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INVITED REVIEW

Decorin treatment of spinal cord injury

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Abstract

The scarring response after a penetrant central nervous system injury results from the interaction between invading leptominingeal/pericyte-derived fibroblasts and endogenous reactive astrocytes about the wound margin. Extracellular matrix and scar-derived axon growth inhibitory molecules fill the lesion site providing both a physical and chemical barrier to regenerating axons. Dec orin, a small leucine-rich chondroitin-dermatan sulphate proteoglycan expressed by neurons and astrocytes in the central nervous system, is both anti-fibrotic and anti-inflammatory and attenuates the formation and partial dissolution of established and chronic scars. Here, we discuss the potential of using Decorin to antagonise scarring in the central nervous system.

Key Words: *spinal cord injury; Decorin; transforming growth factor-beta; scarring; chondroitin sulphate proteoglycan; matrix metalloproteases*

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Introduction

The scarring that occurs after penetrant central nervous system (CNS) injury results from interaction between invading leptomeningeal/pericyte-derived fibroblasts and endogenous reactive astrocytes in the wound margins. The extracellular matrix (ECM) deposited in the lesion core by fibroblasts becomes sequestered from the surrounding neuropil by a laminin-rich basement membrane (glia limitans *accessoria*-GLA) formed at the astrocyte/fibroblast interface through the interaction of astrocyte-derived ephrins and eph-receptors on core fibroblasts (Bundesen et al., 2003). The environment in and around the developing CNS scar is rich in axon growth inhibitory chondroitin sulphate proteoglycans (CSPG), including neurocan, phosphacan, brevican and NG2 (Davies et al., 2004), semaphorin3A (Sema3A) and ephrin B3 (Sandvig et al., 2004), secreted by reactive endogenous astrocytes, oligodendrocyte progenitor cells (synantocytes) and also by immigrated core meningeal/pericyte-derived fibroblasts and leucocytes (Fitch and Silver, 1997; Fawcett and Asher, 1999; Sandvig et al., 2004; Kundi et al., 2013; Cregg et al., 2014). The CNS myelin-derived inhibitory Nogo, myelin associated glycoprotein (MAG) and oligodendrocyte-derived myelin glycoprotein (OMgp) are also released into the peri-lesion neuropil as myelin is degraded (Fawcett and Asher, 1999; Sandvig et al., 2004; Berry et al., 2008; Minor et al., 2008; Kundi et al., 2013; Mei et al., 2013; Ahmed et al., 2014). Binding of these ligands to their respective cognate receptors activates the Rho/ROCK signalling pathway (required for the integrity of growth dynamics) and leads to growth cone collapse and arrest of CNS axon growth.

Fibrogenic growth factors and CNS scarring

Wound healing is orchestrated by many growth factors and cytokines prominent among which are transforming growth factor beta 1 and 2 (TGFβ1/2). After activation, the TGFβ receptor (comprised of two transmembrane serine/threonine kinases – TβRI and TβRII) phosphorylates and activates Smad2 and Smad3 proteins which complex with co-Smad (Smad4), translocate to the nucleus and transcribe genes whose products regulate scarring (reviewed by (Finnson et al., 2013). Immediately after injury, TGF-β1/2 levels rise rapidly, secreted first by extravasated platelets and later by macrophages, leucocytes and reactive glia within damaged neural tissue (Border and Ruoslahti, 1992; Logan et al., 1992, 1999a; Logan et al.; Ahmed et al., 2014). TGF-β1/2 promote scarring by blocking the degradation of leptomeningeal fibroblast-derived ECM through suppression of the activity of metalloproteinases (MMP) and tissue plasminogen activator (tPA), released from endogenous glia (Border and Ruoslahti, 1992; Logan et al., 1992), and activation of tissue inhibitors of MMP (TIMP) and plasminogen activator inhibitor-1 (PAI-1) (Ahmed et al., 2014). Conversely, ECM deposition is increased in CNS wounds after TGF-β1 administration (Logan et al., 1999a; Zhang et al., 2009) and inflammation and scarring are suppressed after both treat-

ment with TGF-β1/2 antibodies (Logan et al., 1999a) and the synthetic TβRI/II blockader LY-364947 (Yoshioka et al., 2011).

