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THE REACTIONS AND ROLE OF NG2 GLIA IN SPINAL CORD INJURY

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Abstract

Oligodendrocyte precursor cells (OPCs) react rapidly to brain and spinal cord injuries. This reaction is characterized by the retraction of cell processes, cell body swelling and increased expression of the NG2 chondroitin sulfate proteoglycan. Reactive OPCs rapidly divide and accumulate surrounding the injury site where they become major cellular components of the glial scar. The glial reaction to injury is an attempt to restore normal homeostasis and reestablish the *glia limitans* but the exact role of reactive OPCs in these processes is not well understood. Traumatic injury results in extensive oligodendrocyte cell death and the proliferating OPCs generate the large number of precursor cells necessary for remyelination. Reactive OPCs, however, also are a source of axon-growth inhibitory proteoglycans and may interact with invading inflammatory cells in complex ways. Here, I discuss these and other properties of OPCs after spinal cord injury. Understanding the regulation of these disparate properties may lead to new therapeutic approaches to devastating injuries of the spinal cord.

Keywords

oligodendrocyte precursor cell; NG2; spinal cord injury; regeneration; remyelination; inflammation

Injury to the brain or spinal cord induces rapid morphological and physiological changes among the glial components at the site of injury. These acute glial reactions are attempts by the nervous system to stabilize the injured tissue and re-establish physiological homeostasis and the *glial limitans*. Following an initial stage of injury-induced glial cell death, oligodendrocyte precursor cells (OPCs) shorten their normally long cell cycle, proliferate and accumulate at and surrounding the injury site. Microglia become activated, migrate to the injury site and slowly proliferate and astrocytes become hypertrophic and increase their expression of multiple proteins including their major intermediate filament protein, glial fibrillary acidic protein (GFAP). Concurrent with these glial reactions, monocytes and other myeloid cells invade the nervous system through the disrupted brain-blood barrier (BBB). These hematopoietic cells together with activated microglia develop into macrophages that

phagocytose cellular debris and secrete a variety of pro- and anti-inflammatory cytokines and chemokines. These acute reactions eventually resolve into a complex tissue known as the glial scar.

In this review, I will review and discuss the injury-induced reactions of a population of unusual adult glia known alternatively as OPCs, NG2 cells and polydendrocytes. For convenience, I will refer to these CNS glial cells as OPCs or NG2+ OPCs in distinction from NG2+ cells which refers to cells that express the NG2 chondroitin sulfate proteoglycan (CSPG4), but may not necessarily belong to the oligodendrocyte lineage. Although much of the data to be reviewed comes from studies involving experimentally induced injury to the adult rodent spinal cord (SCI), OPCs react to most brain pathologies including stroke, demyelinating disease and neurodegenerative disorders and the common features of these reactions will also be discussed as they may offer clues to the functions of these unusual cells in both the normal and diseased CNS. The reader is referred elsewhere to recent reviews of the injury reactions of microglia, astrocytes and myelinating oligodendrocytes (Almad, et al., 2011, David, Kroner, 2011, Karimi-Abdolrezaee, Billakanti, 2012).

Identification and characterization of NG2 cells in vivo

Since their initial description in the 1980s (Stallcup Beasley, 1987, Levine Stallcup, 1987, Curtis et al., 1988, Levine, et al., 1993, Dawson et al., 2000), the functions and properties of OPCs, while much investigated, still remain somewhat mysterious as is their role in CNS injury. In vivo and in vitro, OPCs can be identified using a variety of antigenic markers including the NG2 proteoglycan (CSPG4), the PDGFα receptor (PDGFαR), GD3 ganglioside, A2B5 ganglioside and 2', 3' cyclic nucleotide 3'-phosphodiesterase (CNPase). The development of transgenic animals expressing fluorescent proteins under control of cell type specific promoter elements such as NG2 and the PDGFαR (Rivers, et al., 2008, Zhu, et al., 2008, Kang et al., 2010) not only has enabled numerous studies of OPC development and plasticity, but also has enabled live imaging of OPCs under physiological and pathological conditions.

