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Neurovascular Reactivity in Tissue Scarring Following Cerebral Ischemia

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Abstract: Tissue scarring upon cerebral ischemia entails a cascade of multifaceted cellular and molecular mechanisms that govern the remodeling of the neurovascular unit, which integrates neuronal, glial, and vascular functions. The process encompasses inflammation, Glial and vascular reactivity, and neuronal remodeling. In this chapter we cover three major aspects involved in tissue scarring after cerebral ischemia. First, we outline the primary cellular mechanisms underlying glial scar formation, emphasizing on the interactions between astrocytes, microglia, and mural cells, including pericytes and fibroblasts at the injury core and perilesional areas. Next, we address the key routes of extracellular matrix deposition by reactive and fibrogenic cells, including proteoglycans, tenascins, fibronectin, and collagen. Finally, we discuss the promises and challenges of manipulating tissue scarring as a strategy to promote brain structural remodeling and neurological recovery.

Keywords: brain remodeling; cerebral ischemia; extracellular matrix; fibrotic scar; glial scar

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INTRODUCTION

Neuroglial response to injury was initially reported in 1927 by Pío del Río Hortega and Wilder Penfield in the founding article *"Cerebral cicatrix: the reaction of neuroglia and microglia to brain wounds"* (1). Those detailed observations were the groundwork for elucidating the pathophysiology of central nervous system (CNS) response to injury, as well as the complex mechanisms involved in tissue healing and replacement. From then on, experimental evidence compiled from several CNS diseases (2), including traumatic brain injury (TBI) (3), spinal cord injury (SCI) (4), and cerebral ischemia (5) denotes the importance of neuroglial reactivity in the pathobiology of CNS injuries.

Cerebral ischemia is a multifaceted injury comprising three different phases: (i) cell death and neuroinflammation, (ii) tissue replacement, and (iii) tissue remodeling (6). Diverse experimental models, including middle cerebral artery occlusion (MCAo), photothrombosis, and craniectomy with direct vessel occlusion indicate that neuroglial response takes place through all stroke phases and broadly determines its evolution and the prospects of neurological recovery (7). One of the pivotal consequences of glial reactivity is acute and chronic tissue scarring (6) that comprises the functional reorganization of several components of the neurovascular unit (NVU), including endothelial cells, pericytes (8, 9), polydendrocytes/ neural/glial antigen (NG)2^{+} (10), astrocytes (11), and microglia (12). This cell arrangement known as the glial scar is accompanied by a vast deposition of glial and neuronal-derived extracellular matrix (ECM) proteins that constitute a molecular compartment, namely the fibrotic scar (13). Shortly after the injury, these ECM substrates influence neuroinflammation, glial reactivity, and neuronal survival (14), and participate in debris removal and tissue regeneration in later stages (15).

Notably, the contribution of vascular cells, namely endothelial and mural cells, to tissue scarring has been recognized in recent years (9). Current perspectives in the field of CNS injuries emphasize that platelet-derived growth factor receptor (PDGFR)β^{+} mural cells are essential to regulate the proliferation, fate, migration, and metabolism of glial scar-forming cells (16–18). In addition, the proliferation and migration of PDGFRβ^{+}/fibroblast-like cells are associated with the presence of specific ECM proteins in the fibrotic scar, which provides the tissue peculiar properties to favor structural remodeling (19, 20). In this chapter, we highlight the key regulatory mechanisms underlying the structuring of glial and fibrotic scars in the context of cerebral ischemia and discuss the promises and challenges of scarring manipulation to facilitate recovery.

PERICYTES AS GLIAL ACTIVATORS AND SCAR-FORMING CELLS

Even though microglia have long been considered the first responders to CNS injury and modulators of the innate immune responses (21,22), emergent evidence suggests that PDGFRβ^{+} mural cells, which comprise pericytes, constitute the initial inflammatory mediators that prime acute glial activation (23). PDGFRβ^{+}

cells are a heterogeneous population of perivascular cells embedded within the basement membrane (BM) of arterioles/capillaries (Figure 1) that closely communicate with endothelial cells and astrocytes to regulate diverse vascular functions, including blood-brain barrier (BBB) permeability, vascular stability, inflammation, angiogenesis and neurogenesis (24, 25).

