CD4$^+$ Tregs may be essential for solving astrocyte glial scar deadlock

Michel Edwar-Mickael*, Norwin Kubick

Glial scar is at the heart of the insolvability of spinal cord injury riddle. Spinal cord injury constitutes one of the worst fears for many active individuals. In addition to its economic burden on the global health system, this injury represents a fate of permanent disability for millions of patients who before their injury enjoyed a mobile lifestyle (Silver and Miller, 2004; Yang et al., 2020). Unfortunately, once severed, the central nervous system axons are not capable of regeneration. The main barrier to regeneration attempts is the formation of a glial scar layer which consists mainly of astrocytes.

Astrocytes forming the glial scar employ three mechanisms to inhibit regeneration. (i) They form a physical barrier that prevents regeneration attempts by neurons. (ii) Astrocytes also produce chondroitin sulfate proteoglycans (CSPG) which inhibit neural growth. Although other cell types such as macrophages and oligodendrocytes similarly produce CSPG, astrocytes are considered one of the main resources of these proteoglycans. CSPGs bind to leukocyte common antigen-related phosphatase and in turn inhibit neural axonal growth through inactivating Akt and activating RhoA signals (Fisher et al., 2011). A similar pathway is used by CSPGs to inhibit neural regeneration through binding to the redundant nogo receptor family members NgR1 and NgR3 (Dickendesher et al., 2012). CSPGs can also inhibit neural regeneration through binding to protein tyrosine phosphatase-sigma. This was demonstrated by efficient neural growth of the corticospinal tract in protein tyrosine phosphatase-sigma knockout mice in the presence of CSPG (Chien and Ryu, 2019; Dyck et al., 2019). (iii) Certain astrocytes subpopulations such as A1 were shown to be neurotoxic. A1 astrocytes have been revealed to eradicate neurons *in vitro* (Liddelow et al., 2017). They have also been shown to accumulate around the lesion core during spinal cord injury (Qian et al., 2019). Interestingly, it was demonstrated that inflammatory factors play a critical role in increasing the activation of the A1 subtype, hinting towards a previously unknown role for the immune response during spinal cord injury (Qian et al., 2019).

CD4$^+$ Tregs constitute a new hope to inhibit excess A1 astrocytes activation. CD4$^+$ helper T cells are a versatile group of cells consisting of a large spectrum of various populations (Mickael et al., 2020). CD4$^+$ Th1 and CD4$^+$ Th17 are pro-inflammatory and have been shown to increase astrocyte reactivity during neuroinflammatory diseases (Kubick et al., 2020). Conversely, CD4$^+$ Tregs are known to perform a regulatory function and a neuroprotective role (Bhaumik and Basu, 2017). Interestingly, using adoptive transfer of Treg in mice devoid of CD3e, it was shown that wild-type but not amphiregulin knockout Tregs cells could suppress excess astrogliosis. Furthermore, it was demonstrated that amphiregulin suppressed interleukin (IL)-6 induction in astrocytes *in vitro* and inhibited phosphorylation of STAT3 in ischemic mice brains *in vivo* (Ito et al., 2019). Furthermore, administration of anti-IL6R reduced astrogliosis in DEREG (Tregs depleted) mice (Ito et al., 2019). These observations suggest that Tregs are capable of inhibiting astrogliosis through suppressing the IL6-STAT3 pathway by producing amphiregulin (**Figure 1**).

Collectively, therapeutically applying Tregs at the lesion core after spinal cord injury could prove to be an important strategy in rescuing the ability of neural regeneration. Future experiments are needed to validate this argument and also to investigate the dynamics of the glial scar formation, astrocytes accumulation and CSPG production in terms of the interactions between Tregs and A1 astrocytes on a single-cell level (Kubick et al., 2020).

