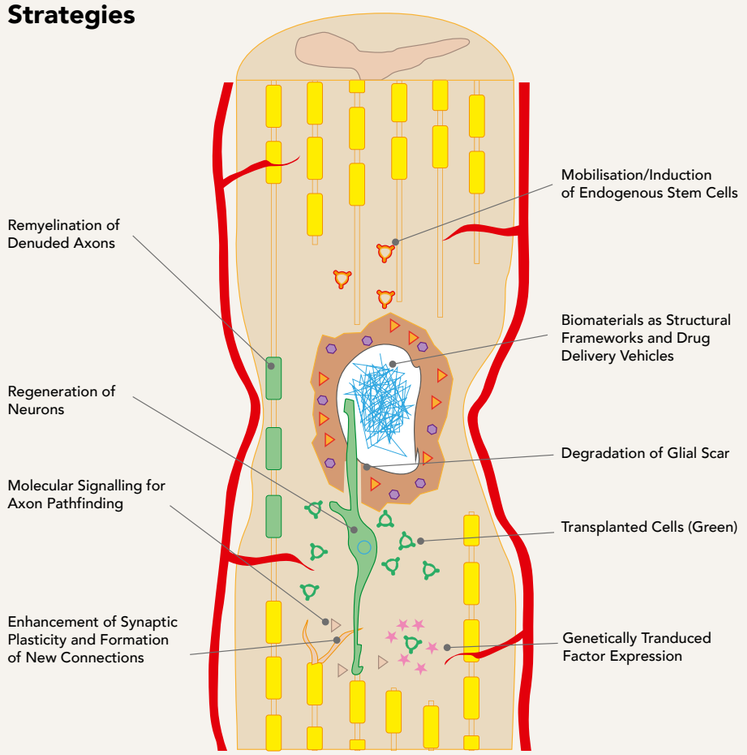
Treating the wounded: neuroprotection strategies in spinal cord injury

Much of the nerve damage associated with spinal cord injury (SCI) is secondary to the initial trauma. **Dr Michael Fehlings** and his team at the Toronto Western Hospital, University Health Network have been successful in developing strategies to limit these effects.

Traumatic SCI affects millions of people each year, with a disproportionate number coming from the under-30 age group. This means that lifetime treatment costs can run to millions of dollars per patient. Dr Fehlings' initial work in the 1990s identified that secondary degeneration of neurons occurs around the initial injury, prompting him to further investigate how this might be prevented as well as developing strategies to promote regeneration of the damaged tissue.

Cellular damage in SCI is not limited to the neurons, but also affects the blood supply by damage to the microvasculature. This potent mix of damaged cells, decreased blood flow and disruption of the endothelial barrier between blood and spinal cord, means the injury site becomes a mass of chemicals with the potential to initiate damaging inflammatory signalling cascades. Cell debris promotes microglia (the protective cells of the nervous system) to release cytokines that activate other elements of the body's response to cell damage. Although intended to assist with clearing cell debris and fighting infection, in any such process collateral damage is inevitable and further cell death results. On top of this, glutamate (a fundamental neurotransmitter) released as part of normal signalling, is not effectively cleared, leading to damage to neurons through over-excitation. There are also systemic and local autoregulation deficits, as the damage affects normal nerve impulses, which further contribute to secondary degeneration. Dr Fehlings has identified each of these elements as potential targets for therapeutic intervention.

Neuroregenerative Strategies



PREVENTION IS BETTER THAN CURE

One such promising target is the toxicity associated with excessive glutamate signalling at the injury site. Dr Fehlings and colleagues have identified a complex process by which increased activation of sodium channels during ischemia (low oxygen related to reduced blood flow) results in more uptake of calcium ions, which promotes glutamate release into the extracellular space. This is toxic to nearby cells, but has the benefit of being able to be addressed by drugs targeting the mechanisms associated with these signalling molecules.

Glutamate in particular, has long been a target for drug-based therapies, as dysregulation is implicated in a range of neurological conditions such as amyotrophic lateral sclerosis (ALS, of ice bucket fame), Huntington's Disease and type 1 spinal muscle atrophy. Dr Fehlings therefore turned to established therapies for these conditions in his search for novel neuroprotective agents that could be utilised in SCI.

