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Review Article

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Role of Glial Cells in Axonal Regeneration

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Axonal regeneration is critical for functional recovery following neural injury. In addition to intrinsic differences between regenerative responses of axons in peripheral versus central nervous systems, environmental factors such as glial cells and related molecules in the extracellular matrix (ECM) play an important role in axonal regeneration. Schwann cells in the peripheral nervous system (PNS) are recognized as favorable factors that promote axonal regeneration, while astrocytes and oligodendrocytes in the central nervous system (CNS) are not. In this review, we evaluate the roles of Schwann cells and astrocytes in axonal regeneration and examine recent evidence that suggests a dual function of astrocytes in regenerative responses. We also discuss the role of Cdc2 pathways in axonal regeneration, which is commonly activated in Schwann cells and astrocytes. Greater insight on the roles of glial cells in axonal regeneration is key to establishing baseline interventions for improving functional recovery following neural injury.

Key words: glial cell, axonal regeneration, Schwann cell, astrocyte, Cdc2

INTRODUCTION

Axonal regeneration can occur spontaneously after peripheral nerve injury as a result of favorable environmental and intrinsic factors. However, axonal regeneration following spinal cord injury (SCI) is nonspontaneous and often inhibited by the resulting glial scar. Evidently, environmental and intrinsic differences between regenerative responses of nerves in the PNS versus CNS play a major role in axonal regeneration following neural injury.

Following peripheral nerve injury, the distal stump degenerates while Schwann cells dedifferentiate and proliferate to create a permissive environment for axonal regeneration [1]. The formation of Bünger bands via proliferating Schwann cells acts as a conduit and facilitates axonal regeneration [2]. In addition to permissive environments, when peripheral nerves are injured, these axons are more likely to regenerate due to their intrinsic growth capabilities [3]. However, regenerative responses after SCI are dramatically different as damaged axons of the CNS are incapable of such spontaneous regeneration. Here, injured axons are unable to regenerate past the lesion site often due to glial scar formation. The glial scar primarily consists of reactive astrocytes and proteoglycans, which are recognized as physical barriers through which axons cannot further elongate [4]. In addition, myelin-associated molecules, which are produced by oligodendrocytes, exert inhibitory actions on axonal growth as they interact with their axonal membrane receptors.

In this review, we consider the differences in regenerative responses of PNS and CNS axons and closely examine the roles of Schwann cells and astrocytes. Both Schwann cells and astrocytes are macroglial cells derived from neural stem cells, the common undifferentiated progenitor cell. Various factors trigger these progenitor cells to differentiate. Schwann cell development occurs through a series of transitional embryonic and postnatal phases regulated by several signals such as neuregulin and Notch signaling pathways [5]. Meanwhile, astrocyte development involves the interplay of extrinsic signals, cell-cell interactions,

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and transcription factors that direct specific cell fates [6]. For example, basic helix-loop-helix transcription factors are crucial for diversifying differentiation of neural stem cells in order to form and specify astrocytes [6, 7]. Thus, while major differences exist, certain commonalities between these two glial cells also exist, which suggests dual functionality of astrocytes resulting in beneficial and detrimental effects for axonal regeneration. Such insight on the roles of glial cells in axonal regeneration is critical for improving functional recovery following neural injury.

There have been significant advances on understanding the role of molecular factors from oligodendrocytes, such as myelin-associated glycoprotein (MAG), Nogo-66, oligodendrocyte-myelin glycoprotein, and their receptor complexes consisting of NgR1, p75, TROY, and LINGO, which has been reviewed elsewhere [8, 9] and is not examined in this paper.

FUNCTION OF SCHWANN CELLS FOLLOWING PERIPHERAL NERVE INJURY

Injured axons of peripheral nerves regenerate spontaneously over long distances, and various factors contribute to this regenerative ability. Following peripheral nerve injury, distal axons degenerate while dedifferentiated Schwann cells and macrophages remove debris via phagocytosis. Dedifferentiation refers to the state in which Schwann cells revert to immature states capable of re-entering the cell cycle to proliferate and assist in nerve regeneration [10]. Schwann cells also aid in the process of remyelination, which is necessary for axon protection and action potential conduction [11]. Extracellular matrix proteins such as laminin and fibronectin [12, 13], neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) [14], and hormones such as progesterone and erythropoietin [15, 16] are also important factors that regulate Schwann cells.

