# Schwann cell myelination

At University College London's Research Department of Cell and Developmental Biology, great progress has been made in understanding the role that Schwann cells play in allowing regeneration of injured nerves. **Professors Kristjan R Jessen** and **Rhona Mirsky** explain how a novel approach has highlighted the importance of these cells

**To provide some background, what role do Schwann cells play in the nervous system, and what has inspired your interest in these cells?**

Let us start by putting Schwann cells in context. It sometimes feels like the best kept secret in neuroscience that the nervous system (brain, spinal cord and peripheral nerves) is only partly made up of nerve cells. The majority of nervous system cells are, in fact, glial cells, which have quite distinct biological properties and function from nerve cells.

As with neurons, there are different types of glial cells. Schwann cells, the cell type we work on, is the main glial cell in peripheral nerves. These cells envelop all nerve fibres and are required for nerve development and function. But the aspect of these cells that we are excited about now is their role in nerve pathology. In particular, we are focused on the intriguing dichotomy that while the glial cells of the brain respond to injury by suppressing repair, Schwann cells respond in the opposite way by promoting repair and functional recovery.

**What are the interlocking issues in Schwann cell biology that have been addressed by your research group?**

Earlier work by our group centred on Schwann cell development. This involved a detailed molecular characterisation of known cell stages and led to the identification of a new cell type – the Schwann cell precursor – that provided the missing developmental link between the neural crest and Schwann cells. This, in turn, motivated the identification of signals that control these transitions and cell types. Importantly we also identified molecules, namely c-Jun and Notch that acted to inhibit the last critical step in Schwann cell development – the formation of an insulating sheath, myelin, around nerve fibres. This finding formed the basis for our current research on nerve repair.

**Can you give an outline of the research currently conducted in your laboratory?**

Damage to peripheral nerves triggers a striking transformation of the Schwann cells at and beyond the injury site, the Schwann cell injury response. This enables peripheral nerve fibres to regrow and restore function, in contrast to what is seen in the brain and spinal cord, where injury results in permanent disability. Our objective is to understand this important response. We have found that it is globally regulated by the transcription factor c-Jun, which on nerve injury activates two cellular programmes in Schwann cells, a dedifferentiation and a repair programme. In this way c-Jun directs the transformation of normal adult Schwann cells to a novel Schwann cell variant that is dedicated to support regeneration. We aim to understand how c-Jun controls the biology of this dedicated repair cell, how it interacts with other signals, including Notch and signals shown by other workers to be involved in Schwann cell injury, and how we can manipulate these factors to boost the repair programme to improve the success of nerve repair, an issue of significant clinical importance.

**Why is it that the molecular mechanisms that control the Schwann cell injury response have been poorly understood?**

In retrospect, we can perhaps see that a main reason was the inadequacy of one of the dominant ideas for describing the process. This viewed the injury response essentially as dedifferentation or reversal of myelination, which is the last step of Schwann cell differentiation. According to this hypothesis, the injury response represents a passive return to a default state, caused by injury-induced removal of signals that maintain differentiation/myelination. Within this framework there was little point in looking for novel signals that actively drive the process. This perspective changed when we realised that the injury response is better described as a double act – dedifferentiation coupled to activation of an alternative differentiation pathway specialised for repair, leading to a change in cellular function, a process that has much in common with processes called transdifferentiation in other systems.

**What would you say has been your most significant finding to date?**

The identification of the Schwann cell precursor made it possible to conceive a comprehensive outline of Schwann cell development, and this finding has led to numerous studies by other groups. Another significant finding is that repair in the peripheral nervous system depends on the activation of c-Jun in injured Schwann cells, and that c-Jun works by globally regulating the transdifferentiation of Schwann cells into dedicated repair cells. This may throw new light on the repair-inhibitory response of brain glial cells to injury, and hopefully result in novel ways to improve peripheral nerve repair.

PROFESSORS KRISTJAN R JESSEN AND RHONA MIRSKY

# Exploring the peripheral nervous system

An important study of Schwann cell myelination and response to nerve damage is unlocking key mechanisms relevant to nerve repair and pathology; mechanisms which could lead to new therapeutic targets for patients suffering from nerve injury or neuromuscular genetic disease

**AFTER INJURY, NERVE** fibres of the peripheral nervous system (PNS) have a remarkable ability to regenerate, leading to recovery of normal function. This process is governed by glial cells known as Schwann cells and by their unusual capacity to metamorphose into a cell that drives the healing process. In uninjured nerves, the Schwann cells are either non-myelinating or myelinating, the latter cells forming myelin sheaths around axons, which allow fast conduction of nerve impulses. In damaged nerves, however, Schwann cells transform their molecular properties and morphology and switch function to that of ensuring repair. These cells support the survival of injured neurons, stimulate nerve fibre growth and deal with breakdown of myelin that otherwise would hinder regeneration. They also form regeneration tracks, called Bands of Bungner, that guide nerve fibres back to appropriate destinations so that function can be restored. Schwann cells in injured nerves, Bungner cells, are therefore central organisers of nerve repair. In contrast, the closely related glial cells of the central nervous system (CNS) actively prevent axon growth and recovery following injury.