THE RISE OF RILUZOLE

Riluzole was conceived in the 1980s as an anti-epileptic for its properties as a sodium channel blocker. Although never particularly successful at improving outcomes for those patients, it has been found to improve outcomes significantly for ALS patients in a number of large and well-controlled clinical trials. Based on its safety profile and approval for use in humans for this purpose, Dr Fehlings' team started to investigate its neuroprotective properties in animal models of cervical spondylotic myelopathy (CSM), an age-related compression of the spinal cord which has similarities to traumatic SCI. Decompression surgery is routinely used to alleviate the stress on the damaged tissue. Dr Fehlings' group coupled this with administration of riluzole in one group while the other had the surgical treatment alone. These studies demonstrated superior neurobehavioral outcomes and preservation of spinal tissue in the riluzole treatment group, strongly indicating a glutamate-related mechanism underlying the condition's effects. An ongoing clinical trial ▶

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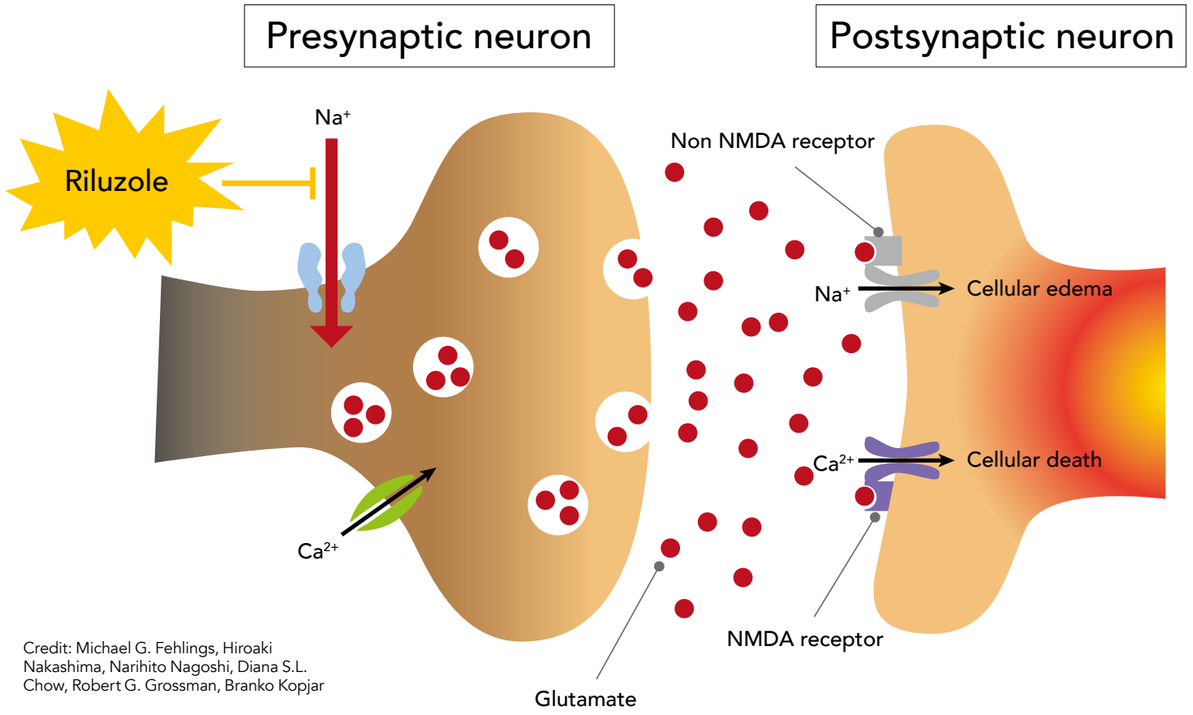

Credit: Michael G. Fehlings, Hiroaki Nakashima, Narihito Nagoshi, Diana S.L. Chow, Robert G. Grossman, Branko Kopjar

is investigating if this is mirrored in humans with CSM.

The success of the CSM projects encouraged movement to clinical cases of SCI, and Dr Fehlings' team began a Phase I trial which provided safety and pharmacokinetic data as well as indicating neuroprotective benefits. A Phase IIb/III trial (the most rigorous test of efficacy on patients with the condition requiring treatment), known as the RISCIS trial, is currently underway. This double-blind, randomised, controlled trial enrols a large cohort of patients from eleven different medical centres. Riluzole is being administered to acute SCI patients for two weeks and its effects examined through motor and sensory scoring criteria after six months. Dr Fehlings' hypothesis is that, 'subjects with acute SCI treated with riluzole will experience superior neurological, functional and quality-of-life outcomes', paving the way for its use in routine clinical management of SCI.

A NEW FRONTLINE

Not satisfied with progressing treatments on just one front, Dr Fehlings and his team have also been investigating possible interventions to further promote recovery of damaged neurons. Stem cell therapy, though showing promise in this area, has been plagued by poor knowledge of the mechanisms of action, difficulty in reproducing results and problems associated with correct differentiation.

