Repairing spinal cord nerves

Ronald Schnaar
The Johns Hopkins School of Medicine
Earliest medical text on battlefield trauma, in which spinal cord injury was deemed: “An ailment not to be treated”
Axon transection in traumatic nerve injury

Modified from Brittis and Flanagan, Neuron (2001) 30, 11
Even after a microcrush injury, nerve axons fail to regenerate after injury

optic nerve microcrush:

Axon retraction
24 h post-injury

Regeneration failure
2 wks post-injury

• The peripheral nervous system (PNS) is more permissive for axon regeneration than the central nervous system (CNS).

• When PNS nerve sheath is grafted into a CNS injury, some CNS axons regenerate through the graft

Adult Rat CNS axon regeneration
In vitro, superior cervical ganglion neurites extend on a surface coated without myelin (P) or on PNS myelin (PR), but not on a surface coated with CNS myelin (CR)

Axon transection in traumatic nerve injury

Modified from Brittis and Flanagan, Neuron (2001) 30, 11
Multiple axon regeneration inhibitors (ARI’s) accumulate at the site of a CNS injury

• Myelin-associated glycoprotein (MAG)
  – on residual myelin

• Nogo
  – on residual myelin

• OMgp
  – on residual myelin

• Chondroitin sulfate proteoglycan (CSPG)
  – on residual myelin and the astroglial scar

Blocking one or more ARI may enhance axon regeneration after spinal cord and other CNS injuries
AXON REGENERATION INHIBITORS
A working model with therapeutic opportunities

Modified from Woolf & Bloechlinger, Science (2002) 297, 1132
MAG on myelin engaging its receptors on axons

Modified from Sharon and Lis (1993) Scientific American
MAG receptor GD1a on axons

NeuAc α3 Gal β3 GalNAc β4 (NeuAc α3) Gal β4 Glc β Cer
Sialidase cleaves the terminal sialic acid from GD1α

Gal β3 GalNAc β4 (NeuAc α3) Gal β4 Glc β Cer
NeuAc $\alpha$3 Gal $\beta$3 GalNAc $\beta$4 (NeuAc $\alpha$8 NeuAc $\alpha$3) Gal $\beta$4 Glc $\beta$ Cer
Sialidase cleaves the terminal sialic acid from GD1a

Gal β3 GalNAc β4 (NeuAc α3) Gal β4 Glc β Cer
MAG inhibits axon outgrowth from nerve cells *in vitro*

Control surface

Myelin-derived MAG

Vyas et al. (2005) J. Biol. Chem. 180, 16301
Myelin-derived MAG inhibition of axon outgrowth is reversed by anti-MAG antibody and by sialidase.

Vyas et al. (2005) J. Biol. Chem. 180, 16301
SIALIDASE PRECLINICAL STUDIES

- Brachial Plexus injury
- Contusion SCI
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BRACHIAL PLEXUS INJURY & REPAIR MODEL

- Cut C8 ventral and dorsal roots
- Insert peroneal nerve graft into cord
- Deliver hydrolases to the site of injury
- After 4 wks cut graft 7 mm from cord
- Immerse cut end in Fluororuby dye
- After 3 d Fix, section, count retrograde labeled spinal neurons

Axon regeneration inhibitors: reversal by bacterial hydrolases

Modified from Woolf & Bloechlinger, Science (2002) 297, 1132
BRACHIAL PLEXUS RESULTS
Sialidase and chondroitinase (but not PIPLC) enhance spinal axon regeneration

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Intrathecal sialidase delivery to treat spinal cord contusion injury in the rat

- Carrier (saline, rat serum albumin)
- Sialidase in carrier

Recombinant *V. cholerae* sialidase plasmid kindly provided by G. Taylor, St. Andrews, UK
2 U/ml delivered intrathecally – 50 μl initial dose then 0.4 μl/h for 14 days via osmotic pump
Spinal cord contusion injury model

Infinite Horizons Impactor, Precision Scientific & Instr.
Sialidase efficacy on spinal tissue *in vivo*

Sialidase promotes motor behavioral recovery after spinal cord contusion injury

Mountney et al. (2010) Proc Natl Acad Sci USA 107, 11561
Sialidase promotes cardiovascular reflex recovery after spinal cord contusion injury

**Baroreceptor reflex**

Arterial pressure is lowered and raised with drugs

Renal sympathetic nerve activity (RSNA) changes reciprocally.

Normal relationship between blood pressure and RSNA

Sialidase promotes cardiovascular reflex recovery after spinal cord contusion injury

Exemplary results

Zahner and Schramm, unpublished
Sialidase promotes cardiovascular reflex recovery after spinal cord contusion injury

Mountney et al. (2010) Proc Natl Acad Sci USA 107, 11561
Sialidase increases axon sprouting caudal to a contusion injury

Mountney et al. (2010)
*Proc Natl Acad Sci USA* 107, 11561
Axon regeneration inhibitors: reversal by bacterial hydrolases

Modified from Woolf & Bloechlinger, Science (2002) 297, 1132
Sialidase alone enhances recovery of hindlimb mechanics after contusion spinal cord injury

Sialidase alone enhances grid walking

Sialidase alone enhances axon sprouting below the lesion (5-HT)

Mountney et al. (2013)
J Neurotrauma 30, 181
• Spinal cord injury is no longer “untreatable”. Rehabilitation, electrical stimulation, and drug treatments are in use or on the horizon.

• Reversal of axon regeneration inhibitors may provide rationally-designed therapies to enhance recovery after traumatic spinal cord injury.
Collaborators

Schnaar Lab

• Jeff Aston
• Ileana Lorenzini
• Andrea Mountney
• Chris Riley
• Elizabeth Sturgill
• Katarina Vajn
• Lynda Yang

Neurology

• Andres Hurtado
• Martin Oudega

Biomedical Engineering

• Lawrence Schramm
• Matthew Zahner

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