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Title: Transglutaminase 2 Inhibition promotes recovery after spinal cord injury: modulating the astroglial response to CNS injury

Abstract:

After traumatic injury to the CNS, reactive astrocytes play a central role in mediating the tissue injury response. While astrocytes play numerous important roles in promoting neuronal health and function, reactive astrocytes may actually inhibit long-term regeneration. The molecular mechanisms that cause reactive astrocytes to adopt either unique phenotype are not well understood. Here we demonstrate that Transglutaminase 2 (TG2), which is rapidly upregulated in astrocytes after injury, plays a key role in regulating the response of astrocytes to insults. We find that inhibition of TG2 activity in a spinal cord contusion injury (SCI) model significantly improves injury outcomes. Conditional deletion of TG2 in astrocytes (TG2-A-cKO) resulted in a significant improvement in motor function following SCI. GFAP and NG2 immunoreactivity, as well as the number SOX9 positive cells – all of which serve as markers of reactive gliosis - were significantly reduced in TG2-A-cKO mice.

To test whether TG2 is a viable clinical candidate for acute treatment of SCI, we next tested the effect of highly specific TG2 inhibitors on SCI outcome. Proof of principle experiments were conducted using the highly specific 2nd generation TG2 inhibitor, VA4. Treatment of wild type mice with VA4 significantly improved functional recovery after SCI similar to the genetic model. Next, we tested the therapeutic benefit of NM72, a 3rd generation TG2 inhibitor. Like VA4, NM72 is an irreversible TG2 inhibitor but with a 30-fold greater kinetic solubility, reduced non-specific protein binding, and a 38-fold greater biological half-life. Like VA4, NM72 significantly improved motor deficits after T9 contusion SCI. In addition, animals treated with NM72 showed a greater and more significant benefit by day 7 post injury, and NM72-treated animals achieved a plateau of functional recovery sooner than VA4 treated animals. Together these findings indicate the beneficial and highly reproducible outcomes of the use of TG2 inhibitors as a novel strategy for the treatment of SCI and potetially other CNS injuries.