Although no single marker or transgenic mouse is absolutely specific for a single cell type, there is general agreement that NG2+ cells, including OPCs, proliferate and accumulate after a variety experimental injuries to the mouse or rat brain or spinal cord. NG2+ OPCs are present in human and non-human primate brain and spinal cord (Peters. Sethares 2004, Wilson et al. 2006) and although their reactions to physical injury have not been studied extensively, there is increased expression of the NG2 CSPG at sites of spinal cord injury in humans (Buss, et al., 2009). In uninjured animals, OPCs are widely distributed in both the gray and white matter, express both the PDGFαR and NG2 CSPG and function as the precursors of myelinating oligodendrocytes (for review, see Nishiyama et al., 2009). After injury to the brain or spinal cord, these cells proliferate and accumulate at the injury site. They increase their expression of the NG2 CSPG, withdraw their finely branched processes and the cell body enlarges.

Whether all the NG2+ cells that accumulate after SCI are OPCs is controversial. Since both the NG2 CSPG and the PDGFαR are also expressed by some pericytes (Ozerdem et al.,

2001, Pringle et al., 1992, Kang et al., 2010) and since pericytes can give rise to the stromal elements within a contusion lesion (Goritz, et al., 2011), not all the identified cells may belong to the oligodendrocyte lineage. Furthermore, while almost all NG2+ cells in normal brain or spinal cord tissue express the PDGFαR, not all the NG2-expressing cells that accumulate at sites of spinal cord contusion injuries or cortical stab wounds do so (Hampton, et al., 2004). The NG2 CSPG but not the PDGFαR is also expressed on a small number of macrophages found within the lesion cavity after SCI (Jones et al., 2002) but not on microglia adjacent to the lesion site (Zai, Wrathall, 2005). Macrophages that invade excitotoxic lesions of the hippocampus or ischemic lesions due to transient occlusion of the middle cerebral artery also express the NG2 CSPG (Bu et al., 2001, Matsumoto, et al., 2008).

Olig2 is a basic helix-loop-helix transcription factor expressed in motor neurons and OPCs in developing animals and in OPCs and oligodendrocytes in adults (Zhou Anderson, 2002, Lu et al., 2002, Ligon, et al., 2006). After stab wound injury to the cortex, there is a large increase in the number of cells stained with anti-olig2-antibodies, many of which also express NG2 (Buffo et al., 2005). Because olig2 is also expressed on GFAP+ astrocytes, CC1+ oligodendrocytes and a population of marker negative cells, one cannot conclude that all the olig2+ cells after injury are OPCs.

The OPC reaction to injury has also been studied in several lines of transgenic animals expressing fluorescent proteins under control of the NG2 promoter Komitova, et al., 2011), the PDGFαR promoter (Hughes, et al., 2013) and the 2', 3' cyclic nucleotide 3'-phosphodiesterase (CNPase) promoter (Lytle et al., 2009). Both stab wounds to the brain and contusion injuries to the spinal cord lead to local increases in the number of fluorescent cells, many but not all of which have the antigenic profile of OPCs.

Because of the inability to unequivocally identify OPCs in tissue sections, it is difficult to accurately measure the extent of OPC accumulation after SCI and estimates vary considerably. For example Rabchevsky et al. (2007) reported a 2-fold in increase in the number of NG2+ cells in the ventral lateral funiculus of rats at 2 days after a contusion lesion. Similar increases of 2–3-fold were reported by Rosenberg et al. (2001) for contusion injuries to rat spinal cord whereas McTigue et al (2001) reported a more modest increase. These increases in the number and density of NG2+ cells surrounding the lesion epicenter were maintained for as long as 42 days (Rabchevsky et al., 2007). Using a metric of NG2 stained area per slide, McTique et al. (2006) reported 3–5-fold increases within lesioned tissue that reached as much as 10-fold at long survival times. Some of this increase is likely due to NG2 CSPG accumulation within the extracellular matrix as well as expression of NG2 by macrophages, especially in the lesion epicenter. The idea that some of the NG2+ cells are macrophages is substantiated by the study of Lytle et al., (2009) who examined the reaction of CNP-eGFP cells after contusion injuries in mice. In addition to an increase in the number of eGFP+, NG2+ cells rostral and caudal to the lesion epicenter, they found a small population of NG2+, eGFP− cells within the lesion epicenter. Unlike the cells surrounding the lesion core, these cell did not bind marker antibodies characteristic of the oligodendrocyte lineage suggesting that they were macrophages that had invaded the damaged CNS.