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To remedy this, Dr Fehlings and his colleagues have developed a combination approach using neural precursor cells (stem cells already destined to be neurons or their supporting glial cells) harvested from and transplanted into rats with SCI. Using multiple imaging and functional assessment techniques, they have identified that axon remyelination (repair of the insulating sheath around nerve fibres) is important in recovering motor function. Although more work is needed to ensure these effects are seen in other models, Dr Fehlings is convinced that, 'strategies to augment remyelination may lead to important functional improvements for patients with spinal cord injury'.

BRINGING IT ALL TOGETHER

These two different strands of Dr Fehlings' work are a good example of his belief that a combinatorial approach needs to be taken if advances in research are to be translated into significant functional gains for patients. Just as SCI is not limited to a single injury factor, so treatments need to be directed at diverse elements of the condition. Similarly, while treatments such as riluzole will have benefits for acute injury patients, there are already those living with severe disability who require neuroregenerative treatments such as stem cells if there is any hope of regaining functionality. Dr Fehlings, working in Toronto Western Hospital, has the sort of access to both clinicians and patients that is necessary to make this move from 'bench to bedside'.

Q&A

How important do you consider the issue of secondary injury to be in the treatment of acute SCI?

Secondary injury, which is a constellation of biomolecular factors initiated by ischemia, contributes in a substantial manner to the amplification of the primary mechanical trauma to the injured spinal cord. While the initial mechanical trauma is a rate-limiting determinant of the ultimate outcome following injury, the secondary injury is critically important as this is potentially modifiable by therapeutic strategies. This becomes particularly critical when one considers that preservation of only 10–20% of axons in the spinal cord can result in substantial recovery of neurologic function.

What possibilities does this create for developing neuroprotective strategies?

Targeting specific critical pathways which mediate the secondary injury provides unique opportunities to attenuate the severity of the secondary injury. The discovery that ischemia promotes the influx of sodium and calcium as well as glutamatergic excitotoxicity following acute spinal cord injury directly led to the discovery that riluzole could have an important potential clinical benefit for acute traumatic spinal cord injury. Ultimately, however, spinal cord injury is a heterogeneous phenomenon and it is likely that a number of complementary neuroprotective strategies will be required to optimise clinical outcomes. Some of the key pathways to target include programmed cell death, or apoptosis, as well as the inflammatory cascade which is initiated as part of the secondary injury mechanisms.

Riluzole has great promise, how do you expect it to progress into treatment?

Currently riluzole is being examined in two phase III randomised controlled trials – one for acute traumatic cervical spinal cord injury (RISCIS trial) and the other for a form of non-traumatic cervical spinal cord injury termed degenerative cervical myelopathy (CMS-Protect trial). Should riluzole show a positive impact in one or the other of these conditions, it is anticipated that the clinical uptake of riluzole for cervical spinal cord injury will be rapid. Riluzole is a safe drug which is readily accepted for use in ALS and thus, the application of this therapeutic strategy for cervical spinal cord injury should be rather straightforward.

Stem cell therapy has long been vaunted as the future of SCI treatment, how does your work build into that?

Our work is principally focused on neural stem cells which represent the developmental building blocks of the central nervous system. Spinal cord injury results in a significant loss of neural tissue and hence it is logical to conceive that the regeneration of lost neural tissue will require the use of neural stem cells. It is anticipated that, despite effective treatments targeting secondary injury, many patients will be left with substantial neurologic deficits following acute traumatic spinal cord injury. It is in these patients that complementary regenerative strategies could have a potential impact. It is anticipated that stem cell approaches, and in particular neural stem cells, could have a major role in optimising neurological recovery in these patients.

How does your position in Toronto assist with transferring your research to clinical practice?

My work in the Krembil Neuroscience Centre, at the Toronto Western Hospital and in the University of Toronto Spine Program combines a multi-disciplinary basic science and translational approach with the translation into clinical populations. In Toronto, we have the benefit of a strong linkage between basic pre-clinical science and clinicians who are adept at translating these discoveries. My role as the Vice Chair of Research in the department of Surgery at the University of Toronto and as the co-chairman of the University of Toronto Spine Program has enabled me to harness some of the remarkable translational scientific opportunities that exist in Toronto.

Detail

RESEARCH OBJECTIVES

Dr Fehlings' research on spinal cord injury has helped increase understanding of what happens after trauma to the spinal cord. He also focuses on ways to prevent further, secondary damage following spinal cord injury.

FUNDING

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BIO

Michael Fehlings is internationally recognized as one of the world's leading translational and clinical researchers in the field of spinal cord injury. His pioneering research has been critical in defining the mechanisms of secondary injury after spinal cord injury and the role of demyelination in post-traumatic neurological deficits.

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