Multiple experimental studies indicate that PDGFRβ$^+$ mural cells are highly reactive to inflammatory signals/alarmins derived by dysfunctional cells resulting from ischemia. Their response repertoire includes the modulation of toll-like receptor (TLR)4 (26) and nuclear factor kappa B (NF-κB) (27) pathways, PDGF-B/PDGFRβ pathway, transforming growth factor (TGF)-β1/TGF-βR2 pathway (28), activin receptor-like kinase (ALK)5/SMAD-2/3 pathway, and integrin-αv complexes (28,29) (Figure 2). The activation of PDGFRβ$^+$ cells triggers a first wave of inflammatory signals that prime neuroglial response (30–32). Specifically, single-cell RNA sequencing (RNA-seq) and *in situ* hybridization (ISH) studies have demonstrated that PDGFRβ$^+$ mural cells are the primary

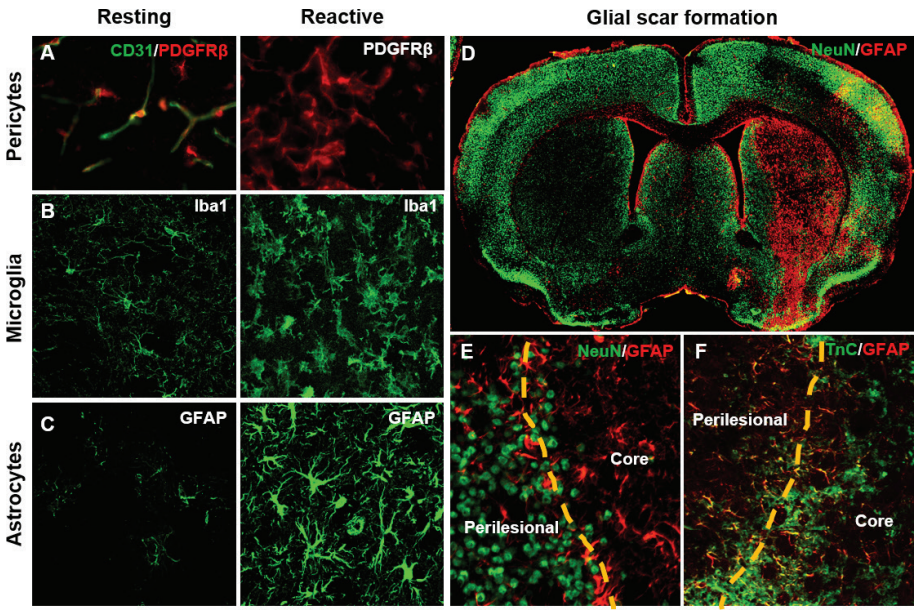

Figure 1. Multicellular reactivity and glial scar formation. A, In the healthy brain, PDGFRβ$^+$ mural cells wrap the vasculature (green) to regulate neurovascular functions. Following ischemia, reactive PDGFRβ$^+$ pericytes detach from the vascular wall and migrate towards the brain parenchyma to adopt fibrogenic properties (×63). **B,** Microglia are highly ramified cells that react to ischemic insult by upregulating proteins like Iba1 and CD45, while adopting amoeboid morphologies, and populating the injury core as integral building blocks of the glial scar (×63). **C,** Reactive astrocytes are featured by prominent upregulation of GFAP and prominent cell hypertrophy (×63). **D,** Following ischemia, reactive astrocytes invade the injury core, where no NeuN$^+$ (healthy) cells are present (×10). **E,** The cell barrier separates the perilesional tissue to prevent the infiltration of inflammatory signaling to the healthy tissue comprising vulnerable cells that could recover (×20). **F,** This cell alignment is accompanied by a molecular barrier of fibrotic scar-forming cells as TnC that exerts immunoregulatory and healing roles (×20).

