1997), is correlated with an increase in the expression levels of the cell cycle inhibitor $p27^{kip-1}$, reductions in the expression levels of cyclins (Sherr, 1993), including cyclin A, and changes in the relative phosphorylation levels of Rb (Weinberg, 1995; Nakatsujji and Miller, 2001). Alterations in the expression of these components would all tend to inhibit the progression through the cell cycle and thus reduce proliferation (Nakatsujji and Miller, 2001). Density-dependent alterations in the expression of cell cycle proteins were reversible. Replating the cells at low density caused a reversion in expression levels and the cells rapidly reentered the cell cycle (Nakatsujji and Miller, 2001). These studies support the concept that proliferative control is not directly tied to the differentiation program in oligodendrocyte precursors.

Differentiation of oligodendrocyte precursors into oligodendrocytes also influences both precursor and oligodendrocyte cell numbers. The transition from a precursor to a differentiated oligodendrocyte is a critical step in the development of the myelinating lineage. Studies on rat optic nerve oligodendrocyte precursors suggest that individual precursor cells undergo a defined number of cell divisions prior to differentiation. In clones of cells derived from a single cell all the progeny cease proliferation and differentiate at approximately the same time (Raff et al., 1990; Raff and Lillien, 1988; Temple and Raff, 1986). This coordinated regulation of clonally related proliferation and differentiation may reflect an intrinsic cell clock that depends in part on AP-1 activity (Barres and Raff, 1994). The intrinsic clock regulating oligodendrocyte precursor proliferation not only counts cell divisions but also can sense time (Ibarrola et al., 1996; Tang et al., 2000), although how this is accomplished is currently unclear. Indeed, the significance of this timing mechanism is also unclear since environmental factors can override the normal action of the cell intrinsic clock. Thus, in complex cellular environments such as spinal cord

cultures, most clones of oligodendrocyte precursors contain both differentiated and non-differentiated cells (Zhang and Miller, 1995). Exposure of precursor cells to a combination of PDGF and FGF results in the extended proliferation of precursors and an inhibition of differentiation (Bogler et al., 1990; McKinnon et al., 1990). Likewise, removal of growth factor stimulation results in the rapid and precocious induction of differentiation of oligodendrocytes indicating that the differentiation of oligodendrocytes is closely correlated with cessation of precursor cell proliferation of precursor cells (Raff et al., 1990). It does not seem likely, however, that the identical regulatory pathway controls both cessation of proliferation and differentiation but rather that the temporal regulation of both pathways is coincident.

3.2. Control of oligodendrocyte cell number

The final number of oligodendrocytes in any particular region of the CNS is the product of precursor differentiation and survival. Differentiation of the precursors is dependent on thyroid hormone and its derivatives, although the mechanism of action is currently unclear (Barres et al., 1993). In addition, the redox state of a particular precursor cell appears to regulate the differentiative propensity of that cell to proliferate or differentiate (Smith et al., 2000). The link between cell proliferation and oligodendrocyte differentiation is clearly evident in animals lacking cell cycle regulatory proteins such as $p27^{kip-1}$. In these animals the number of oligodendrocytes is significantly altered, although they appear to differentiate at the appropriate time (Casaccia-Bonnefil et al., 1997). By contrast, in animals lacking the cell cycle regulatory protein $p21^{cip-1}$ the differentiation of oligodendrocyte precursors is disrupted, suggesting this molecule is required for the normal differentiation of the cells (Zezula et al., 2001). A major regulator of oligodendrocyte number appears, however, to be the control of cell death. In the rat optic nerve the final number of oligodendrocytes is regulated by competition for local survival factors including PDGF (Barres et al., 1992; Barres and Raff, 1994) and possibly axonal derived neuregulin (Fernadez et al., 2000). Quantitative analyses of oligodendrocyte precursors proliferation and cell death imply that as many as 50% of the newly formed differentiated oligodendrocytes die during normal development (Barres et al., 1992). In vitro, both PDGF and insulin-like growth factors can rescue newly formed oligodendrocytes from cell death, and increasing the amount of PDGF in the postnatal optic nerve reduced cell death in the nerve by up to 90% (Barres et al., 1992). Cell death of newly formed oligodendrocytes occurs in most other regions of the CNS including the cerebral cortex and spinal cord (Trapp et al., 1997). While competition for survival factors likely contributes to cell death in these other regions, oligodendrocyte cell death can be induced by nerve growth factor binding its p75 receptor (Casaccia-Bonnefil et al., 1996; Casaccia-Bonnefil, 2000).

