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Regulation of Oligodendrocyte Development

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Abstract

Oligodendrocytes are the cells responsible for the formation of myelin in the central nervous system. Recent studies demonstrated that cells of the oligodendrocyte lineage initially arise in distinct regions of the ventricular zone during early development. These cells or their progeny migrate to developing white matter tracts where they undergo the majority of their proliferation and subsequently differentiate into myelinating cells. Oligodendrocyte-precursor cell proliferation is regulated by a number of distinct growth factors that act at distinct stages in the lineage and the final number of oligodendrocytes in any region of the CNS is regulated by local influences. A density-dependent feedback inhibition of proliferation reduces the responsiveness of the cells to their growth factors and the final matching of oligodendrocyte and axon number is accomplished through the local regulation of cell death. In this review, we discuss the major factors that regulate three distinct stages in the development of the oligodendrocyte lineage: The initial induction of oligodendrocyte progenitors, the regulation of expansion and dispersion of the committed precursor cell population, and the final regulation of oligodendrocyte precursor number through the local inhibition of oligodendrocyte precursor proliferation and cell death.

Index Entries: Myelination; oligodendrocytes; proliferation; migration.

Introduction

The vertebrate central nervous system (CNS) is composed of three major classes of neural cells: neurons, astrocytes, and oligodendrocytes (Peters et al., 1990). Like the majority of other cells in the CNS, oligodendrocytes are generated from the neuroepithelial cells of the neural tube. In the adult nervous system, 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,

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1968). An individual oligodendrocyte is capable of myelinating multiple different axons depending on the specific axon tract (Butt and Ransom, 1989).

Myelination is essential for the normal functioning of the mature CNS. Disruption of CNS myelin through injury, pathological degeneration, or genetic intervention 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 (Prineas, 1985; Raine, 1984), results in rapid loss of motor function. The necessity for continuous myelination along the entire length of an axon requires that the number of oligodendrocytes generated appropriately match the number of axons to be myelinated. Not surprisingly, in any particular region of the CNS, most neurons and astrocytes are generated several days prior to the generation of oligodendrocytes (Skoff et al., 1976a,b) so that oligodendrocytes are among the last cells to mature. Indeed, in most vertebrates the majority of CNS myelination occurs in the first few postnatal weeks of life.

The generation of the correct number of oligodendrocytes involves several steps. First, oligodendrocyte precursors must be induced from cells of the neuroepithelium. Since oligodendrocyte precursors arise a significant distance from presumptive white matter, precursors cells must then actively migrate through the CNS. Driven by defined growth factors, oligodendrocyte precursors undergo extensive proliferation in developing white matter. After a sufficient number of cells have been generated, proliferation is downregulated and 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 (Pfeiffer et al., 1993) has allowed for substantial insights into how many of these processes are controlled in the vertebrate CNS.

Oligodendrocyte Precursors Arise in Restricted Regions of the CNS

Although the majority of spinal cord gliogenesis occurs postnataly (Gilmore, 1971), the onset of oligodendrocyte development begins during early embryogenesis and while myelination occurs throughout CNS white matter, the founder cells of the oligodendrocyte lineage arise in distinct locations in the ventricular zone (Warf et al., 1991).

The best evidence for the localized origin of oligodendrocyte-precursor cells comes from studies in the spinal cord. Oligodendrocyte precursors can be identified 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), and immunological 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 (Noll and Miller, 1993). When placed in culture approx 60% of these proliferating cells differentiate into oligodendrocytes (Noll and Miller, 1993). One of the major oligodendrocyte precursor mitogens is platelet-derived growth factor (PDGF) (Noble et al., 1988; Richardson et al., 1988) and oligodendrocyte precursors express the PDGFα Receptor (PDGFα-R) (Pringle et al., 1992). *In situ* hybridization has demonstrated that cells expressing the PDGFα-R are initially seen in the developing spinal cord in the same region as the proliferating glial precursors (Pringle and Richardson, 1993). Similarly, a distinct population of cells expressing mRNA for the myelin genes CNP (2′, 3′-cyclic-nucleotide 3′-phosphodiesterase) (Yu et al., 1994) and DM20, an isoform of the major myelin proteolipid protein (PLP) gene, have been localized to the ventral ventricular zone of the developing mammalian spinal cord (Timsit et al., 1995).

