Toll-like Receptor 9 Antagonism Inhibits Spinal Cord Astrocyte Proliferation and Migration

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Introduction

The glial scar has been considered as an impediment to axonal regeneration, albeit studies also show that astrocytes are necessary for axonal re-growth following spinal cord injury (SCI). The principal cell type that form the glial scar are proliferating and migrating reactive astrocytes, which secrete both helpful and harmful effectors. Modulation of astroglial proliferation and migration can alter the properties of the glial scar and thereby, influence the outcomes of SCI. Evidence indicates that Toll like receptors (TLRs), which are expressed by SC neurons, glia and infiltrating immune cells, play important roles in SCI. Our laboratory has previously shown that a TLR9 antagonist, CpG ODN 2088, administered intrathecally, improves the functional and histopathological outcomes of SCI, and attenuates the pro-inflammatory phenotype of SC astrocytes, in vitro, through direct actions. The current studies were undertaken to determine whether the TLR9 antagonist modulates astroglial functions pertinent to glial scar formation such as proliferation and migration.

Methods

Mixed glial cultures, derived from the SC of postnatal day 2-3 mouse pups were used to isolate astrocytes,

Results

CpG ODN 2088 significantly reduced by 40% the number of proliferating astrocytes ($p<0.001$; $n=4$). The antagonist also significantly decreased the astroglial migration into the gap formed by the scratch. These effects necessitated TLR9 since CpG ODN 2088 did not affect the proliferation or migration TLR9-/- astrocytes.

Conclusions

Astroglial TLR9 antagonism inhibits both proliferation and migration, in vitro. Thus, CpG ODN 2088 has the potential of targeting astrocyte functions pertinent to glial scar formation.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the importance of TLR9 in astroglial function especially as it relates to glial scar formation following SCI, 2) Discuss, in small groups, whether inhibition of TLR9 in the spinal cord following injury is beneficial or detrimental to the injury outcomes, 3) Identify a potential therapeutic approach to modulate glial scar formation following SCI.

References