Other injury responsive growth factors include connective tissue growth factor (CTGF), hepatocyte growth factor and pro-inflammatory cytokines *e.g.*, tumour necrosis factors (TNF) and interleukins (IL). CTGF promotes fibrobloblast cell adhesion and the production of the ECM components collagen I/III, the integrin β1 subunit and fibronectin in scars (Frazier et al., 1996; Vial et al., 2011), is expressed in reactive astrocytes, invading fibroblasts and endothelial cells in CNS wounds (Schwab et al., 2001) and regulated by TGF-β (Frazier et al., 1996). Hepatocyte growth factor (HGF) promotes the proliferation of macrophages by binding to its tyrosine kinase receptor cMet present on macrophages and NG2 producing synantocytes (Moransard et al., 2010). Pro-inflammatory cytokines bind to the toll-like family of receptors (TLR) expressed by microglia and astrocytes and effect their transformation into reactive phenotypes (Crack and Bray, 2007).

Decorin suppresses CNS scarring

Decorin is a small, leucine-rich, chondroitin-dermatan sulphate proteoglycan expressed by neurons and astrocytes in the CNS, but also sequestered in the ECM of many tissues (Hocking et al., 1998; Davies et al., 2004; Minor et al., 2008). Decorin is anti-fibrotic and anti-inflammatory in many tissues (Border and Ruoslahti, 1992; Hildebrand et al., 1994) including the brain (Logan et al., 1999) and greatly attenuates the formation of acute and causes the partial dissolution of established chronic SCI scars (Davies et al., 2004, 2006; Ahmed et al., 2014) by abrogating inflammation, CSPG/ECM deposition, and glia and macrophage responses to injury (Lagord et al., 2002; Davies et al., 2004, 2006). More specifically, Decorin regulates scarring by: (1) blocking TβRI/II activation and subsequent signalling through Smad 2 and Smad 3 (Yamaguchi et al., 1990; Akhurst, 2006); (2) binding to type I collagen to inhibit fibrogenesis (Reese et al., 2013); (3) inhibiting CTGF activity (Vial et al., 2011); (4) inhibiting cell adhesion and fibroblast migration by binding to fibronectin (Winnemoller et al., 1991); (5) stimulating the release of plasminogen from glia and its conversion to tPA (Davies et al., 2006); (6) regulation of angiogenesis (Neill et al., 2012) and inflammation (Hamada et al., 1996) by interaction with EGFR, cMet) and TLR; and (7) reducing mRNA and protein levels of Sema3A within CNS scar tissue (Minor et al., 2011; Ahmed et al., 2014) and suppressing Sema3A and fibronectin expression by invading leptomeningeal/pericyte-derived fibroblasts (Minor et al., 2011). Decorin modulates the acute phase of scarring by suppression of injury-induced TGF-β1/2 (Logan et al., 1999a) and inhibition of cell adhesion and migration by sequestration of TGF-β1/2 after binding to fibronectin (Zhang et al., 2009; Vial et al., 2011; Reese et al., 2013), and causes dissolution of the established chronic scar through induction of MMP and tPA activity and simultaneous suppression of TIMP and PAI-1 (Renckens et al., 2005; Davies et al., 2006; Ahmed et al., 2014). EGFR activation stimulates CSPG production (Asher et al., 2000; Dobbertin et al., 2003) and Decorin counteracts this activity by competing with EGF for EGFR binding (Yamaguchi et al., 1990; Logan et al., 1999a; Santra et al., 2000; Davies et al., 2004; Ahmed et al., 2014). Here, we review the use of Decorin both for suppression of acute CNS scar formation and for dissolution of the mature scar after SCI, and discuss the corollary that concomitant reductions in axon growth inhibitory ligands are conducive to the regeneration of spinal axons.