In the chick spinal cord oligodendrocyte precursors express an antigen recognized by the

O4 monoclonal antibody (MAb) (Ono et al., 1995). These O4+ cells initially appear around stage 29, several days after the generation of motor neurons is complete and are initially localized as two foci on either side of and immediately dorsal to the floor plate (Ono et al., 1995; Orentas and Miller, 1996). The onset of the O4+ phenotype occurs while the cells retain a ventricular attachment as well as other characteristics of immature neuroepithelial cells (Ono et al., 1995). In vitro, addition of the O4 MAb and complement to chick spinal cord cultures specifically eliminates the avian oligodendrocyte lineage by complement-mediated cell lysis (Ono et al., 1995). Taken together, these observations indicate that the earliest cells in the oligodendrocyte lineage express the O4 antigen.

The localized origin of oligodendrocyte precursors is not restricted to the spinal cord. In more rostral regions of the CNS oligodendrocyte precursors arise in specific regions of the ventricular and subventricular zone at particular stages of development (Timsit et al., 1995; Ono et al., 1977). For example, a group of cells in the ventricular mantle zone of the ventral diencephalon of the E13 rat express mRNA for the PDGFα-R (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). It is unclear, however, whether expression of the PDGFα-R within the CNS gives an accurate and complete representation of the distribution of oligodendrocyte precursors. Several studies have suggested that regions of the CNS that lack detectable expression of PDGFα-R+ cells contain oligodendrocytes (Warrington and Pfeiffer, 1992) and have the capacity to give rise to oligodendrocytes when grown in isolation (Goyne et al., 1994). Similarly, a variety of cell types, including distinct subpopulations of neurons and astrocytes, express PDGFα-R during development (Oumesmar et al., 1997). In the avian system, the expression of the O4 antigen appears to be directly correlated with the ability of the tissue to give rise to oligodendrocytes in isolation. For example, explant cultures of dorsal spinal cord fail to develop oligodendrocytes if isolated prior to stage 32/33 (Ono et al., 1995). In vivo, O4+ cells are first seen entering the dorsal spinal cord at stage 33 correlating directly with the capacity of that region to give rise to oligodendrocytes. Likewise, in more rostral regions of the CNS, areas of the neural tube that contain O4+ cells such as the ventral metencephalon or optic chiasm give rise to oligodendrocytes in isolation, whereas areas that do not contain O4+ cells fail to develop oligodendrocytes in isolation (Ono et al., 1977)

The initial appearance of spinal cord oligodendrocytes is dependent on local influences from the adjacent notochord (Orentas and Miller, 1996; Pringle et al., 1996) (Fig. 1). The notochord, a transient mesodermally derived structure, is located ventral to the developing neural tube. Signals from the notochord have been shown to be involved in the formation of the dorsal/ventral axis in the developing CNS and the subsequent specification of distinct spinal cord cell types found in the ventral spinal cord (Van Straaten et al., 1988, 1989; Jessell and Dodd, 1990). Transplantation of an additional notochord adjacent to the dorsal spinal cord resulted in the local induction of an ectopic cluster of oligodendrocyte precursors in chick and *Xenopus* embryos (Orentas and Miller, 1996; Maier and Miller, 1997). The ability of the transplanted notochord to induce oligodendrocytes was restricted to a period during early embryonic chick development that reflected both a reduction in the signaling capacity of the notochord and a temporal loss of responsiveness of the dorsal spinal cord cells (Orentas and Miller, 1996). The notochord 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). Similarly, oligodendrocytes failed to develop in the spinal cord adjacent to the