During peripheral nerve regeneration, ECM components are crucial for guidance, elongation, trophic support, and axonal remyelination [17, 18]. Laminin is an ECM glycoprotein and component of the Schwann cell basal lamina. It is expressed in intact nerves and upregulated in injured nerves as it stimulates neurite outgrowth and helps ensheath and remyelinate regenerating axons [19-21]. In an experiment where laminin γ1 gene expression is stopped, all other known laminin chains are also disrupted in Schwann cells [12]. As a result, axonal regeneration is poor because of partial myelination and improper ensheathment [22, 23]. It is clear that Schwann cell dedifferentiation, proliferation, and even survival are severely impaired when laminin is disrupted. In addition, when laminin is absent, cell polarity signaling pathways fail to induce axonal growth [20]. Thus, this ECM glycoprotein plays a critical role in contributing to successful axonal regeneration following peripheral nerve injury by indirectly supporting Schwann cells or acting as a substrate for axonal regeneration [1].

Without laminin, Schwann cells cannot differentiate into myelinating phenotypes. Moreover, the resulting poor myelination and regeneration between phenotypes in mice with a Schwann cell defect in β1 integrin, a component of laminin receptors, and laminin γ1 indicate that integrin plays an important role in laminin signaling [22, 24]. In response to signals from laminin-activated integrin receptors, it has been shown that growth cones integrate myosin II-dependent contraction for rapid, coordinated turning at borders of laminin stripes, indicating that laminin acts as a stimulator and guide for axonal regeneration [25].

The important role that Schwann cell responses play in successful PNS axon regeneration can be seen in the effects of fibrinogen following peripheral nerve injury. Fibrinogen first infiltrates extracellular space of injured peripheral nerves and then converts into fibrin, which inhibits Schwann cell migration and remyelination during regeneration [26]. Here, fibrin triggers ERK1/2 phosphorylation and p75 NGF receptor production, which downregulates gene expression involved with myelin production. This eventually inhibits Schwann cell differentiation because cells are held in a predifferentiation state. Yet in normal pathophysiological situations, fibrolytic plasminogen activator (PA) is induced in peripheral nerves after injury, where it converts plasminogen to plasmin that degrades ECM proteins including fibrin and assists in axonal regeneration [27, 28].

Furthermore, different types of neurotrophins are upregulated in Schwann cells following peripheral nerve injury [29, 30]. Induction of neurotrophin receptors occurs in both axons and Schwann cells and mediates axonal regeneration [31, 32]. Binding of neurotrophic factors to their selective receptors initiates entrapping of activated receptors in the axon terminal. Activated receptors are then retrogradely transported into the nucleus of cell body, where target gene expression is induced and protein factors for axonal regrowth are transported back to the growth cone [33]. In Schwann cells, while neurotrophins such as BDNF typically aid in myelination, certain in vitro and in vivo systems have also shown neurotrophins such as NT3 to act as inhibitors of myelination [31, 34]. Thus, BDNF serves as a positive modulator of myelination and motor neuron regeneration [35], while NT3 serves as a negative modulator of peripheral nerve myelination.

After peripheral nerve damage, Schwann cells and macrophages remove cell debris and inhibitory molecules in the injury area. Here, it deserves mention that the role of Schwann cells in removing myelin-associated inhibitory molecules is an important

environmental aspect to axonal regeneration of injured peripheral nerves. The removal of myelin sheaths with myelin-associated glycoprotein following neural injury creates a permissive environment for regeneration [36, 37]. The presence of laminin, a Schwann cell basal lamina component, demonstrated that effects of inhibitory molecules such as MAG may be overcome by neurite outgrowth-promoting molecules [38]. Evidently, the removal and downregulation of inhibitory molecules such as MAG from Schwann cells during Wallerian degeneration is critical to optimizing axonal regeneration following peripheral nerve injury [37]. This notion of removing myelin-associated inhibitory molecules was also supported in previous experiments as transgenic mice overexpressing Nogo-A resulted in poor regeneration [39].

