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Gas6/Axl requirement for taming inflammation and enhancing remyelination

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MS is a disease of unknown etiology in which the body's immune cells target myelin, the protective and insulating coating of nerves in the CNS. The CNS damage resulting from MS causes wide-ranging symptoms in the estimated 2.3 million people affected by the disease worldwide. Several animal models of demyelinating diseases aid in the study of MS, including myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (MOG-induced EAE) and cuprizone induced demyelination/remyelination. Gas6 is the sole ligand for the Axl receptor, a member of the Tyro3/Axl/Mertk family of receptor tyrosine kinases shown to have anti-inflammatory and promyelinating effects. Previous research demonstrates that $Gas6^{-/-}$ and/or $Axl^{-/-}$ single knockout mice undergo more severe demyelination and more inflammation than WT mice in response to EAE. Additionally, delivery of Gas6 to the CNS dampens the immune response and improves the clinical outcome of this disease. Furthermore, cuprizone fed $Axl^{-/-}$ and $Gas6^{-/-}$ mice exhibit a lag in debris clearance, contributing to their delay in recovery. Current studies are examining the disease course and remyelination process of EAE and the cuprizone model, respectively, in $Axl^{-/-}Gas6^{-/-}$ double knockout mice (DKO). The DKO mice display an atypical EAE disease course demonstrating that Gas6-Axl signaling may play a crucial role in the disease. Furthermore, DKO mice show little to no remyelination in the cuprizone model, as well as significantly fewer oligodendrocytes in the corpus callosum at 5 weeks and 6 weeks, and axonal damage at 6 weeks cuprizone+3-weeks cuprizone withdrawal compared to WT mice.

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Activation of α7 nicotinic acetylcholine receptor improves blood-brain barrier integrity

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Stroke is an important risk factor and one of the most devastating complications of bone fracture. We showed previously that bone fracture at the acute stage of ischemic stroke worsens, and activation of α7 nicotinic acetylcholine receptor (α7 nAchR) improves stroke recovery through attenuation of inflammation. We hypothesized that activation of α7 nAchR also reduce astrocyte oxidative stress and improves blood-brain barrier integrity. Stroke model was created by permanent occlusion of the distal middle cerebral artery (pMCAO). Tibia fracture was performing 1 day after pMCAO. Mice were treated intraperitoneally with 0.8 mg/ kg PHA 568487 (PHA, α7 nAchR-specific agonist), 6 mg/kg methyllycaconitine (MLA, α7 nAchR antagonist), or saline 1 and 2 days after pMCAO. Brain water content was assessed by measuring the wet and dry weight 3 days after pMCAO. The expression of monoamine oxidase B (MAO-B) in astrocytes and tight junction proteins were quantified. We found tibia fracture increased water content in the ischemic stroke brain ($p<0.001$) and MAO-B positive astrocytes, and decreased tight junction protein expression. Compared to saline treatment, PHA treatment reduced and MLA increased water content, and MAO-B positive astrocytes in pMCAO and pMCAO plus tibia fracture mice. PHA treatment also increased and MLA decreased tight junction protein expression. Therefore, in addition to inhibiting inflammation, activation of α7 nAchR also reduces astrocyte oxidative stress and improves blood-brain barrier integrity. Thus, the α7 nAchR-specific agonist can be developed into a new therapy for improving recovery of patients with stroke or stroke plus bone fracture.

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