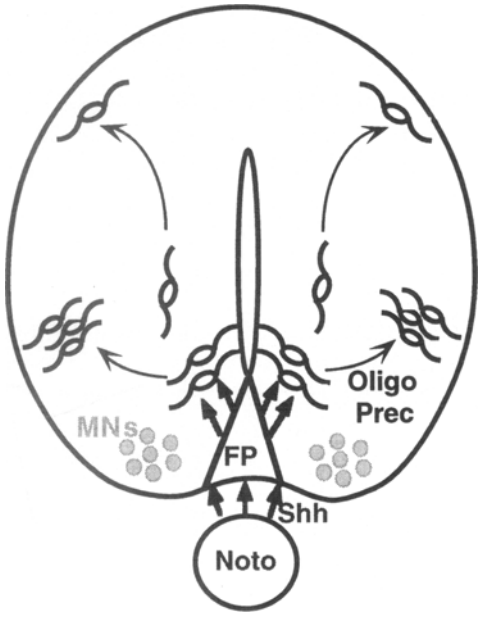

Fig. 1 Schematic representation of a model for the development of oligodendrocyte in the spinal cord. Soluble signals from the notochord (Noto) including Sonic hedgehog (Shh) directly or indirectly induce the local development of floor plate (FP) motor neurons (MN) and oligodendrocyte precursors (Oligo Prec) in the ventral ventricular region of the spinal cord. The oligodendrocyte precursors then migrate dorsally and radially to populate developing spinal cord white matter. Oligodendrocyte precursors proliferate extensively in white matter until a critical density is reached. Further proliferation is inhibited by a density-dependent feedback mechanism and local cell number is regulated through cell death. Maturation of oligodendrocytes results in myelination of spinal cord axons.

site of notochord ablation at embryonic or larval stages (Maier and Miller, 1997).

Many of the inductive properties of the notochord appear to be caused by 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 motor neurons in a concentration-dependent manner (Roelink et al., 1994, 1995). Oligodendrocytes can be induced in vitro at similar concentrations of Shh required for the induction of motor neurons (Pringle et al., 1996) (Fig. 1), suggesting that the development of these two cell types is closely linked.

The hypothesis that the development of oligodendrocytes and motor neurons is closely linked is supported by cell-lineage analysis. In vitro studies of cerebral cortex cultures suggest that neurons and oligodendrocytes share a common lineage (Williams et al., 1991). In chick spinal cord, clonal studies further support the hypothesis that motor neurons and oligodendrocytes share a common precursor cell (Leber et al., 1990; Leber and Sanes, 1991). Thus, signals that regulate the induction of motor neurons would also regulate the induction of oligodendrocytes. Three general models may explain the choice of different cell fates from a single precursor. First, a neuroepithelial stem cell may undergo asymmetric divisions giving rise to a neuron and another stem cell. After a defined number of divisions, the stem cell then intrinsically gives rise to oligodendrocyte precursors. Alternatively, a neuroepithelial cell may give rise to neurons through a constitutive pathway unless acted on by environmental signals (Shah et al., 1994), altering the fate of subsequently generated cells to that of an oligodendrocyte. A more likely hypothesis is that the choice between and neuron or oligodendrocyte fate is determined stochastically, and the survival or maintenance of distinct precursors is regulated by local environmental factors. If motor neurons were a source of oligodendrocyte-precursor survival factors then ventralization of the spinal cord would lead to the local generation of motor neurons and subsequently oligodendrocytes.