FUNCTION OF ASTROCYTES FOLLOWING SPINAL CORD INJURY

In intact nerves of the CNS, astrocytes are principal macroglial cells that provide critical support including regulation of blood flow and energy metabolism [40, 41]. Moreover, astrocytes respond to any degree of CNS injury and disease via reactive astrogliosis, where astrocytes become hypertrophic, change in molecular expression and morphology, and result frequently in glial scar formation [42, 43]. Further, phagocytes produce interleukin-1, which initiates inflammatory responses in astrocytes [44]. Reactive gliosis is comprised of changes in gene expression and cellular changes regulated via inter- and intracellular signaling [45, 46]. However, because reactive astrogliosis varies in response to severity of CNS injury and disease, reactive astrocytes may also exert beneficial effects. Changes experienced by reactive astrocytes are regulated based on context via specific cascade signaling events and can result in astrocytes gaining or losing functions, which translates into beneficial or detrimental effects [46]. Various signals including cytokines, growth factors, and adhesion molecules exerted by reactive astrocytes and injured neurons play critical roles in response to CNS injury.

Astrocytes respond to CNS injury at varied degrees as evidenced by different categories of reactive astrocytes that exist as biochemically heterogeneous [42, 47]. In mild-to-moderate reactive astrogliosis, astrocytes occupy non-overlapping domains in a similar manner to non-injured tissue [48, 49]. In response to extensive CNS injury, reactive gliosis results in newly proliferated astrocytes and glial scar formation. Interestingly, these astrocytes occupy overlapping domains as opposed to non-overlapping domains as seen in non-injured tissues [50, 51]. Moreover, structural changes as a result of glial scar formation persist over long periods of time and lead to failed CNS axon regeneration [46].

Various factors induce glial scar formation. Transforming growth factor (TGF) β1, TGFβ2, and interleukin-1 are recognized as mediators of macrophage-induced glial scarring. Cytokine interactions between interferon-γ and fibroblast growth factor 2 (FGF2) have also been linked to glial scar induction [4, 52]. Additionally, FGF2 also increases astrocyte proliferation, leading to glial scar formation [8].

Glial scar formation presents major obstacles for successful axonal regeneration as microglia, oligodendrocytes, meningeal cells, and astrocytes are recruited to the injury site via glial reaction [53]. Astrocytes, which mainly compose the glial scar, become hypertrophic and release inhibitory ECM molecules called proteoglycans that largely contribute to poor CNS axon regeneration [54]. The four classes of proteoglycans produced by astrocytes include: heparan sulfate proteoglycan (HSPG), dermatan sulfate proteoglycan (DSPG), keratan sulfate proteoglycan (KSPG) and chondroitin sulfate proteoglycan (CSPG) [55]. Highly sulfated glycosaminoglycan (GAG) chains characterize proteoglycan molecules [56] and are known to be critical in mediating inhibitory action of axonal growth [54, 57]. Following SCI, reactive astrocytes upregulate CSPG expression, which is then excreted extracellularly [58, 59]. A CSPG gradient is formed along the injury site, with the highest concentration of inhibitory molecules at the center of the injury site and decreasing concentrations outwards [60, 61]. CSPGs inhibit neurite outgrowth of different neuronal populations at varied degrees. As such, growth cones can extend along a proteoglycan gradient until a threshold is reached, where the gradient is no longer tolerable for growth cone extension [62]. Regenerating axons eventually become dystrophic and fail to regenerate near the lesion epicenter as a result of extremely inhibitory and non-growth conducive environments [4, 63]. GAG chains were identified as a critical component of CSPGs responsible for inhibiting axonal growth as the potent inhibitory effects no longer persist following treatment with chondroitinase ABC (ChABC) enzymes, which remove GAG chains [64, 65].

BENEFICIAL FUNCTIONS OF REACTIVE ASTROCYTES

Recent studies suggested that, in certain circumstances, reactive astrocytes recruited to the injury site may have a permissive role for axonal regeneration and functional recovery [46, 66]. Some evidence also demonstrates the ability to regulate inflammation or even minimize cellular degeneration [53, 67]. In vivo and in vitro evidence exists in which reactive astrocytes protect the CNS via uptake of excitotoxic glutamate [68], protection from oxidative stress [69, 70] or NH4+ toxicity [71], protection via adenosine

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release [72] or degradation of amyloid β peptides [73], and stabilization of extracellular fluid and ion balance [74].