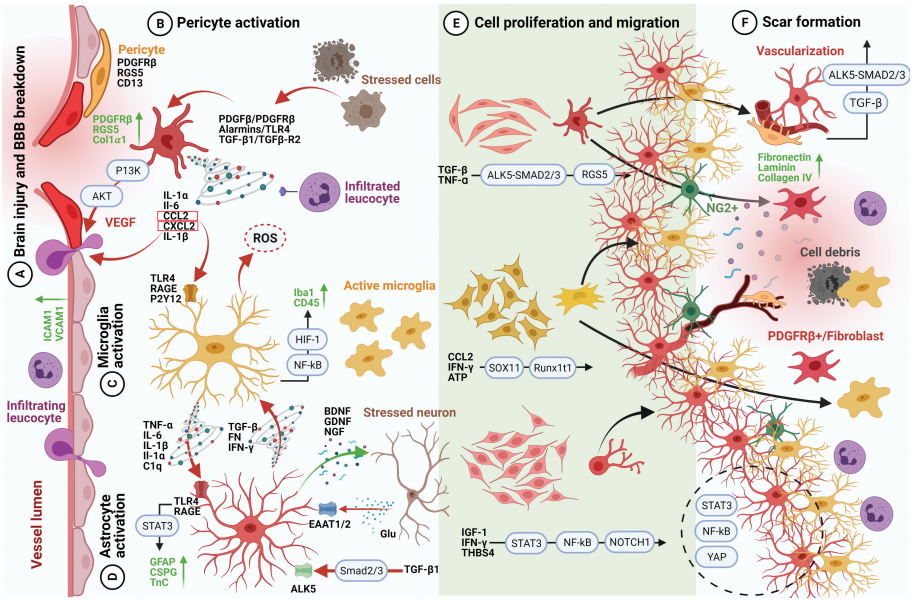

Figure 2. Cellular and molecular pathways implicated in glial scar formation. A, Brain injury upon ischemia leads to blood-brain barrier breakdown and neuroinflammation. **B,** Mural cells, including pericytes, are among the first cells at the neurovascular unit to respond to injury by secreting diverse inflammatory mediators that trigger glial activation and leukocyte recruitment. **C,** Microglia respond to pericyte-derived cytokines and damaged cells by adopting an amoeboid morphology to facilitate migration and phagocytosis, and by releasing a second wave of inflammatory cytokines that sustain the inflammatory loop and initiate astrocyte reactivity. **D,** Astrogliosis, or astrocyte activation, entails the upregulation of glutamate receptors to modulate neuronal excitotoxicity and the deposition of numerous ECM proteins that establish the structure the fibrotic scar. **E,** Following the initial responses, numerous cells at the neurovascular unit, including PDGFRβ$^+$ pericytes, microglia, and astrocytes proliferate *in situ* or in the neurogenic zones, and migrate towards the injury core to form the glial scar. **F,** The glial scar is a stratified arrangement of neuroglia and fibrotic cells that separate the damaged from healthy tissue. This structure relies on the metabolic support offered by endothelial/pericyte-driven revascularization.

sources of CC-chemokine ligand (CCL)-2, also known as monocyte chemotactic protein (MCP)-1 (33), a well-known alarmin that influences the immune response and glial reactivity shortly after injury (33–35). Additional evidence donates that mural cells are relevant sources of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX)-4, a molecule tightly linked to the generation of reactive oxygen species (ROS) by microglia, which act as a potent inflammation amplifier (36).

By this means, the initial stimulation of PDGFRβ$^+$ cells prompt the secretion of additional pro-inflammatory cytokines by various cellular components of the NVU, namely interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-3, IL-9, IL1-3, IL-6, and chemokines, such as CCL-3, CCL-4, CCL-5, MCP-1, and the macrophage inflammatory protein (MIP)-1 (30–32). Collectively, these substrates shape long-standing inflammatory loops that are decisive for the recruitment of

peripheral leukocytes and the formation of the glial scar by reactive neuroglia and fibroblast-like cells in the injury site.

Apart from the secretion of inflammatory signals, reactivity of PDGFRβ$^+$ cells also involves the upregulation of specific mural/fibrosis markers, including PDGFRβ (Figure 1), desmin, NG2 (37), collagen type I alpha 1 chain (COL1-α1), and the regulator of G-protein signaling (RGS)5 (33) that are associated with cell proliferation, migration, and secretion of scar-forming proteins (37–39). Some of these markers have been identified as crucial players in the context of ischemic lesions. More precisely, PDGFRβ has been associated with neuroprotective effects (decreased infarct size/edema) in acute and chronic phases following ischemia, as well as enhanced cell proliferation, angiogenesis, and deposition of scar-forming molecules like fibronectin and collagen (40–42). Besides, the upregulation of RGS5 facilitates cell detachment from the vascular wall and the subsequent migration of mural cells towards the ischemic core (Figure 2). Interestingly, in contrast to PDGFRβ-deficient mice, RGS5-deficient animals exhibit enhanced vascular density, mural cell coverage, and tight junction (TJ) integrity (43, 44), denoting that mural cell migration provokes a contextualized weakening of vascular function in lesioned regions and favors tissue scarring.