Decorin suppresses titres of axon growth inhibitors in SCI sites

The anti-scarring effects of Decorin significantly lower the build-up of titres of scar-derived axon growth inhibitors by degradation and suppression of their synthesis (Davies et al., 2004; Davies et al., 2006) in and around the SCI injury site, leading to reduced binding of inhibitory ligands to their receptors expressed on axon growth cones, including the protein tyrosine phosphatase receptor sigma (PTPRS) and the leucocyte common antigen related receptor (LAR) for CSPG (Shen et al., 2009; Sharma et al., 2012); the neuropilin/plexin receptor complex (reviewed by Sandvig et al., 2004) for Sema3A; and NgR and PirB for the myelin-derived inhibitory ligands (Liu et al., 2002; Wang et al., 2002). After ligand binding, these receptors activate intracellular signalling pathways which converge on the ras homolog gene family member A (RhoA)/Rho associated protein kinase (ROCK) (RhO/ROCK) intracellular signalling pathway (which regulates actin polymerisation in axon growth cones) inducing growth arrest through growth cone collapse (Sandvig et al., 2004; Ahmed et al., 2014). However, it is not known if suppression of EGFR activity by Decorin (Iozzo et al., 1999; Csordas et al., 2000; Zhu et al., 2005) is correlated with concomitant inhibition of Rho/ROCK signalling to protect against growth cone collapse (Minor et al., 2011).

Axon regeneration in SCI lesions after Decorin treatment

The expectation that suppression of growth inhibitory ligands by Decorin would promote axon regeneration after SCI has not been realised since very few axons traverse Decorin-treated spinal cord wounds (Moon and Fawcett, 2001; Davies et al., 2004, 2006; Ahmed et al., 2014) and might be deemed counter-intuitive if the motoring analogy applies that releasing the brake will not initiate forward motion unless the accelerator is engaged. This concept implies that robust CNS axon regeneration may only be possible when disinhibitory (including anti-fibrotic) and axogenic treatments are combined and is borne out by the observations that treatment with an NgR signalling blocker must be supplemented with NTF to achieve axon growth through a CNS wound (Douglas et al., 2009; Berry et al., 2011). Nonetheless, Decorin does have limited axogenic properties, exemplified *in vivo* and by the growth of neurites in Decorin-treated adult dorsal root ganglion neurons grown

on inhibitory CSPG and CNS myelin substrates without the presence of plasmin (Minor et al., 2008). Since EGFR blockade promotes some spinal cord motor neuron (Erschbamer et al., 2007) and retinal ganglion cell axon growth (Koprivica et al., 2005) (although the latter claim has been challenged by Douglas et al. (2009)), this axogenic effect of Decorin has been attributed to the suppression of EGFR (Minor et al., 2008). NTF stimulate axon regeneration by activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway, which promotes axogenic protein synthesis and protects against growth cone collapse through down-stream mammalian target of rapamycin (mTOR) and glycogen synthase kinase 3β (GSK3β), respectively (Morgan-Warren et al., 2013). Moreover, NTF induce regulated intramembranous proteolysis (RIP) of the transmembrane p75/TROY signalling moieties of the NgR trimeric complex (Ahmed et al., 2005, 2006) blocking Rho/ROCK pathway-mediated depolymerisation of actin in growth cones thereby preserving their functional integrity. Moreover, it has been suggested that binding of Decorin to the transcription factor STAT3 regulates Sema3A expression and that activation of the ErB4 receptor (an EGFR family member) by Decorin suppresses STAT3 through suppressor of cytokine signalling 3 (SOCS3) and Src homology phosphatase-1 (SHP-1) production (Minor et al., 2011) resulting in reduced levels of Sema3A in a SCI wound.

The assertion that Decorin treatment is a panacea for SCI is tempered by the caveat that scar tissue may develop by default if axon regeneration fails, since scarring is universally absent in experimental CNS lesions when they are traversed by significant numbers of regenerating axons (Berry et al., 2008; Park et al., 2008; Liu et al., 2010); a phenomenon that may be explained by the observation that regenerating axons stimulate MMP/tPA release from astrocytes and inhibit the production of TIMP/PAI-1, thereby impairing the formation and promoting the dissolution of CNS scar tissue (Ahmed et al., 2005). Massive scarring and cavitation are unfailing sequelae of spinal cord trauma (Edgar and Quail, 1994; Fitch et al., 1999; Ahmed et al., 2014; Surey et al., 2014), demonstrating that the growth cones of the few axons spontaneously regenerate after SCI has no impact on scar deposition. Accordingly, we suggest that a combined NTF and Decorin treatment regimen would act synergistically to depress scar formation and have added value in promoting the regrowth of lost connections, offering the hope of functional recovery in SCI patients.

Conclusions

Delivery of Decorin to SCI sites greatly reduces scarring and the accumulation of associated axon growth inhibitory ligands in both acute and chronic scenarios, but has restricted effects on the promotion of axon growth. Thus, we suggest that return of function in SCI patients requires the application of a combined Decorin and NTF treatment.

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