The reactions of OPCs to cortical stab wounds has been studied extensively especially using transgenic reporter mice. Buffo et al (2005) reported a 3-fold increase in the density of olig2-eGFP+ cells surrounding a cortical stab at 7dpl (days post-lesion) whereas Tatsumi et al., (2008) reported a 5–6-fold increase. Approximately half of these cells expressed marker antigens associated with either OPCs, astrocytes or oligodendrocytes but half were not easily identifiable (Buffo, et al., 2005). Komitiva et al. (2011) showed an increase in eGFP+ cells after stab wound injuries in a line of NG2creBAC:ZEG mice, a small number of which expressed antigens characteristic of astrocytes as did 20% of the olig2- eGFP+ cells studied by Tatsumi et al. (2008). These studies suggest that cells of the oligodendrocyte lineage may be phenotypically plastic especially after injury. This topic has been much debated (Richardson et al., 2011) and is discussed in other reviews in this issue. The fate of proliferating OPCs and NG2+ cells will be discussed below.

In the uninjured CNS, OPCs are regularly spaced with little cell-cell contact (Hughes, et al., 2013). This distribution, known as tiling, is maintained via homotypic repulsion and an individual filopodium retracts upon contact with a filopodium of a neighboring cell. The high density accumulation of OPCs after injury indicates that the normal mechanisms responsible for their tiling no longer function. In other systems, homotypic repulsion is mediated by Dscam (for review, see Cameron, Rao, 2010), but little is known about Dscam expression in normal or reactive OPCs. Different surface properties of reactive OPCs as well as adhesive interactions with the extracellular matrix that accumulates at injury sites could be responsible for the altered self-avoidance behavior of OPCs after SCI.

Based on the above discussion, I suggest that some caution be applied when using single markers to identify cells as OPCs within the damaged spinal cord or brain. One cannot exclude the possibility that marker expression may be altered relative to uninjured tissue. Therefore, I suggest the use of multiple markers such as both the OPC-specific promoter driven expression of fluorescent proteins and antigenic markers. There is general and widespread agreement that OPCs rapidly accumulate at the lesion site after a variety of CNS experimental injury paradigms and that they are major components of the glial scar. Quantitative differences in the extent of cell accumulation are likely due to different lesion protocols, cell labeling methods and different means of cell identification. This increase in cell number raises important questions regarding the extent of proliferation, the identification of potential mitogenic factors, the fate of the dividing OPCs and the consequences of OPC accumulation for wound healing and axonal and glial repair. These will be discussed below.

OPC proliferation after injury

OPCs are the major dividing cell of the CNS (Dawson et al., 2003) and the cell cycle time in adult animals is estimated at 9 days in the post-natal day 60 corpus callosum and 18 days in the cortex. This increases as animals age reaching 72 and 76 days in the corpus callosum and cortex respectively (Psachoulia, et al., 2010). The long cell cycle of cortical OPCs is characterized by a prolonged G1 phase (Simon, et al., 2011). The injury-induced increases in OPC density described above are mostly due to proliferation although short distance cell migration into areas of OPC cell death cannot be excluded (Hughes, et al., 2013). The

accumulations of microglia and reactive astrocytes, however, might restrict OPC migration as the injury resolves. Pulse BrdU labeling of either rats or mice after contusion or dorsal hemisection injuries shows that the initiation of the incorporation of BrdU is rapid, increasing as early as 1 dpl and reaching a maximum between 3 and 5 dpl (McTigue et al., 2001, Zai, Wrathall, 2005, Horkey et al., 2006, Lytle et al., 2006, Tripathi, McTigue, 2007). Lower levels of OPC proliferation can continue for as long as 4 weeks post-injury (McTique et al., 2001). The mitogenic response of OPCs to stab wounds of the cortex or cerebellum follows a similar time course (Levine, 1994, Hampton et al., 2004). At early post-lesion stages (ie, 1–7 days dpl), most BrdU-incorporating cells express markers of OPCs such as NG2 or olig2 (Buffo et al., 2005). In the injured spinal cord, proliferating OPCs are found close to the lesion site and are particularly enriched in the penumbra region but at later post-injury time points, proliferation can occur in the spared white matter (Hesp et al., 2015). Curiously, after some lesions, the proliferation of OPCs may be more robust in the spared gray matter than spared white matter (Horkey et al., 2006, Tripathi, McTigue, 2007) whereas OPC proliferation in uninjured tissue is greater in the white matter than the gray matter (Dawson et al., 2003, Dimou et al, 2008).