Experimental evidence suggests that while a group of PDGFRβ$^+$/NG2$^+$ mural cells remains at the lesion borders (45), other migrating PDGFRβ$^+$/glial high-affinity glutamate transporter (GLAST)$^+$ cells (type A pericytes) give rise to scar-forming fibroblast-like cells that become a key source of collagen, laminin, fibronectin, and neurocan in the lesion core (19, 20, 46–48). Deposition of these proteins is highly dependent on TGF-β1 (49, 50) and Wnt/β-catenin pathways (47) (Figure 3), impacting tissue elasticity and stiffness, and thus influencing key pathophysiological cascades such as glial reactivity (51, 52), cell differentiation (53), and neurite outgrowth (54, 55). Notably, evidence from cerebral ischemia has revealed that reactive PDGFRβ$^+$/fibroblast-like cells influence astrocyte reactivity in perilesional regions and promote oligodendrocyte precursor cells (OPC) differentiation to favor post-stroke myelination (40).

Furthermore, the response of PDGFRβ$^+$ mural cells to cerebral ischemia is also associated with revascularization of the injured area, which is required for the migration of newborn neurons (56) or the proper organization of the glial scar (9, 17, 57) (Figure 2). The evidence indicates that this process occurs due to the interchange of mural and endothelial cells through TGF-β and the TGFβ-R2/ALK5-SMAD-2/3 signaling pathway (58), or by connexin-43, N-cadherin, and prostaglandin E2 (EP1/4) receptors (59, 60) that facilitate the structuring of new blood vessels and an adequate BM production, including fibronectin, laminin, and collagen IV (61).

Collectively, the previous reports offer substantial grounds to consider PDGFRβ$^+$ mural cells as important responders to cerebral ischemia (62). First, they act as inflammatory amplifiers and demarcate the injured territory to mediate glial reactivity and the recruitment of resident and peripheral macrophages in the infarcted area. Next, they modulate tissue scarring by forming cell networks implicated in the revascularization of the injured tissue and the deposition of fibrotic proteins in the infarct core.

