

● PERSPECTIVE

Anti-inflammatory properties of the glial scar

Glial cells comprise ~90% of the human brain and are divided into two subtypes: microglia and astrocytes. Astrocytes play a vital role in maintaining central nervous system (CNS) homeostasis, regulating ion concentrations and providing metabolic support for neighboring neurons, stabilizing synapses, supporting the neurovascular system including maintenance of the blood-brain barrier (BBB) and also producing the extracellular matrix (ECM). Astrocytes are activated into reactive astrocytes following insults to the CNS. Immediately after injury (acute phase) astrocytes in and surrounding the injury site become highly proliferative, undergo morphological changes and up-regulate the production of extracellular proteins culminating in the formation of a glial scar, which is not permissive to axonal growth and therefore inhibits regeneration. Over the past decade a number of studies have targeted the glial scar as a means to promote regeneration; however, the results have been highly controversial and the projected beneficial outcomes were never obtained. Therefore, it is possible that the glial scar poses a beneficial role after injury, at the cost of limiting regeneration.

Given the lack of significant regeneration and any robust improvement by targeting the glial scar formed after injury, some groups have targeted astrocytes immediately after injury in an attempt to limit formation of the glial scar. Various studies have demonstrated beneficial effects of reducing the number of reactive glial cells following injury, which culminated in the attenuation of reactive gliosis with distinct pathophysiological and clinical consequences. Studies using GFAP and vimentin (Vim) genetic animal models have shown that *GFAP*^{-/-} and *Vim*^{-/-} mice present less post-traumatic glial scarring due to impaired astrocyte activation (Pekny, 2001). However, the inhibition of astrocyte proliferation prolongs the healing period following CNS injury (Faulkner et al., 2004). Further studies with the genetic animal models have demonstrated increased axonal sprouting after lower thoracic spinal cord hemisections in *GFAP*^{-/-} and *Vim*^{-/-} mice when compared to wild-type mice (Menet et al., 2003). Moreover, *GFAP*^{-/-} and *Vim*^{-/-} astrocytes have been shown to be a better substrate for neurite outgrowth than wild-type astrocytes. These groups hypothesize that it is the decrease in glial scar deposition that leads to the increase in axonal sprouting after injury. However, studies such as those from the Sofroniew group have provided valuable insights into the detrimental effects of targeting astrocytes (Anderson et al., 2016). Targeting scar-forming astrocytes indeed ablates the formation of glial scars; however, instead, these mice present large astrocyte-free areas of non-neuronal tissue in

and around the lesion. Interestingly, the lack of astrocytes and the glial scar fails to promote spontaneous axonal growth, and instead these mice present significantly increased axonal dieback.