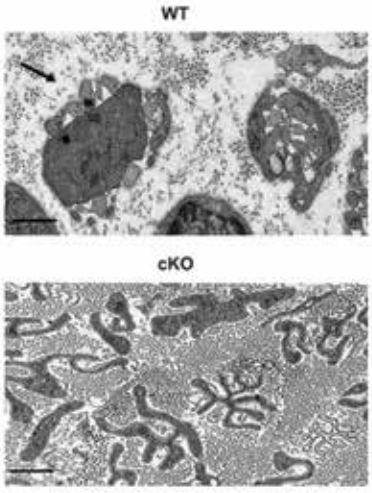


**FIGURE 1**. Electron micrographs showing normal and dysfunctional regeneration tracks in peripheral nerves, distal to an injury. The upper picture shows two normal regeneration tracks (one is arrowed). Each track is composed of a number of narrow, elongated Bungner Schwann cells shown here in a transverse section. The lower picture shows a comparable area from an injured nerve of a mouse without c-Jun in Schwann cells. Classical regeneration tracks do not form and the Schwann cells are irregular and flattened. WT: normal mice; cKO: mutant mice in which c-Jun in Schwann cells has been inactivated. Bar: 1 µm.

The remarkable plasticity of Schwann cells, and their ability to switch between differentiation states, is unparalleled in most other mammalian systems, and if manipulated could lead to improved nervous system repair and treatment for those suffering from neuropathies.

## SCHWANN CELL PRECURSOR

To analyse the processes that govern Schwann cell plasticity and to understand how this enables the regeneration of peripheral nerves, Professors Kristjan R Jessen and Rhona Mirsky of the Department of Cell and Developmental Biology at University College London, UK began by identifying the steps involved in the development of Schwann cells: "We sought to define cellular transitions and intermediary cell types that are required for a developing nerve to build adult Schwann cells from a transient stem cell population, the neural crest that is found in the mid-term embryo," they reveal.

As a result of these studies, Jessen and Mirsky were the first to identify the Schwann cell precursor. This cell type, which arises from the neural crest, goes on to form immature Schwann cells which then differentiate into myelin and non-myelin (Remak) adult Schwann cells. Building upon this clearer understanding of cellular transitions, Jessen and Mirsky were able to determine and investigate signals involved in controlling the transitions, including Neuregulin, transforming growth factor β (TGF β), Notch and Desert hedgehog (Dhh).

More recently, Jessen and Mirsky have adopted a fresh approach to study the Schwann cell response to nerve injury, which has led to some exciting findings. It was known that the Bungner cells generated after injury are dedifferentiated, losing the myelin sheaths and other features relevant to Schwann cell function in undisturbed nerves. Jessen and Mirsky realised, however, that perhaps of even greater significance, these cells also gain a number of other features that specifically promote repair. Therefore, the injury response taken as a whole represents reprogramming and a change of function, a process that resembles transdifferentiation which is well-described in other biological systems. On this basis, Jessen and Mirsky began a search for signals that control this important phenotypic

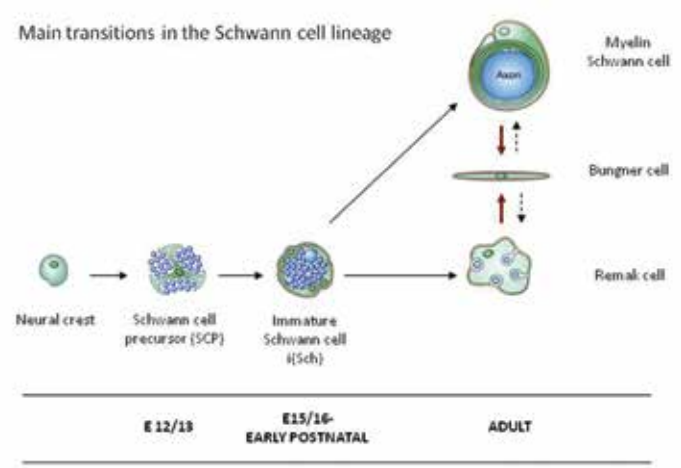


**FIGURE 2**. The main cell types and developmental and injury-induced transitions in the Schwann cell lineage. Black uninterrupted arrows: normal development. Red arrows: the Schwann cell injury response, resulting in the formation of the Bungner repair cell. Stippled arrows: post-repair reformation of myelin and Remak cells.

switch: "This alternative hypothesis immediately raised new and, as it has turned out, fruitful questions about how the repair programme is activated, how the dedifferentiation and redifferentiation programmes are coupled and whether we can identify pathways that amplify the repair programme to promote repair".