The intrinsic capacity of neuroepithelial cells to give rise to oligodendrocytes is not restricted to specific regions of the neural tube, but rather during normal development this capacity is only manifested in discrete locations. For example, dorsal spinal cord cells have the capacity to give rise to oligodendro-

cytes under the influence of the notochord or Shh (Orentas and Miller, 1996; Pringle et al., 1996). In addition, chick/quail chimera studies suggest that dorsal spinal cord cells may actually contribute to the cohort of spinal cord oligodendrocytes during later development (Cameron-Currey and LeDouarin, 1995). During normal development, however, the majority of the dorsal cells do not receive the appropriate instructive signals to become oligodendrocytes and are thus diverted to other neural cell fates. Stem-cell studies in the cerebral cortex indicate that the majority of stem cells have the capacity to give rise to oligodendrocytes (Davis and Temple, 1994) and that increasing concentrations of fibroblast growth factor 2 (FGF2) result in increased numbers of oligodendrocytes among the progeny (Qian et al., 1997). Thus, it is possible that growth factors such as FGF2 may be responsible for the switch of cell fate in cerebral cortical stem cells (Qian et al., 1997). The repertoire of molecular signals required for the induction of oligodendrocytes in other regions of the CNS remain to be determined.

Myelination of Developing White Matter Is Dependent on Oligodendrocyte Precursor Migration

The spatially discrete origins of oligodendrocytes means that successful myelination of developing white matter tracts is critically dependent on the dispersal of the progenitor cells from their source. This dispersal involves a significant long-distance migration of progenitor cells (Qian et al., 1997). Indirect evidence suggests that oligodendrocyte precursors migrate into the rat optic nerve from the brain (Small et al., 1987; ffrench-Constant et al., 1988) and that this migration is inhibited at the nerve/retina junction (ffrench-Constant et al., 1988). In the spinal cord, oligodendrocyte precursors migrate both laterally and dorsally from their origin in the ventral ventricular zone to populate the developing white matter (Ono et al., 1995; Canceron-Curry and LeDouarin, 1995). (Fig. 1), whereas in the metencephalon of the chick, oligodendrocyte precursors migrate laterally and dorsally from a focus in the medial pons (Ono et al., 1997). The nature of the cellular terrain navigated by the migrating oligodendrocyte precursor cells is unknown. By analogy with the migration of immature neurons, the radial migration of oligodendrocyte precursors could be guided through interactions with radial glial cells (Rakic, 1971, 1972; Hatten, 1990). Migration of oligodendrocyte precursors along the optic nerve and dorsally in the spinal cord would appear to require an alternative cellular substrate. One attractive candidate is that oligodendrocyte precursors utilize axons as their cellular terrain during migration. Thus, retinal ganglion cell axons may support migration down the optic nerve, whereas circumfrential axons support migration through the intermediate zone to the dorsal spinal cord. Finally, the rostral-caudal dispersal of oligodendrocyte precursors would occur along ascending and descending tracts within the white matter.

The majority of long-distance migration of oligodendrocyte precursors is accomplished by immature cells. Transplantation of purified populations of oligodendrocyte precursors at different stages of maturation indicate that immature oligodendrocyte precursors defined by expression of MAb A2B5 immunoreactivity are far more migratory than more mature cells defined by expression of MAb O4 immunoreactivity (Warrington et al., 1993). Similarly, in vitro, A2B5+ immature bipolar cells are more motile than O4+ cells when grown on a monolayer of type 1 astrocytes (Noble et al., 1988). During normal development, retrospective analysis of the nature of the oligodendrocyte precursors that initially migrate into the cerebellum suggest that they are highly immature (Goyne et al., 1994).

The molecular mechanisms mediating oligodendrocyte precursor migration are not well understood. Chemotactic in vitro assays

suggest that soluble factors such as PDGF may act as chemoattractants for oligodendrocyte precursors (Armstrong et al., 1991). Cell-surface components such as adhesion molecules have been also been proposed to play a role in regulating migration (Kiernan and ffrench-Constant, 1993; Kiernan et al., 1996). In explant studies, removal of NCAM-associated polysialic acid (PSA) inhibits the dispersal of oligodendrocyte precursors (Wang et al., 1994, 1996). Oligodendrocyte precursors also express an array of integrin receptors that may play important roles in regulation of both migration and cell differentiation (Milner and ffrench-Constant, 1994). Since differentiated oligodendrocytes are not migratory, it is likely that the control of differentiation and migration are closely linked. Local inhibitors of oligodendrocyte precursor migration may also help to regulate the dispersal of these cells throughout the CNS. The extracellular matrix molecule tenascin-C is found in distinct regions of the CNS that correlate with barriers to precursor migration such as the optic nerve/retina junction (Bartsch et al., 1994) In vitro, tenascin-C blocks oligodendrocyte precursor migration by both adhesion-dependent and adhesion-independent mechanisms (Kiernan et al., 1996). Thus, oligodendrocyte precursors may be funneled into distinct regions of the CNS where myelination is required through the combination of motility stimulating, chemoattractant, and inhibitory influences.