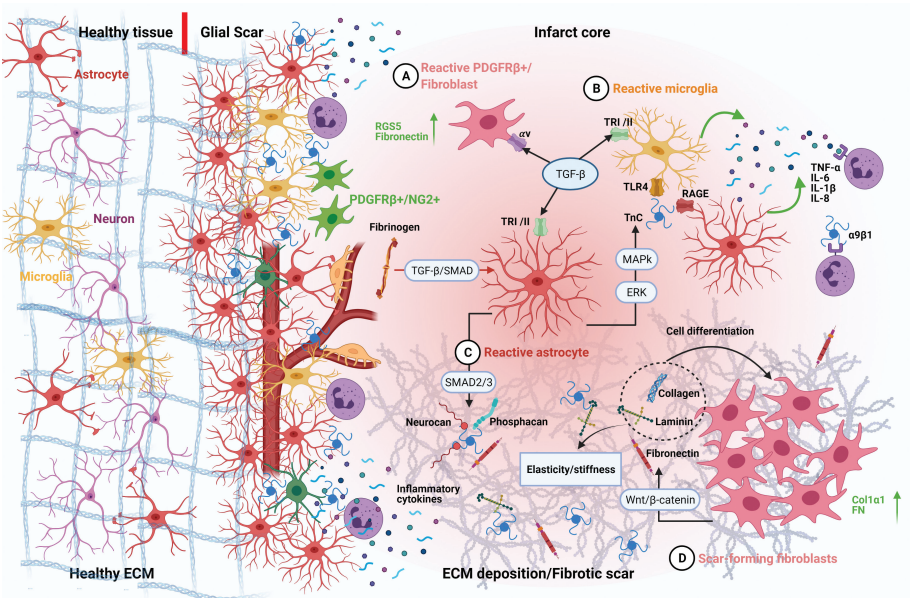

Figure 3. Fibrotic scar deposition by reactive neurovascular unit cells. Glial scar formation entails the deposition of fibrotic molecules at the injury core to prevent the infiltration of peripheral leukocytes and inflammatory signaling into the healthy tissue. **A,** Mural PDGFRβ$^+$ cells give rise to scar-forming fibroblasts that migrate to the injury core and become a major source of fibrotic molecules. **B,** At the injury site, microglia respond to multiple signaling, including TGF-β and TnC to modulate the recruitment of peripheral immune cells and astrocyte activation. **C,** In turn, reactive astrocytes constitute the primary reservoirs of scar-forming TnC as well as CSPGs, which exert immunoregulatory roles and facilitate tissue replacement. Due to its high ligand capacity, TnC allows determining the action of distinct ECM molecules at the fibrotic scar. **D,** The abundant deposition of fibrotic proteins, including collagen, laminin, and fibronectin by fibroblast-like cells deriving from PDGFRβ$^+$ cells that invade the lesion core, determines tissue elasticity and stiffness, and thus control neuronal plasticity inhibition or promotion balance.

MICROGLIAL ACTIVATION AND INNATE IMMUNE RESPONSE

Microglial activation implicates neuroinflammatory signaling that broadly defines immune cell infiltration, glial response, and tissue repair (63). Microglia reactivity is triggered promptly after ischemia by numerous mechanisms, such as BBB disruption, neuronal hyperactivity/excitotoxicity, and inflammatory mediators secreted by various cells, including reactive PDGFRβ$^+$ mural cells (64, 65). These substrates bind to TLR, advanced glycation end products (RAGE), or P2Y12 receptors to sustain numerous neuroinflammatory loops (65–67), evidenced by the expression of hypoxia-inducible factor (HIF)-1α and microglial activation markers, such as ionized calcium-binding adapter molecule (Iba-1), CD45, CD68, CD206, MCP-1, and the neurotrophic factor insulin-like growth factor (IGF)-1

(68–70) (Figure 1). This microglial response is followed by the secretion of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, NO, ROS (71–73) that jointly amplify the neuroinflammatory signals initiated by pericytes and fosters the recruitment of peripheral immune cells that exacerbate glial reactivity (Figure 3). Furthermore, microglial activation after ischemia involves morphological changes from highly ramified towards amoeboid-shaped cells (68,74) that facilitate cell migration (75) and phagocytosis in the injury core (76) (Figure 1). Transcriptomic analyses of "resting" and "active" microglia have revealed that ramified cells express low levels of cytokines and chemokines, as well as genes related to neuronal maturation and synaptic integrity. In contrast, amoeboid cells exhibit prominent transcription factors involved in migration, proliferation, and differentiation, such as SRY (sex determining region Y)-box 4 (SOX4), SOX11, and Runt-related transcription factor 1 (RUNX1) partner transcriptional co-repressor 1 (Runx1t1) (77).

In experimental models of SCI, reactive microglia are essential components of the glial scar (12) and are involved in a bi-directional interaction with neighboring reactive astrocytes (78, 79). On the one hand, it has been found that microglial-derived TNF-α, IL-1α, complement (C)1q, and IL-6 cytokines determinedly shape the astrocytic pro-inflammatory profile via TLR4 and RAGE receptors (80–82) (Figure 2). Likewise, whole-genome expression profiling of cultured astrocytes has revealed that exposition to inflammatory mediators secreted by microglia like TGF-β1 and IFN-γ alters the transcriptional pathways of G-protein-coupled receptors (GPCRs) associated with cell injury and proliferation, such as P2RY1, CXCR4, and adrenoceptor alpha (ADRA)2A (83). On the other hand, the evidence suggests that reactive astrocytes can modulate microglial activation, proliferation, and migration by different pathways, including inflammatory mediators such as IFN-γ, ATP, nitric oxide (NO), IL-6, IL-1β, and IL-1ra (81, 84, 85), or by the secretion of ECM proteins like fibronectin/β1 integrin pathway (86) or tenascin-c (TnC) (87, 88) (Figure 2). Conversely, astrocyte-derived TGF-β inhibits microglial response to lipopolysaccharide (LPS) and IFN-γ and reduces the subsequent secretion of inflammatory mediators (89).