Local conditions at the injury site are likely responsible for this enhanced cell proliferation and several well characterized mitogenic and trophic factors for OPCs including platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), ciliary neurotrophic factor (CNTF), leukemia-induced growth factor (LIF) are increased at sites of spinal cord injury (Hesp, et al., 2015, Hawryluk, et al., 2012, Lee et al. 1998, Tripathi, McTigue, 2009, Zai, et al., 2005). The role of these endogenous growth and trophic factors in vivo is difficult to ascertain since changes in receptor levels, intracellular signal transduction mechanisms and the expression of endogenous antagonists and other inhibitory factors can alter their functions. Most studies of growth and trophic factors after SCI have focused on the exogenous application of these diverse molecules to the damaged spinal cord and analyzing their effects on functional recovery. For example, the infusion of mixtures of endogenous growth factors increases the number of OPCs after injury (Karimi-Abdolrezaee, et al., 2012a). For more detail, the reader is referred to several recent reviews (Harvey, et al., 2015, Boyce, Mendell, 2014, Tetzlaff et al., 2011). NT3 can also be mitogenic to OPCs, particularly in combination with PDGF (Barres, et al., 1994) but NT3 levels decline after brain injury (Ip et al., 1993). The morphogen sonic hedgehog (SHH) is produced by astrocytes after brain injury (Amankulor et al., 2009) and it may promote OPC proliferation and remyelination in the injured spinal cord, especially when applied together with NT3 (Thomas et al., 2014). More recently, a role for Wnt signaling in the injury-induced proliferation of OPCs has been established. Both multiple Wnt ligands and their receptors are increased at sites of SCI (Fernandez-Martinos, et al., 2011, Gonzales, et al., 2012). Suppressing canonical Wnt signaling by genetic deletion of β-catenin specifically in OPCs prior to contusion injury leads to reduced proliferation of OPCs and reduced accumulation of OPCs in the lesion penumbra (Rodriguez, et al., 2014). The new mouse model used in these studies provides an opportunity to explore the consequences of a reduced OPC reaction to injury and may provide useful insights into OPC function in the damaged CNS (see below).

Lastly, the normal homeostatic mechanisms that control OPC and oligodendrocyte number may also contribute to the enhanced proliferation of OPCs after injury. In vitro, OPCs proliferation is reduced by contact inhibition as cells grow to high densities (Zhang, Miller, 1996) and similar homeostatic mechanisms control cell density and proliferation in the uninjured mouse cortex in vivo (Hughes et al., 2013). When a small laser lesion of the cortex kills OPCs, adjacent cells proliferate and migrate short distances into the vacated space. The extensive OPC cell death after SCI may be a sufficient stimulus for the proliferation of OPCs adjacent to the injury site that subsequently accumulate in the injury penumbra.

OPCs and inflammation

Although considered “immunologically privileged”, the breakdown of the BBB after SCI and the resulting influx of leukocytes along with the activation of resident microglia and astrocytes leads to widespread inflammation. Inflammation, in turn, contributes to the glial and neuronal cell death associated with SCI and is responsible for much of the secondary damage (David, Kroner, 2011). The host of pro-inflammatory and anti-inflammatory cytokines, chemokines and other proteins secreted by these invading and reactive cell types (David, Kroner, 2011, Knerlich-Lukoschus, et al., 2010, Bastien, Lacriox, 2014) has complex effects on OPC reactivity and biology and conversely, injury-reactive OPCs may have complex effects on the inflammatory response.

One of the first and major cytokines to be expressed in the injured spinal cord is tumor necrosis factor α (TNFα). There is increased expression of TNFα and its receptors within 6hr of SCI, principally by cells in the lesion penumbra (Bartholdi, Schwab, 1997, Chen et al., 2011). Blocking TNFα action with entanercept, a TNFα antagonist, reduces these increases and also reduces neuronal and oligodendroglial cell death (Chen et al., 2011) as does administration of an anti- TNFα antibody (Lee, et al., 2000). Interestingly, entanercept treatment also reduced edema and cyst formation and increased Basso-Beattie-Bresnahan (BBB) hindlimb locomotor scores suggesting a central role for TNFα in regulating the inflammatory response to SCI and its resolution. TNFα kills OPCs in vitro and inhibits their differentiation into oligodendrocytes (Su, et al., 2011) and this TNFα-induced cell death may require cell-cell contact with astrocytes (Kim, et al., 2011). The study of Chen et al., did not examine directly the response of OPCs to entanercept treatment so the exact role of TNFα in the OPC reaction to injury is unknown. The direct injection of TNFα into the uninjured brain, however, induces reactive changes in OPCs, such as increased expression of NG2, at the injection site (Rhodes et al., 2006).