Expansion of the Oligodendrocyte Population Is Regulated by a Variety of Growth Factors

The majority of oligodendrocyte-precursor proliferation occurs in developing white matter tracts after most long-distance cell migration has taken place. The regulation of oligodendrocyte-precursor proliferation has been extensively studied using a variety of in vitro models including oligodendrocyte precursors derived from the rat optic nerve (Raff et al., 1990).

The earliest well-characterized cells in the rodent oligodendrocyte lineage express cell-surface antigens recognized by the monoclonal antibody A2B5 (Raff et al., 1984; Raff, 1989). In vitro, these cells are bipotential and 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 (Lillien et al., 1990; Hughes et al., 1988). Whether O-2A progenitors manifest this type of phenotypic plasticity in the normal CNS is currently unclear. Oligodendrocyte precursors mature into pro-oligodendroblasts and begin to express cell-surface antigens recognized by the monoclonal antibody O4, which includes sulfated galactocerebroside (sulfatide) and a novel POA antigen (Pfeiffer et al., 1983; Bansal et al., 1992). Pro-oligodendroblasts are multiprocessed, less motile, and no longer retain the capacity to give rise to type-2 astrocytes (Pfeiffer et al., 1983; Fok-Seang and Miller, 1994; Gard et al., 1995). Immature and pro-oligodendroblasts 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 A2B5+ cells is platelet-derived growth factor (PDGF) (Noble et al., 1988; Richardson et al., 1988) and A2B5+ oligodendrocyte precursors express the PDGFα-R (Pringle et al., 1992). In the intact CNS, PDGF is ubiquitously distributed, being synthesized by both astrocyte and neuronal populations, (Yeh et al., 1991). A2B5+ cells also proliferate in response to basic FGF (bFGF), which appears to be widely distributed in the embryonic CNS but the levels decrease significantly during development. In contrast to immature A2B5+ cells, O4+ pro-oligodendroblasts do not proliferate in response to PDGF, but retain a proliferative response to

bFGF (Fok Seang and Miller, 1994; Gard and Pfeiffer, 1993). The differentiation of oligodendrocyte precursors is characterized by a rapid decline in proliferation and expression of the major myelin glycolipid glactocerebroside (GC) (Raff et al., 1978). Differentiated GC+ oligodendrocytes exhibit a multiprocessed phenotype and no longer proliferate in response to PDGF or bFGF. Continued maturation of oligodendrocytes results in the elevated expression of major myelin proteins such as myelin basic protein (MBP) and proeteolipid protein (PLP).

Not only do growth factors such as PDGF and bFGF promote the proliferation of oligodendrocyte precursors, but they also regulate their differentiation (Bogler et al., 1990; McKinnon et al., 1990). The expression of PDGF-αRs on immature oligodendrocyte precursors is upregulated by bFGF. In combination with PDGF, bFGF blocks the maturation and promotes extended proliferation of oligodendrocyte precursors (Bogler et al., 1990; McKinnon et al., 1990). Pro-oligodendroblasts, which continue to proliferate in response to bFGF, are also blocked in their differentiation by bFGF (Gard and Pfeiffer, 1993; Mayer et al., 1993). 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 oligodendrocyte lineage, FGF-receptor 2 is expressed predominantly in differentiated oligodendrocytes, whereas FGF-receptor 3 is predominantly expressed in pro-oligodendroblasts (Bansal et al., 1996). The differential expression of distinct FGF receptors may underlie the different responses of oligodendrocyte lineage cells during progression through the lineage (Bansal et al., 1996).