Ultimately, the number of oligodendrocytes in any particular region of the CNS becomes directly matched to the number of axons that require myelination. Such a direct correlation is evident in the increased numbers of oligodendrocytes present in the optic nerve of animals in which the number of optic axons is significantly increased through inhibition of cell death (Burne et al., 1996). Conversely, removal of axons results in a decrease in the number of oligodendrocytes that develop, although the development of the residual cells was relatively normal (Ueda et al., 1999).

3.3. Oligodendrocyte maturation and myelination depends on axons

The final step in the generation of an oligodendrocyte is the development of a mature myelinating phenotype, and this is largely regulated by axonal signals. It seems likely that both soluble and cell mediated signals from adjacent axons are integrated into the developmental profile of oligodendrocyte precursors resulting in cell differentiation, up-regulation of myelin gene expression and formation of the myelin organelle. Candidates for axonally derived soluble factors include FGFs (Bansal et al., 1996; Qian et al., 1997) and thyroid hormone (Barres et al., 1994a,b), while axonal cell surface molecules such as L1, MAG, NCAM and N-cadherin may regulate formation of the myelin sheath (Payne and Lemmon, 1993; Trapp, 1990). Oligodendrocyte maturation is influenced by neuregulins that are expressed on many axons. Neuregulin exposure induces morphological changes in cultured oligodendrocytes (Vartanian et al., 1994). Furthermore, in the absence of the neuregulin receptor ErbB2, while many oligodendrocyte precursors develop, few of these cells mature and those that do fail to interact with axons and do not produce myelin (Park et al., 2001). The generation of a complex structure such as the myelin sheath requires a coordinated response in the myelinating cell. The synthesis and assembly of many myelin specific components such MBP, PLP and GC have to be correctly orchestrated to give rise to myelin (Campagnoni, 1988, 1995; Madison et al., 1999). The functional properties of different myelin proteins are highlighted in relevant mutant animals (Nave, 1995), and a detailed understanding of the regulation of assembly of the myelin sheath remains a major goal. The interactions between the axon and myelinating glial cells are bidirectional and complex. Myelination leads to local changes in the cytoarchitecture of the axon (de Waegh et al., 1992) as well as more systemic changes in the biology of myelinated neurons (Brady et al., 1999).

4. Oligodendrocytes precursors in the adult CNS

Not all oligodendrocyte precursors differentiate during the developmental period. The adult CNS contains a significant number of oligodendrocyte progenitor cells that retain significant proliferative capacity (Wolswijk and Noble, 1989,

1992; Wolswijk et al., 1991). The adult oligodendrocyte precursors differ from those during development in detailed antigenic phenotype and proliferative rate (Wolswijk and Noble, 1989; Wolswijk et al., 1990). Under normal conditions the turnover of these cells is relatively low, and limiting levels of mitogen (Fruttiger et al., 2001) or local cell–cell interactions such as density-dependent inhibition of proliferation (Nakatsujji and Miller, 2001; Zhang and Miller, 1996) may regulate their division. Consistent with this model, exposure of adult cells to growth factors in vitro will convert them to cells with the characteristics of perinatal cells (Wolswijk and Noble, 1992). The presence of significant numbers of oligodendrocyte precursors in the adult CNS (Dawson et al., 2000; Nishyama et al., 1999) raises the question as to whether these cells have functions other than supplying oligodendrocytes during normal turnover or disease. In fact, the ability of adult progenitors to remyelinate in a number of disease conditions such as multiple sclerosis appears to be relatively limited (Chang et al., 2000), although they may be capable of myelin repair under certain conditions (Levine et al., 2001; Reynolds et al., 2001). Further understanding of the biology of oligodendrocyte precursors in the adult CNS should allow these precursors to be effectively utilized to repair the injured or diseased adult CNS.

5. Conclusions

Understanding the development of oligodendrocytes has advanced significantly in recent years. The sites of origin of the precursors, the regulation of commitment to the oligodendrocyte lineage and the control of precursor migration are beginning to be understood. It is clear that the behavior of oligodendrocyte precursors is influenced by multiple different signals. Given the critical nature of myelin for the normal functioning of the adult vertebrate CNS, such diversity in signaling systems may have developed to ensure production of an appropriate cohort of oligodendrocytes. Loss of myelin is associated with a variety of pathological conditions, and the presence of significant numbers of oligodendrocyte precursors as well as neural stem cells in the adult CNS raises the possibility of therapeutic intervention in a number of demyelinating diseases. Detailed understanding of the molecular mechanisms regulating oligodendrocyte development is critical to developing such effective repair strategies.

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