In several experiments, ablation of proliferating reactive astrocytes disrupted scar formation. This led to intensified inflammatory responses, failed repairing of the blood-brain barrier, greater tissue damage and lesion site, increased neuronal loss and demyelination, and impaired functional recovery [50, 58, 75-77]. In addition, genetic depletion of Stat3 and SOC3 in astrocytes resulted in reduced migration of reactive astrocytes into the injury cavity, widespread infiltration of inflammatory cells, and failed compaction of the injury area as demarcated by glial scar formation; all of which were related to inhibition of axonal regeneration after SCI [51, 78]. The difference between permissive and non-permissive gliosis may be partly determined by expression of particular recognition molecules [45]. Astrocytes produce intercellular effector molecules or alter molecular expression with regards to cell structure, energy metabolism, intracellular signaling, and membrane transporters and pumps [42, 79-81]. These changes may dramatically influence surrounding neural cells and eventually affect axonal regeneration in a positive or negative manner.

COMMONALITIES BETWEEN SCHWANN CELLS AND ASTROCYTES

Despite differences that exist between Schwann cells and astrocytes, these two cell types share some common features in mediating regenerative responsiveness after nerve injury. As mentioned above, both Schwann cells and astrocytes have scavenger functions that remove cell debris following neural injury in normal physiological and pathological conditions. They proliferate rapidly after nerve injury, migrate into the injury area, and regulate axonal regeneration. Migration of Schwann cells toward the leading edge of regenerating peripheral axons functions to guide axonal regeneration [2, 82, 83]. Migratory responses of astrocytes after SCI restrict inflammation and preserve tissue function, and thus contributing to successful axonal regeneration as myelinated fibers are spared [78, 84]. Moreover, recent studies suggest that both astrocytes and Schwann cells are involved in synapse formation [85, 86].

We found that Cdc2, a prototypical cell cycle protein kinase, was strongly but transiently induced from Schwann cells and that phosphorylation of caldesmone by Cdc2 was linked to Schwann cell migration and axonal regeneration in the sciatic nerve [83]. Furthermore, vimentin phosphorylation by Cdc2 in Schwann cells was involved in axonal regeneration [87]. Interestingly, induction of Cdc2 and vimentin phosphorylation was similarly found in primary astrocytes, which were prepared from spinal cord tissue given injury and subjected to long-term culture (LTC) for a week [88]. These LTC astrocytes, but not short-term cultured astrocytes, appeared to facilitate neurite outgrowth of co-cultured DRG neurons, suggesting that the Cdc2 pathway may play an important role in determining phenotypic expression of astrocytes such that astrocytes provide permissive environments for axonal regeneration following SCI.

Our studies further show that the Cdc2-vimentin pathway is linked to integrin activation. Schwann cells prepared from pre-injured sciatic nerve and LTC astrocytes revealed induction of integrin protein (β1 integrin in Schwann cells versus β3 in astrocytes), and integrin activation in these cells were related to enhanced neurite outgrowth of co-cultured neurons [88]. Since integrin receptors interact with extracellular proteins such as laminin and fibronectin [89], Cdc2 activity may play a part in mediating intercellular communication between glial cells and axons undergoing regeneration (Fig. 1).

It should, however, be noted that our studies on Cdc2 activity mentioned above used in vitro cultured cells. In regenerating peripheral nerves, the endoneurium wraps around radial surfaces of Schwann cells through the interaction between integrin and laminin [24]. In the early stages of PNS axon regeneration, Schwann cells interact with regenerating axons at the leading edge, but whether the interaction between Schwann cells and growth cones involves integrin signaling remains to be explored. Unlike Schwann cells in the injured peripheral nerve, reactive astrocytes after SCI do not form basal lamina structures. Integrin function of astrocytes has been shown in polarized interaction with ECM proteins during the wound healing process [90, 91] and cerebral microvasculature [92]. Interestingly, loss of β1 integrin in reactive astrocytes facilitates astrocyte migration and contributes to glial scar compaction [84]. It is uncertain at this moment whether LTC astrocytes may provide a permissive environment for spinal axon regeneration after lesion. A pattern of interaction of LTC astrocytes with spinal axons may be examined after the implantation of LTC astrocytes into the injury cavity.