Findings from cerebral ischemia models indicate that CX3C chemokine receptor (CX3CR)1$^+$ or Iba-1$^+$ microglia proliferate in the perilesional regions and accumulate in the injury core during the first week after injury before the astrocytic barrier is formed (88, 90). Interestingly, the depletion of this reactive microglia leads to a disorganized astrocytic wall, exacerbated inflammation, and increased neuronal death (12,91), suggesting that microglial response effectively delineates the injured territory and guides the organization of astrocytes around the lesion. Overall, the overwhelming experimental evidence outlines the importance of astrocytes and microglia crosstalk in modulating the spatial properties of the glial scar following ischemia.

ASTROGLIOSIS AND GLIAL SCARRING

Astrocyte reactivity or astrogliosis takes place in all stroke phases (6,92) and is featured by the upregulation of glial fibrillary acid protein (GFAP) (Figure 1) and the abundant secretion of inflammatory and fibrotic scar-forming mediators,

including chondroitin sulfate proteoglycans (CSPGs) and TnC (93, 94) (Figure 4). During the tissue repair phase after cerebral ischemia, microglia-derived cytokines prime local astrocyte proliferation (12) or in neurogenic niches depending on the distance to the infarcted area (95). Proliferating astrocytes migrate to the injury core displaying distinct organization patterns (96, 97) (Figure 1). In particular, astrocytes derived from radial glial progenitors cells (RGPCs) exhibit a strong astrogliosis profile with profound morphological alterations and form a highly dense barrier separating the infarcted and healthy tissue (11) (Figure 1). On the other hand, slow proliferating/NOTCH1$^+$ astrocytes display mild astrogliosis profile and are recruited to the scar border, extending their processes towards the injury. Finally, a third group of non-proliferating astrocytes located in perilesional regions exhibit moderate astrogliosis features (95, 98).

The activation and organization of astrocytes at the glial scar involve distinct signaling pathways. For instance, it has been reported that STAT3 regulates several astrogliosis mechanisms, including astrocyte migration, GFAP expression, and cell hypertrophy. Consequently, deletion of STAT3 in astrocytes is translated into disrupted glial scar formation, accompanied by enhanced neuroinflammation and behavioral deficits (99, 100). Likewise, STAT3-mediated inhibition of RhoA is associated with proper astrocyte migration and adhesion at the scar (101). Evidence from *in vitro* experiments also suggests that this signaling pathway is implicated in PDGFRβ$^+$ cells and astrocyte communication, as the pericyte-conditioned medium after PDGFB treatment promotes astrocyte proliferation and astrocyte-mediated OPC differentiation via STAT3 (42). Remarkably, additional evidence indicates that thrombospondin (THBS)4 expression induced by cerebral ischemia prompts the transcription of the nuclear factor I A (NFIA) in subventricular zone (SVZ) stem cells to promote astrogenesis. Therefore, THBS4-deficient mice exhibit astrocyte deficiency and inappropriate scar formation (102). Remarkably, astrocyte reactivity following ischemia is also associated with endothelin-1 (ET-1)-meadited deposition of amyloid-β (Aβ) (103). Accretion of this protein is linked to diminished Aβ clearance by glial RAGE receptors and the progress of long-term cognitive deficits (104).

Of particular interest in the context of cerebral ischemia is TGF-β signaling. TGF-β is a multifunctional cytokine secreted by glia, pericytes, and endothelial cells, that is implicated in numerous processes during brain injury and remodeling, including regulation of astrogliosis and fibrosis (105) (Figure 3). Specifically, findings from cerebral ischemia models indicate that TGF-β1 stimulation via ALK5 receptor or the intermediate-conductance calcium-activated potassium channel (KCa3.1) is required for GFAP upregulation, cell hypertrophy, and astrocyte arrangement at the scar, as well as CSPGs deposition (106, 107). Likewise, it has been reported that fibrinogen entering the parenchyma through the disrupted BBB stimulates astrogliosis via TGF-β/SMAD signaling pathway. Genetic or pharmacological inhibition of fibrinogen diminishes astrocyte activation and deposition of fibrotic scar-forming molecules like neurocan (108). Additionally, TGF-β1 or SMAD2/3 signaling has also been associated with the deposition of TnC, phosphacan, chondroitin synthase (ChSy)-1, 4-sulfated chondroitin-4-sulfotransferase-1 (C4st1) at the injury core (109, 110).