TNFα may also have protective effects on injured OPCs. OPCs express both TNFR1 and TNFR2 and while R1 is generally considered pro-apoptotic, R2 is anti-apoptotic and protective (for review, see McCoy, Tansey, 2008). Activation of TNFR2 in OPCs protects the cells against oxidative stress in vitro (Maier, et al., 2013) and activation of TNFR2 in OPCs during cuprizone induced demyelination is necessary for the proliferation of OPCs and their subsequent differentiation into oligodendrocytes (Arnett, et al., 2001). Thus the effects of TNFα during injury on cells of the oligodendrocyte lineage are complex and may vary according to lesion type (i.e., injury versus induced demyelination). In addition, other cytokines and inflammatory agents may have significant effects on TNFα production and its

effects on its target cells (Kadota, et al., 2012). The effects of TNFα on OPCs after injury is a ripe area for future study especially since knock-out mice for both ligand and receptors are available.

While the expression of many other cytokines is increased after SCI, again little is known about their direct effects on OPCs. For example, IL-6, a proinflammatory cytokine, enhances OPC survival in vitro but this effect is reversed when IL-6 is given together with TNFα (Taylor, et al., 2010). The effects of IL-6 on OPCs after SCI is unknown. The effects of several inflammatory cytokines has been investigated extensively during demyelination/remyelination. IL-1β, another potent pro-inflammatory cytokine that is elevated immediately after SCI (Rice et al., 2007), is necessary for remyelination after cuprizone-induced demyelination of the corpus callosum (Mason, et al., 2001). During demyelination, IL-1$\beta^{-/-}$ mice have the normal complement of OPCs but these cells fail to differentiate into myelinating oligodendrocytes. This differentiation failure may be due to a failure of macrophages/microglia to up-regulate IGF-1 production. Contusion injury up-regulates the expression of CXCR4 in OPCs and of the CXCL12 ligand in astrocyte-like cells (Knerlich-Lukohshus, et al., 2010). Although activation of CXCR4 by CXCL12 (SDF-1) promotes OPC differentiation under demyelinating conditions (Patel, et al., 2010), the functional significance of these changes after SCI is unknown. Lastly, IL-17 increases the production of IL- 6 and matrix metalloproteases (MMP3, MMP9) by OPCs in vitro suggesting that OPCs may participate directly in the regulation of the inflammatory response to injury (Kang et al., 2013). There is reduced accumulation of activated microglia and macrophages at contusion injuries in mice where the proliferative response of OPCs to injury has been reduced by knocking out β-catenin specifically in OPCs (Rodriguez, et al., 2014) raising the possibility that OPCs are a source of the chemokines that attract leuokocytes and monocytes to sites of SCI.

One consequence of inflammation is the secretion of matrix-metalloproteinases by leukocytes and reactive glia including microglia, OPCs and astrocytes (Allan et al., 2005). MMP9 level increase rapidly after SCI (Noble et al., 2002) where it functions to open the blood-spinal cord barrier and degrade the extracellular matrix (ECM) thus facilitating the migration of leukocytes and astrocytes into the damaged area (Noble, et al., 2002, Hsu, et al., 2008). IL-1β stimulated OPCs secrete MMP9 in vitro (Sao et al., 2013) suggesting that OPCs may participate in the opening of the BBB. MMPs also degrade the inhibitory CSPGs that accumulate at sites of SCI and this can have complex effects on scar resolution, function and repair. For example, CSPGs directly activates microglia in vitro (Rolls, et al., 2008). Activated microglia remove debris but they also are a source of pro-inflammatory cytokines. The NG2 CSPG, which accumulates at injury sites, may participate in microglia activation and migration since there is reduced accumulation of activated microglia after lysolecithin-induced demyelination in NG2-null mice (Kucharova, et al., 2011) and in mice where OPC proliferation is reduced after SCI (Rodriguez, et al., 2014). NG2 can also inhibit OPC differentiation into oligodendrocytes in vitro, but cleavage of NG2 by MMP9 reduces this inhibition (Larsen et al., 2003, Pendleton, et al., 2013). CSPGs promote an anti-inflammatory M2 phenotype among invading macrophages (Shechter et al., 2011) and this activity also is sensitive to MMP-mediated degradation. It will be important in future studies

to determine how to regulate and the balance the beneficial and negative effects of CSPG accumulation and degradation after SCI in order to promote repair and control inflammation.