Several other factors have been suggested to regulate the development of oligodendrocytes in vitro. The neurotrophin NT3 has been proposed to be mitogenic for purified optic nerve (Barres et al., 1994), but not spinal cord oligodendrocytes (Robinson and Miller, 1996). In some conditions, NT3 may be required for extensive PDGF-driven proliferation (Barres et al., 1994) but can also suppress oligodendrocyte generation in the presence of PDGF (Ibarrola et al., 1996). Retinoic acid and its derivatives appear to inhibit progression of immature oligodendrocyte through the lineage (Noll and Miller, 1994) but at later stages to promote the differentiation of oligodendrocytes (Barres et al., 1993). Thyroid hormone (T3) and its derivatives enhance the differentiation of oligodendrocytes (Barres et al., 1993) although the mechanism of action is currently unclear. One role of T3 appears to be to increase the number of oligodendrocytes once they have begun to appear rather than regulate their initial appearance (Ibarrola et al., 1996). How all these different factors operate or cooperate during normal development, and their relative importance awaits molecular dissection in a more physiological system.

The Local Number of Oligodendrocyte Precursors Is Regulated by a Density-Dependent Feedback Inhibition of Cell Proliferation and Cell Death

The number of oligodendrocytes in a mature axon tract must be sufficient to myelinate all of the appropriate axons. Although an individual oligodendrocyte can wrap many different axons, sufficient numbers of oligodendrocytes must be generated to ensure that all the axons destined to be myelinated are ensheathed along their entire length. A number of mechanisms may regulate the final number of oligodendrocytes in a particular region of the CNS. Analysis of rat optic nerve oligodendrocyte precursors suggests that individual cells undergo a defined number of cell divisions so that single-cell clones cease proliferation and differentiate at approximately the same time (Temple and Raff, 1986;

Raff et al., 1988). 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). Thus, the total number of oligodendrocytes in the optic nerve is directly related to the initial number of progenitor cells and their number of divisions. It is unlikely, however, that the genesis of oligodendrocytes is totally regulated by this simple intrinsic clock (Ibarrola et al., 1996; Zhang and Miller, 1995). Several other mechanisms may also influence oligodendrocyte-precursor proliferation. Conditioned medium from cultured oligodendrocytes inhibits the proliferation of oligodendrocyte precursors and this effect may be mediated in part by transforming growth factor B (Louis et al, 1992; McKinnon et al., 1993). However, neither of these mechanism are obviously capable of regulating the local number of oligodendrocytes in a tract or specific region, such as occurs in the developing CNS.

The local control of proliferation of spinal cord oligodendrocyte precursors appears to be mediated through a contact-dependent inhibition of cell proliferation (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. This normalization of cell number reflects a feedback inhibition of precursor expansion at high density, is cell-type specific, and is not mediated through the release of a soluble factor (Zhang and Miller, 1996). Local autocrine signals that regulate the expansion of oligodendrocyte precursors would allow for fine temporal/spatial regulation of oligodendrocyte development in complex regions of the CNS such as spinal cord. One model for the regulation of spinal cord oligodendrocyte number compatible with these observations, is that oligodendrocyte precursors arise in specific regions of the ventricular zone. The progeny of these cells then migrate laterally to populate the developing white matter. The precursors continue to proliferate in white matter and begin to mature (Fig. 1). The local density of precursors increases through proliferation until, depending on the size and number of available axons, a critical density is reached. As a result of this elevated density, further expansion of oligodendrocyte precursors is inhibited by a density-dependent feedback inhibition of precursor expansion. Oligodendrocyte precursors subsequently differentiate and myelinate axons in their vicinity.

The molecular mechanism that regulates the density-dependent inhibition of oligodendrocyte proliferation are unknown. However the concept that cell proliferation may be regulated in a density-dependent fashion is not new (Wieser et al., 1990). Studies on several cell types indicate that specific cell-surface molecules may regulate autocrine proliferation in a contact-dependent fashion and many of these signals will likely act on regulators or inhibitors of the cell cycle.