The dynamics of fibrotic proteins turnover remain elusive. Human samples from injured spinal cord indicate that phosphacan is upregulated at the scar border, while neurocan and versican are in the injury core (111). Interestingly, the

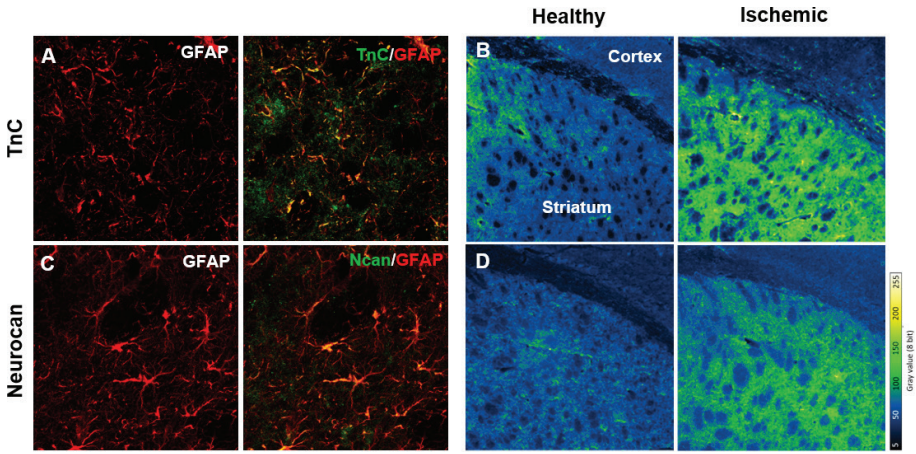

Figure 4. Tenascin-C and neurocan deposition at the fibrotic scar. A-B, TnC is one of the main ECM proteins deposited by reactive astrocytes after cerebral ischemia. Following injury, TnC is prominently upregulated in the injury core (striatum) and is degraded by MMPs (A, ×63; B, ×10). **C-D**, Neurocan is a CSPG secreted by astrocytes at the injury core, which tightly interacts with TnC and acts as an inhibitory cue for cell reorganization in specific contexts (C, ×63; D, ×10).

evidence suggests that CSPGs are differentially expressed and degraded upon injury (112), as neurocan, brevican, and versican are upregulated at the lesion core shortly after SCI, while phosphacan immunoreactivity appears two months after the lesion. Similarly, brevican expression persisted for two months in contrast to neurocan and versican that lasted for 30 days (111). In line with these observations, increased neurocan and phosphacan expression in GFAP$^+$ reactive astrocytes was reported after one month at the injured area in a cortical injury model (113) (Figure 4).

The role of TnC is particularly relevant in injury settings. TnC is abundantly secreted by reactive astrocytes (114, 115) dependently upon extracellular signal-regulated kinases (ERK) and mitogen-activated protein kinase (MAPK) pathways (116) (Figure 4). Following ischemia, TnC remains in the lesion core during the first two weeks after injury (88) (Figure 4), and it is subsequently degraded by matrix metalloproteinases (MMPs), namely MMP2/9 (117). TnC possesses a multicellular domain that provides an ample ligand capacity, thus enabling the synthesis of other ECM proteins (118) and controlling how long these proteins will be retained at the fibrotic scar (119). TnC interacts with ICAM1, fibronectin, and perineural nets (PNNs) components (120), or glial and leukocyte integrins, such as α9β1, αVβ3, α8β1, and αVβ6, as well as the collagen receptor α2β (118) (Figure 3). For instance, it has been reported that TnC-deficient mice exhibit fibronectin insufficiency following SCI or that TnC interaction with α9β1 and αVβ3 integrins control the fate and proliferation of cultured astrocytes or hematopoietic stem and progenitor cells (HSPCs) (118, 121).

Furthermore, it has been also demonstrated that TnC exerts immunoregulatory roles following injury. Findings from cerebral ischemia suggest that astrocyte-derived TnC binds to glial and leukocyte TLR4 and RAGE to regulate

microglial activation and immune cell infiltration in association with ICAM1 expression (88). Likewise, TnC-deficient mice experience increased lymphocyte and neutrophil infiltration following SCI (122), and TnC-shRNA treatment reduces the production of inflammatory mediators (123). The previous implies that TnC is a signaling substrate for recruiting scar-forming cells and modulate their activation state.