Despite the detrimental effect the glial scar has on neuroregeneration, studies have shown it plays an essential role in rapidly repairing the BBB, reducing inflammatory cell infiltration and decreasing neuronal degeneration, thereby confining the detrimental effects of the injury (Faulkner et al., 2004). In addition, astrocytes play a role in reducing demyelination and the loss of oligodendrocytes in white matter adjacent to the injury site (Faulkner et al., 2004). As a result of limiting tissue degeneration, the glial scar has been shown to prevent functional deterioration and to enable recovery of motor functions following minor and medium spinal cord injuries (Faulkner et al., 2004). Signal transducer and activator of transcription 3 (STAT3) is a critical regulator of astrocytes, astrogliosis and consequently scar formation after injury (Sofroniew, 2015). Astrocytes in the glial scar form a scar border that surrounds and separates the damaged tissue from adjacent tissue (containing viable neurons) *via* STAT3-dependent mechanisms (Wanner et al., 2013). These astrocytes have elongated cell processes, which associate into overlapping bundles forming a dense mesh-like arrangement (Wanner et al., 2013). The importance of this scar border can be seen in STAT3 knockout mice (Herrmann et al., 2008; Wanner et al., 2013). STAT3 knockout mice fail to form a scar border around the injury site which results in increased inflammation and neuronal degeneration (Herrmann et al., 2008; Wanner et al., 2013). STAT3 is a signaling molecule for many cytokines and growth factors and plays a role in a variety of biological processes (Sofroniew, 2015). Stimulation of gp130 cytokine receptors activates Janus kinase (JAK), which phosphorylates STAT3 to p-STAT3, which in turn increases the transcriptional activity of genes involved in brain ischemia, traumatic injury and neurotoxin injection in reactive astrocytes (Sofroniew, 2015). The loss of p-STAT3 specific signaling disrupts the hallmarks of astrogliosis, such as cellular hypertrophy, up-regulation of filament proteins and formation of a structurally organized glial scar (Okada et al., 2006; Herrmann et al., 2008). A recent study identified that the Yes-associated protein (YAP) is expressed in astrocytes, and that the loss of YAP increases astrocyte activation, which is associated with microglial activation. Controversially, YAP hyper activation of the JAK/STAT inflammatory pathway prevents reactive astrogliosis in a SOCS dependent manner, negatively regulating neuroinflammation (Huang et al., 2016). Taken together, these results suggest that the JAK2-STAT3-YAP pathway may not mediate the initial microglial activation, but the pro-inflammatory responses surrounding the glial scar. These findings suggest that astrocyte reactivity is controlled by a multitude of events, requiring a combination of strategies to understand multiple aspects of astrogliosis in spinal cord injury.

Recent studies have established that acute astrogliosis restricts inflammation preserving the surrounding neuronal tissue; however, the precise mechanism by which the glial scar suppresses inflammation remains elusive. Interestingly, we have recently demonstrated that tumor necrosis factor-inducible gene 6 protein (TSG-6) is secreted by astrocytes and present in the glial scar (Coulson-Thomas et al., 2016). TSG-6 is a powerful suppressor of the immune response, and studies have shown it reduces the detrimental effects of acute and chronic inflammatory response. We show that TSG-6 expression is up-regulated by astrocytes following injury and participates in formation of the hyaluronan rich glial scar. Interestingly, in this study we also detected the presence of heavy chains from inter-alpha-inhibitor (also known as I α I) associated with the glial scar. TSG-6 is known to transfer heavy chains from I- α -I onto hyaluronan forming a specific matrix with immunomodulatory properties. Therefore, we hypothesize that TSG-6 could participate in modulation of neuroinflammation after injury, thereby reducing damage to the adjacent tissue during the acute phase. Studies targeting astrocytes would prevent the secretion of TSG-6, and consequently the injury site would be devoid of TSG-6 and more susceptible to the detrimental effects of inflammation.

TSG-6 has been shown to also interact and bind to chondroitin sulfate and also chondroitin sulfate proteoglycans, such as aggrecan and versican. Chondroitin sulfate proteoglycans such as aggrecan and versican in the glial scar inhibit axon regeneration. Many studies have administered chondroitinase ABC (glycosidase that digests chondroitin sulfate side chains) targeting the glial scar to promote regeneration. However, these studies have yielded contradictory findings. This could be due in part to the loss of TSG-6 in the glial scar as a consequence of chondroitinase ABC treatment. Upon chondroitinase ABC treatment, chondroitin sulfate and hyaluronan in the glial scar are cleaved, which would also lead to the loss of TSG-6, and consequently the glial scar would lose its anti-inflammatory properties. The precise role of TSG-6 in the glial scar remains to be elucidated; however, increasing TSG-6 expression following injury shows great expectations for enhancing the anti-inflammatory properties of the acute glial scar, which have been shown to provide beneficial outcomes after injury.

Taken together, current findings suggest that acute astrogliosis is necessary for preserving the surrounding spared tissue while chronic astrocytic scars are detrimental and inhibit regeneration without providing any beneficial value. However, Anderson et al. (2016) were also able to show that ablation of the chronic astrocytic scar does not result in spontaneous regrowth, even after stimulating axon regeneration. Thus, these recent findings demonstrate the importance of the chronic astrocytic scar in limiting inflammation and providing vital cues for axon regeneration.

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