CONCLUSION

A clear understanding of the role of glial cells, specifically Schwann cells of the PNS and astrocytes of the CNS, in axonal regeneration is critical for establishing a baseline intervention toward improving functional recovery following neural injury. For instance, successful PNS axon regeneration is largely attributed to Schwann cell response via proliferation, migration, and remyelination. Further, reactive astrocytes are the most abundant

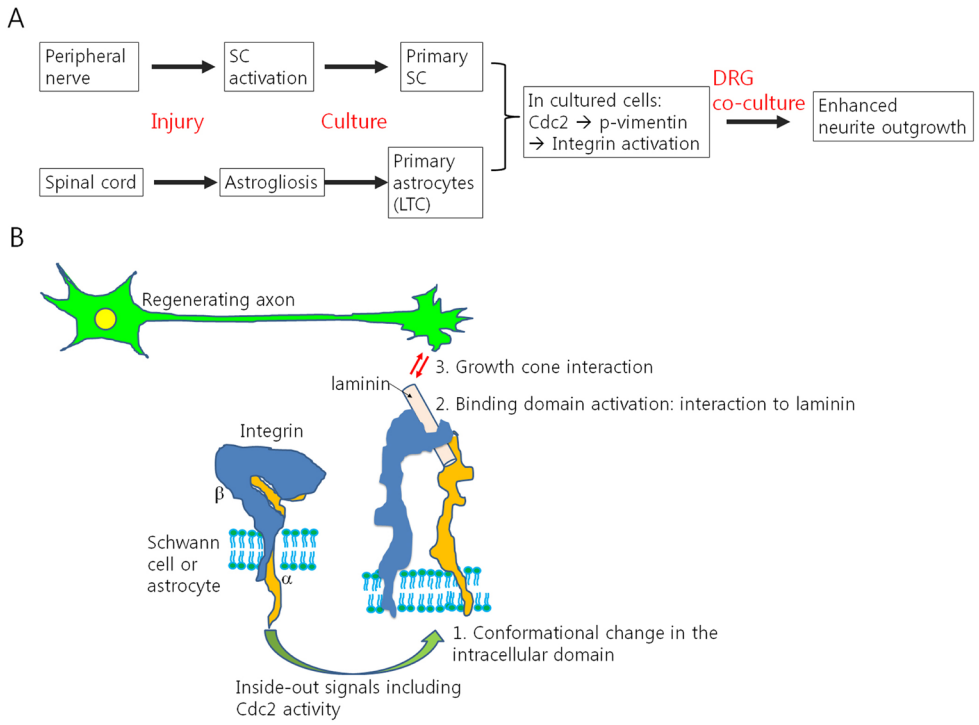

Fig. 1. Cdc2 signaling pathway mediating axon regeneration in both PNS and CNS. (A) Schematic representation depicting how activated Schwann cells and astrocytes can facilitate neurite outgrowth. Cdc2 activity induced from pretreated Schwann cells and astrocytes may be involved in vimentin phosphorylation and integrin activation. Co-culture with DRG neurons promotes neurite outgrowth. SC, Schwann cell; LTC, long-term culture. (B) Proposed role of activated integrin in intercellular signal transmission. Transmembrane protein intergrin is composed of α and β subunits and exists as an inactive state in native Schwann cells or astrocytes. Interaction of intracellular domain of integrin with Cdc2-linked signals may induce inside-out signaling that leads to communication for regrowing axons via ECM protein interactions. .

cell type found in the CNS after injury and have been regarded as detrimental toward successful CNS axon regeneration. However, emerging evidence implicates its dual role in regulation of axonal regeneration. Considering the heterogeneity of astrocyte cell types and varied biochemical and pathophysiological properties [45, 47], the diverse responsiveness of different types of astrocytes is not surprising. In our recent study, reactive astrocytes revealed phenotypic expression in terms of increased phosphorylation by Cdc2 and integrin activation, which are positively associated with facilitated neurite outgrowth of co-cultured neurons. Evidently, further studies to better understand the roles of astrocytes and compare the common features shared with Schwann cells may provide insight on how to overcome regenerative response obstacles that contribute to poor functional recovery.

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