Finally, it is important to note that reactive astrocytes do not solely promote pathophysiological cascades leading to tissue scarring, but also control neuronal excitotoxicity via the excitatory amino acid transporter (EAAT1/2) glutamate transporters (124) and are major sources of neurotrophic factors (125, 126), including brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and nerve growth factor (NGF) (94, 127), that promote chronic brain remodeling (Figure 2).

MODULATION OF TISSUE SCARRING TO ENHANCE NEUROLOGICAL RECOVERY

The downsides and benefits of glial/fibrotic scar for structural brain remodeling and neurological recovery have been widely discussed during the last two decades (128). A long-standing hypothesis postulates that glial and fibrotic scars act as physical and molecular inhibitory cues for cellular reorganization following injury (106, 129, 130). In particular, it has been shown that increased CSPGs and TnC expression are correlated with diminished axonal rewiring (122, 131) and that ECM degradation by treatments like chondroitinase ABC improves neurological recovery by facilitating the regeneration of neurites after SCI (132, 133). In the same way, it has been reported that experimental inhibition of pericyte-derived scarring enhances neurological recovery by preserving tight junctions and reducing vascular leakage (44), and promoting axonal growth (134).

Nonetheless, recent evidence is suggesting that the excessive experimental attenuation of tissue scarring diminishes functional recovery (131, 135). For instance, it has been demonstrated that glial/fibrotic scarring exerts neuroprotective roles by limiting the spread of inflammatory mediators into the intact tissue (136–138) and favoring tissue reorganization by ameliorating debris removal and activation of plasticity-related factors such as FGF and BDNF (139, 140). Notably, a study by Anderson et al. (141) in a model of SCI strongly implies that the glial scar aids, rather than prevents, tissue reorganization after CNS lesion. Indeed, depending on the context, scar-forming proteins like TnC and CSPGs may exert inhibitory effects (142) or behave plasticity substrates (109, 140, 143). Alternatively, approaches depleting key mediators of astrocyte reactivity such as GFAP, vimentin, and Yap exacerbated infarct size, neuroinflammation, ECM deposition, and diminished neurological recovery (131, 135, 144). Interestingly, ablation of reactive astrocytes at the glial scar also impairs revascularization (145), which is required for proper metabolic sustenance of newly proliferated neurons and glia repopulating the lesioned site.

The previous reports entail that the effects of glial/fibrotic scars must be evaluated by considering the disease models and context (146). While the cellular and molecular remodeling governing scarring at the injury site in the early phases could be beneficial by limiting neuroinflammation and excitotoxicity, degradation of ECM deposits in the chromic phase enables tissue plasticity. The promotion of neuroprotective astrocyte phenotypes through the use of biomaterials (147) or direct astrocyte reprogramming (148, 149), as well as the functional reprogramming of PDGFRβ+ mural cells (150, 151) may be promising strategies to enhance matrix degradation or neuronal repopulation in chronic stages post-ischemia to favor the formation of new functional cell networks.

CONCLUSION

Tissue scarring is one of the primary pathobiological processes that determine structural and functional reorganization of the injured CNS. It involves a tightly regulated spatiotemporal and multicompartmentalized reactivity of diverse cells that compose the NVU, including asrocytes, microglia, and mural PDGFRβ+ cells that comprise pericytes. The crosstalk between the different cellular and molecular elements within the scar exerts essential immunoregulatory functions that aim at limiting the infiltration of inflammatory cells and mediators into the healthy tissues. In this context, scar-forming cells communicate through cytokines and ECM proteins to promote proliferation, differentiation, and migration of cells to the lesion core, and ultimately orchestrate an orderly cellular and molecular barrier that will be the basis for reorganization and replacement of the injured tissue. Neurological recovery after cerebral ischemia is strongly linked to the molecular properties of the central fibrotic scar, which determines to a large extent the inhibitory or promoting effects on neuronal plasticity. Because complete suppression of glial or fibrotic scar formation has been shown to have adverse effects, approaches seeking a time and context-dependent regulation of tissue scarring appear more promising, including strategies aiming to reprogram the functions of scar-forming cells.

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