In summary, there is a complex interplay between OPCs, microglia and invading macrophages at sites of SCI. Several in vitro studies demonstrate direct effects of inflammatory cytokines on OPC death, proliferation and differentiation, but their functions within the complex multi-cellular environment of the injured spinal cord or brain have not been investigated extensively. Conversely, how reactive OPCs interact with inflammatory cells is another emerging area for future study.

Properties of injury-reactive OPCs

What are the consequences of the accumulation of OPCs in terms of repair? This is a major question in spinal cord injury research and a source of much controversy. Oligodendrocyte cell death leads to immediate demyelination at the injury site and the secondary degeneration of long-projecting fibers may lead to continued oligodendrocyte death (Crowe et al., 1997). Demyelination is followed by remyelination after most injuries in mice and rat spinal cord (for review, see Almad, et al., 2011, Plemel, et al., 2014), although the extent of myelin repair is debatable (Totoiu, Keirstead, 2005, Lasiene, et al., 2008). There may be long-term demyelination after human spinal cord injuries, especially at the lesion epicenter (Guest, et al., 2005). Proliferating OPCs are the major source of myelinating oligodendrocytes after injury and there is a small contribution from Schwann cells that either invade the damaged CNS or develop directly from OPCs (Totoiu, Kierstead, 2005, Zawadzka, et al., 2010). As Schwann fail to migrate in the proteoglycan-rich environment of the damaged spinal cord (Afshari, et al., 2010), survive poorly in the CNS (Hill et al., 2007) and make only a single internode, their contributions to longterm remyelination are likely small. Reactive OPCs are major components of the glial scar and the discussion below will focus on their contributions to the barrier functions of the scar. For more complete reviews of remyelination after SCI, the reader is referred to several recent reviews (Almed, et al., 2011, Pemel, et al., 2014).

The glial scar is considered a physical and biochemical barrier to successful axon regeneration and CSPGs, along with myelin-associated molecules and axon guidance molecules, are responsible for this barrier function (Yiu, He, 2006). The NG2 CSPG is a major component of the glial scar. It is produced principally by reactive OPCs and accumulates on cell surfaces and within the ECM. Numerous in vitro studies show that the NG2 CSPG as a substrate has axon growth inhibitory properties although this is controversial (Dou, Levine, 1994, Fidler, et al., 1999, Uhgrin et al., 2003, Yang et al., 2006, Busch, et al., 2010). Application of anti-NG2 antibodies to dorsal hemisected rat spinal cord stimulates the regeneration of large and medium diameter sensory axons (Tan et al., 2006) but this finding has been questioned since axon ends associate with NG2+ cells within the glial scar and in vitro (McTigue et al., 2006, Yang et al., 2006) and there is no regeneration after injuries to the spinal cord and dorsal roots of NG2null mice (de Castro, et al., 2004, Hossain-Ibrahim, et al., 2007).

Several recent studies offer clues to resolve these discordant observations. Although the NG2 binding site on neurons remain unknown (Dou, Levine, 1997), NG2 binding to neonatal cerebellar granule neurons activates atypical PKCζ and via the Par complex, leads to dysregulation of Rac activity (Lee, et al., 2013). This over-activation of Rac results in shorter neurite growth. When embryonic hippocampal neurons were treated with the extracellular domain of NG2, their normal polarity was also perturbed and the cells extended multiple axons. This behavior can be interpreted as enhancing growth, however, the growth is abnormal. Thus, NG2 can perturb neuron polarization, growth cone formation and axon formation and extension (see also, Uhgrin et al., 2003). Since a damaged neuron must reform a growth cone in order to regenerate (Bradke, et al., 2012), hyper-activation of Rac and dysregulation of the Par complex provides a molecular basis for the inhibition of axon regeneration and barrier functions of the NG2 CSPG after SCI.

After a dorsal column crush injury, ascending sensory axons make rounded endings on NG2+ OPCs cells in the lesion penumbra but retract further from the lesion site in NG2null mice (Filous et al., 2014) suggesting that contact leads to stable adhesive contact between dystrophic axon ends and NG2+ OPCs in the glial scar. These stable contacts prevent axonal sprouting and regeneration. Together both the surface properties of reactive OPCs and the extracellular accumulation of the NG2 CSPG contribute to a post-injury environment that is non-permissive to axon regeneration. Identifying the cellular receptor or receptors for NG2 and understanding the mechanisms by which axon regeneration is suppressed may have significant impact on the clinical treatment of brain and spinal cord injuries.