## C-JUN AND SCHWANN CELL INJURY RESPONSE

A key signal that appeared to determine the Schwann cell injury response was the transcription factor c-Jun, highly expressed in Schwann cells of cut nerves. Initially, Jessen and Mirsky found that mutant mice with conditional deletion of Schwann cell c-Jun showed a delayed loss of myelin proteins and mRNA in response to nerve transection. Because c-Jun in this way took part in controlling the Schwann cell response, and because Schwann cells in turn are potent regulators of nerve cells, this raised the question of whether Schwann cell c-Jun also controlled the way nerve cells reacted when peripheral nerves were damaged.

To address this, their laboratory first looked at the relative levels of neuronal death in mutant mice without Schwann cell c-Jun and control mice. They found that, following nerve injury, the mutant mice showed substantially higher levels of neuronal death. For example, following injury, small, unmyelinated dorsal root ganglia (DRG) sensory neurons were approximately twice as likely to die when Schwann cell c-Jun was absent. Importantly, about a third of the large myelinated DRG neurons died in the injured mutants, although these neurons are highly resistant to damage, both in control mice and in other species.

They also found that Schwann cell c-Jun controlled the rate of axonal regeneration, both *in vivo* and in cell culture models of nerve repair, and that this protein was key to the functional recovery of nerves following injury. When sensory and motor function in the mutant mice was measured, minimal functional recovery was reported even after 70 days, whereas in control mice, function was restored after 3-4 weeks.

## C-JUN ACTS AS A GLOBAL REGULATOR

Jessen and Mirsky have also unveiled the important role that c-Jun plays in gene expression in Schwann cells. Interestingly, this function of c-Jun appears restricted to injury and other pathological conditions such as genetic demyelinating diseases. Uninjured nerves of mutant mice were found to be physiologically normal, and comprehensive analysis of gene expression revealed only two differentially expressed genes. c-Jun does therefore not appear to have a significant role during the normal function of Schwann cells or in Schwann cell development.

In contrast, the Bungner cells generated after injury were strikingly dysfunctional. Analysis of gene expression in the injured nerve stumps of mutant and control mice revealed 172 significant differences. A wide range of molecules that have been reported to influence neuronal regeneration were abnormally expressed, including growth factors such as GDNF, artemin and BDNF, growth-associated proteins, cell surface adhesion molecules, as well as other transcription factors. Through these studies, Jessen and Mirsky have revealed that c-Jun controls the molecular reprogramming involved in the transformation of mature Schwann cells into the Bunger cells generated after injury. This finding has allowed them to conclude that c-Jun acts as a 'global regulator' of the Schwann cell repair programme that drives regeneration of injured nerves. This realisation could lead to better strategies for repair after accidental injury to peripheral nerves.

## NEUROPATHY TREATMENT

Identification and increased understanding of the role of Schwann cell c-Jun could also prove important in the quest for treatment of demyelinating or axonal neuropathies affecting the myelin sheath and axon, respectively. The most common inherited neuropathy is Charcot-Marie-Tooth disease (CMT). This disease can be demyelinating or axonal and is characterised by progressive loss of muscle tissue, touch sensation and motor function. There is currently no known cure for CMT and treatment options are limited.

Together with colleagues, Jessen and Mirsky are currently investigating the presence of c-Jun in the Schwann cell nuclei of pathological nerves. Preliminary results indicate that c-Jun is absent in intact, normal nerves yet present in diseased/dysfunctional nerves. Future studies should shed further light on these findings and determine whether c-Jun plays a positive or detrimental role. This in turn could inform the search for new therapeutic targets.

## INTELLIGENCE

### MECHANISMS OF SCHWANN CELL MYELINATION AND DEDIFFERENTIATION: RELEVANCE TO NERVE REPAIR AND PATHOLOGY

### OBJECTIVES

Unlike the brain and spinal cord, peripheral nerves regenerate when injured. This is because the nerve glial (Schwann) cells have a striking capacity to transform to a cell specialised for supporting repair. Two Schwann cell factors – c-Jun and Notch – control this transformation and have major impacts on neuronal injury responses. The aim is to understand how these factors work and to manipulate them to improve the outcome of nervous system injury.

### KEY COLLABORATORS

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**PROFESSOR RHONA MIRSKY** obtained her PhD degree in Chemistry from the University of Cambridge. She has been Professor of Neurobiology in the Research Department of Cell and Developmental Biology, UCL since 1990. Mirsky became a Fellow of the Academy of Medical Sciences in 1999.