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References

Bhaumik S, Basu R (2017) Cellular and molecular dynamics of Th17 differentiation and its developmental plasticity in the intestinal immune response. Front Immunol 8:254.
Chien PN, Ryu SE (2019) Protein tyrosine phosphatase σ in proteoglycan-mediated neural regeneration regulation. Mol Neurobiol 47:220-227.
Dickendesher TL, Baldwin KT, Mironova YA, Koriyama Y, Raiker SJ, Askew KL, Wood A, Geoffroy CG, Zheng B, Liepmann CD, Katagiri Y, Benowitz LI, Geller HM, Giger RJ (2012) NgR1 and NgR3 are receptors for chondroitin sulfate proteoglycans. Nat Neurosci 15:703-712.
Dyck S, Kataria H, Akbari-Kelachayeh K, Silver J, Karimi-Abdolrezaee S (2019) LAR and PTPσ receptors are negative regulators of oligodendrogenesis and oligodendrocyte integrity in spinal cord injury. Glia 67:125-145.
Fisher D, Xing B, Dill J, Li H, Hoang HH, Zhao Z, Yang XL, Bachoo R, Cannon S, Longo FM, Sheng M, Silver J, Li S (2011) Leukocyte common antigen-related phosphatase is a functional receptor for chondroitin sulfate proteoglycan axon growth inhibitors. J Neurosci 31:14051-14066.
Ito M, Komai K, Mise-Omata S, Iizuka-Koga M, Noguchi Y, Kondo T, Sakai R, Matsuo K, Nakayama T, Yoshie O, Nakatsukasa H, Chikuma S, Shichita T, Yoshimura A (2019) Brain regulatory T cells suppress astrogliosis and potentiate neurological recovery. Nature 565:246-250.
Kubick N, Flournoy PCH, Enciu AM, Manda G, Mickael ME (2020) Drugs modulating CD4$^+$ T cells blood-brain barrier interaction in Alzheimer's disease. Pharmaceutics 12:880.
Kubick N, Henckell Flournoy PC, Klimovich P, Manda G, Mickael ME (2020) What has single-cell RNA sequencing revealed about microglial neuroimmunology? Immunity Inflamm Dis 8:825-839.
Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung WS, Peterson TC, Wilton DK, Frouin A, Napier BA, Panicker N, Kumar M, Buckwalter MS, Rowitch DH, Dawson VL, Dawson TM, Stevens B, et al. (2017) Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541:481-487.
Mickael ME, Bhaumik S, Basu R (2020) Retinoid-related orphan receptor RORγt in CD4$^+$T cell mediated intestinal homeostasis and inflammation. Am J Pathol 190:1984-1999.
Qian D, Li L, Rong Y, Liu W, Wang Q, Zhou Z, Gu C, Huang Y, Zhao X, Chen J, Fan J, Yin G (2019) Blocking Notch signal pathway suppresses the activation of neurotoxic A1 astrocytes after spinal cord injury. Cell Cycle 18:3010-3029.
Silver J, Miller JH (2004) Regeneration beyond the glial scar. Nat Rev Neurosci 5:146-156.
Yang T, Dai Y, Chen G, Cui S (2020) Dissecting the dual role of the glial scar and scar-forming astrocytes in spinal cord injury. Front Cell Neurosci 14:78.

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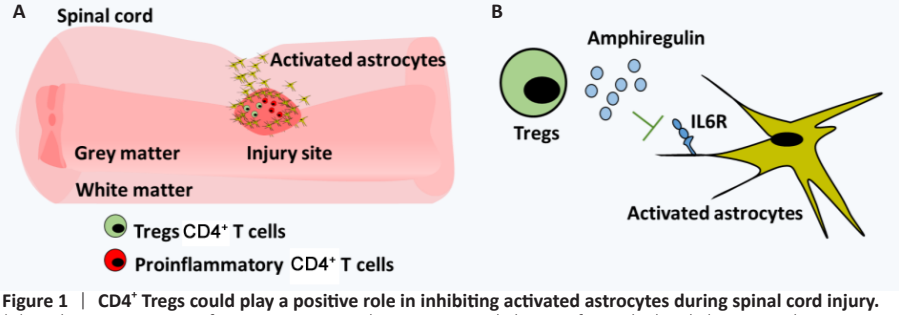

Figure 1 | **CD4$^+$ Tregs could play a positive role in inhibiting activated astrocytes during spinal cord injury.** (A) As the injury progress from an acute to a chronic state, a glial scar is formed. The glial scar mainly consists of fibroblasts, immune cells, and reactive astrocytes. Reactive astrocytes hinder neuro-regeneration through forming a barrier, being neurotoxic, or producing chondroitin sulfate proteoglycans (CSPGs). Proinflammatory immune cells are known to increase astrocyte reactivity. (B) Anti-inflammatory immune cells such as Tregs constitute a novel approach for constraining astrocytes activation through the production of amphiregulin that inhibits the IL6-STAT3-GFAP pathway. Experimental validation of this approach is yet to be performed. IL: Interleukin.