OPCs and extracellular NG2 may also affect the physiological properties of axons within the injured spinal cord. After a lateral hemisection, there is a slow loss of transmission through spared fibers in the contralateral ventral lateral funiculus (VLF)(Arvanian et al., 2009). This failure correlates temporally with an accumulation of CSPGs within the damaged spinal cord and can be prevented by injecting chondroitinase ABC, the enzyme that degrades chondroitin sulfate glycosasminoglycan chains, into the spared VLF (Hunanyan, et al., 2010). The processes of OPCs contact nodes of Ranvier in the CNS (Butt, et al., 1999) and exogenous NG2 accumulates at nodes of Ranvier after injection into the intact spinal cord (Hunanyan et al., 2010) as does endogenous NG2 in the peripheral nervous system (Martin et al., 2001). This suggests that the extracellular accumulations of NG2 after SCI might alter electrical transmission through the damaged area. In support of this idea, the injection of exogenous NG2, but not other CSPGs such as aggrecan or neurocan that are also increased at sites of SCI, into the uninjured spinal cord reduced EPSP amplitude in the VLF without changing latency and this effect was partially reversed by infusion of anti-NG2 antibodies (Hunanyan, et al., 2010, Petrosyan et al., 2013). In rats that received lateral hemisection injuries to the thoracic spinal cord, infusion of anti-NG2 antibodies increased electrical excitability, promoted sprouting of 5-HT-positive axon fibers and improved locomotor performance. Thus, the accumulation of extracellular NG2 due perhaps to the actions of inflammatory cytokines (Wennstrom et al., 2014) and extracellular and membrane-associated proteases (Sakry, et al., 2014, Larsen, et al., 2003) may have multiple detrimental effects on the recovery and function of neural pathways in the damaged spinal cord.

Plasticity of OPCs after injury

The ability of neonatal OPCs to be directed towards an astrocytic or neuronal fate in vitro has prompted much speculation as to the phenotypic plasticity of developing OPCs in vivo and especially after brain and spinal cord injury. If dividing OPCs have a neurogenic potential, it may be possible to harness this potential for neuronal repair after SCI. Despite earlier reports that NG2+ OPCs give rise to neurons of the olfactory bulb (Aquirre, Gallo, 2004) and cortex (Rivers et al., 2007), in the normal CNS, OPCs give rise to mostly oligodendrocytes (Kang et al., 2010). It is also possible that prenatal NG2+ cells can develop into a small number of astrocytes, mostly in the basal forebrain (Zhu, et al., 2008), but these astrocytes may be the progeny of cells distinct from oligodendrocyte progenitor cells (Zhu et al., 2011).

After most brain or spinal cord injuries, proliferating OPCs generate more OPCs and oligodendrocytes (for review, see Almed, et al., 2011, Pemel, et al., 2014). The contribution of proliferating OPCs to reactive astrocytes is small at best (Komitiva, et al., 2011) and most reactive astrocytes are the progeny of preexisting astrocytes (Buffo, et al., 2008). Olig2+ cells, on the other hand, may make a more substantial contribution to reactive astrocytes (Dimou, et al., 2008, Tatumsi, et al, 2008) and they may represent a progenitor cells with a greater degree of phenotypic plasticity than NG2+OPCs. Nevertheless, because it is relatively easy to have access to and manipulate the genome of dividing cells in vivo, it may be possible to manipulate the fate of reactive OPCs after injury (Guo, et al., 2014, Heinrich, et al., 2014).

