Biophysical Stimuli Induce Demyelination via an Integrin Dependent Mechanism

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Chronic nerve compression (CNC) Injury

- Thoracic outlet, Spinal Nerve Root Stenosis, Cubital Tunnel syndrome, Tarsal tunnel syndrome
- Caused by chronic mechanical insult to the peripheral nerve
- Presenting symptoms:
  - Pain
  - Tingling
  - Weakness

Ulnar nerve at the elbow after external neurolysis
Treatment of CNC Injury

- Steroid Injections
- NSAIDS, rest, physical therapy
- Surgery
- Limited effectiveness of non-surgical management and surgical treatment in later stages of disease
- Limited understanding about the molecular pathogenesis
In vitro model of CNC injury
In vitro model: biophysical stimuli

Friebos L and Gupta R. Journal of Neurotrauma 2009
Hydrostatic Compression Chamber Design

- Houses several isolated culture wells of equal dimensions.
- Allows for microscopic visualization and imaging of the cells during pressurization using an inverted microscope.
- Neurons and Schwann cells are cultured on coverslips and transferred into the chamber prior to experimentation.
Hydrostatic Compression Chamber

- pH Meter
- In-Line Air Filter
- Flowmeter with Control Valve
- Micro pH Electrode
- Pressure Sensor
- Dissolved O$_2$ Sensor
- dO$_2$ Meter
- Diaphragm Air Compressor
- LabView Software
Demyelination assayed by immunostaining myelin basic protein (MBP)

Scale bar = 50um
Biophysical Stimuli induces Demyelination

* P=0.04
Are integrins mediating the observed in-Vitro response?
In-Vitro Injury Alters Phosphorylation of Integrin associated 2nd Messengers
The effect of functional blocking integrin antibodies

- blocking Ab
+ blocking Ab
GAPDH
functional blocking integrin antibodies alleviate demyelination

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P = 0.01
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Summary

• Hydrostatic pressure induces demyelination. Biophysical stimuli appears to potentiate its effect.

• The 2\textsuperscript{nd} messenger pSrc is upregulated with biophysical stimuli
  − This process appears to be mediated by integrins.

• Blocking integrin signaling reduces compression-induced demyelination

• 2\textsuperscript{nd} messengers co-localize with Schwann cells.