The function of the density-dependent inhibition of oligodendrocyte precursor proliferation may not be restricted to early developmental stages. The adult CNS contains a significant number of oligodendrocyte progenitor cells that retain significant proliferative capacity (Wolswijk and Noble, 1989; Wolswijk et al., 1991; Noble and Wolswijk, 1992). Under normal conditions the turnover of these cells is relatively low, and local cell–cell interactions may act to control their proliferation. Similarly, tumors arising from the oligodendrocyte lineage both during development and in the adult may result from aberrant signaling through the density-dependent inhibition pathway. Elucidation of the molecular mechanisms mediating this inhibition will allow the direct test of these hypotheses.

Density-dependent inhibition feedback of cell proliferation is not the only regulator of local oligodendrocyte cell number in developing white matter, rather this mechanism may operate to control exuberant precursor proliferation. Studies in the rat optic nerve suggest

that the final number of oligodendrocytes may be controlled by competition for local survival factors including PDGF (Barres and Raff, 1994; Barres et al., 1992). Analysis of oligodendrocyte cell death in the developing rat optic nerve suggest that as many as 50% of newly formed oligodendrocytes die during normal development (Barres et al., 1992). In vitro, both PDGF and insulin-like growth factors can rescue oligodendrocytes from cell death such that increasing the amount of PDGF in the nerve reduced oligodendrocyte lineage cell death by up to 90% (Barres et al., 1992). Although, death of cells of the oligodendrocyte lineage has been reported in other regions of the CNS, including spinal cord, it is currently unclear whether this is of the same order of magnitude as seen in the optic nerve. Thus, the combination of the density-dependent regulation of oligodendrocyte-precursor proliferation and the subsequent control of cell death, act in concert to regulate the total number of oligodendrocytes in any specific region of the CNS.

Oligodendrocyte Differentiation and Myelination Are Controlled by Axon–Glial Interactions

The final step in the generation of a myelinating cell is the development of a mature myelinating phenotype. What controls the switch from a proliferative precursor to a myelinating cell is not clear. In optic nerve oligodendrocyte precursors, an intrinsic clock that senses, either the number of cell divisions or time may regulate the cessation of proliferation of clonally related progenitor cells. (Temple and Raff, 1986; Raff et al., 1985). In more complex regions of the CNS, such as the spinal cord, this transition appears not to be controlled through a similar intrinsic clock. Clonal analysis of oligodendrocyte differentiation in rat spinal cord indicates that the majority of clones contain both proliferating and nonproliferating progenitor cells as well as differentiated oligodendrocytes (Zhang and Miller, 1995).

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, upregulation of myelin gene expression, and formation of the myelin organelle. Candidates for axonally derived soluble factors include FGFs (Qian et al., 1997; Bansal et al., 1996) and thyroid hormone (Barres et al., 1994), whereas axonal cell-surface molecules such as L1, MAG, NCAM, and N-cadherin may be important in regulating the formation of the myelin sheath (Trapp, 1990; Payne and Lemmon, 1993). Clearly the generation of a complex organelle 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 the myelin organelle (Campagnoni and Macklin, 1988; Campagnoni, 1995) and a detailed understanding of the regulation of assembly of the myelin sheath remains a major goal.

Conclusions

Recent advances have provided remarkable insight into the early development of oligodendrocytes. Much is known of the sites of origin, regulation of proliferation, migrational properties, and control of differentiation of oligodendrocyte precursors. One striking feature that emerges is that oligodendrocyte precursors have the capacity to respond to broad range of different signals. Which of these signals is essential for normal oligodendrogenesis in vivo remains to be resolved. Given the essential nature of the myelin sheath for the normal functioning of the adult vertebrate CNS, it may be that the diversity in signaling systems developed to ensure the correct production of an appropriate cohort of CNS myelinating cells.

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