OPCs in human disease

The reactions of human OPCs to injury and neurodegenerative disease have not been studied extensively due, in part, to the difficulties in obtaining well fixed post-mortem material for analysis. Nevertheless, the reactions of OPCs are not limited to rodent models of brain and spinal cord injury and similar reactive changes in OPCs have been seen in injury and neurodegenerative diseases. There is increased expression of NG2 on both stellate-shaped cells and round, oval shaped cells in the injured human spinal cord (Buss et al., 2009) but the clinical significance of these reactive changes is not known. Curiously, there is reduced total NG2 immunoreactivity in Alzheimer's disease (AD) brains but individual OPCs display the characteristic morphology of a reactive phenotype (enlarged cell bodies, fewer and shorter processes) (Neilsen et al., 2013). NG2 levels in CSF are reduced in AD and there are unusual aggregated deposits of NG2 immunoreactivity, often in close apposition to astrocytes. Considering the recent report of Sakry et al.(2014) showing that the soluble ectodomain of NG2 can restore normal α-amino-3-hydroxy-5-methyl-4-isoxazolepr opionicacid (AMPA) currents in NG2 knock-out mice, it is tempting to speculate that the unavailability of soluble NG2 in AD, possibly because of unusual aggregation, underlies some of the cognitive decline associated with AD.

Because of the difficulties of working with post-mortem material, several lines of transgenic mice have been created that express mutant genes implicated in human diseases. These mice lines are useful tools for examining the role of OPCs in disease states and

neurodegeneration. For example, in mice carrying mutant NF1 alleles (Brannan et al., 1994), there is increased accumulation of NG2+, Olig2+ OPCs in embryonic spinal cord (Bennett et al., 2003). Altered OPC dynamics could lead to myelin pathologies in neurofibromatosis patients. In the motor cortex of amyotrophic lateral sclerosis (ALS) patients, OPCs show typical reactive changes and there is demyelination (Kang et al., 2013). In mice expressing the mutant SOD1 gene, there is increased proliferation of OPCs, but as the cells differentiate into oligodendrocytes, they degenerate. This degeneration is most prominent in the gray matter surrounding motor neurons suggesting that a loss of trophic support from oligodendrocytes (Nave, 2010) may be a contributing factor in ALS.

Lastly, there is growing body of evidence suggesting that oligodendrocytes and their precursor cells may be involved in cognitive disorders ranging from autism to schizophrenia (for review see, Haroutunian, et al., 2014, Takahishi, Sakuri, 2013). The balance between OPC proliferation and survival and their differentiation into myelinating oligodendrocytes affects the maturation and function of developing and mature circuits (McKenzie, et al., 2014). Premature termination of OPC proliferation and precocious myelination may be as equally disastrous as delayed myelination or ongoing low-level demyelination in its effects on functioning and newly forming circuits. One can expect rapid progress in this area in the future as the circuitry underlying cognitive functions is identified and characterized.

Concluding remarks

OPCs are among the very first glial cells to react to a variety of brain and spinal cord injuries yet the full significance of these reactions are not well understood. On one hand, proliferation of OPCs is necessary to generate cells with the potential to remyelinate the damaged area but, on the other hand, as major constituents of the glial scar, OPCs contribute to an environment that is non-permissive for axon regeneration. In this review, I have tried to summarize what is known about the OPC reaction to injury as well as point out emerging areas where our knowledge may not yet be complete.

Perhaps, most exciting of these are the interactions between reactive OPCs and inflammatory cells. When the proliferation of OPCs after injury is reduced, there are fewer activated microglia and macrophages in the injury cavity (Rodriguez, et al., 2014). Reactive astrocytes are thought to provide a barrier to the invasion of leukocytes and other cells from the lesion cavity into the parenchyma of the damaged spinal cord (Bush, et al., 1999, Faulkner, et al., 2004) and it seems likely that OPCs are a potential source of both the chemokines that attract leukocytes and the extracellular proteases that open the BBB (Sao, et al., 2013). Reducing inflammation by reducing the reactions of OPCs may limit secondary damage after SCI.

The effects of reactive OPCs on damaged and regenerating axon tips are complex and also not well understood. Reducing NG2 availability with function-blocking antibodies is beneficial to axon sprouting and functional recovery (Tan et al., 2005, Petrosyan et al., 2013) suggesting that the NG2 CSPG is a barrier to repair. It will be important to evaluate the effectiveness of these antibodies when used in combination with other treatments such as chondroitinase ABC to degrade glycosaminglycans, biomaterial scaffolds to support growth

and neurotropic factors to improve synaptic transmission. A major challenge for the future will be how to reduce the detrimental effects of reactive OPCs on axon regrowth while preserving their ability to remyelinate spared nerve fibers and preserve functionality.

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- The reactions of OPCs to spinal cord injury are reviewed.
- Inflammation after injury can affect OPC biology and OPCX reactivity ma affect the inflammatory response.
- OPC accumulation after spinal cord injury is detrimental to axon repair and regeneration.
- Opportunities for future research are discussed.