

FOREWORD

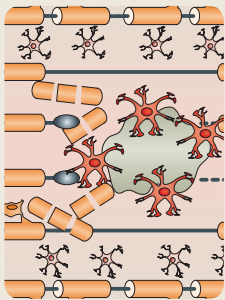
FOCUS CONTENTS

603 Can regenerating axons recapitulate developmental guidance during recovery from spinal cord injury?

Noam Y. Harel and Stephen M. Strittmatter

617 Glial inhibition of CNS axon regeneration

Glenn Yiu and Zhigang He



628 Therapeutic interventions after spinal cord injury

Sandrine Thuret, Lawrence D. F. Moon and Fred H. Gage

644 OPINION Spinal cord repair strategies: why do they work?

Elizabeth J. Bradbury and Stephen B. McMahon

Albert Aguayo
Centre for Research in
Neuroscience,
McGill University,
Montréal,
Quebec H3G 1A4,
Canada.
e-mail: albert.
j.aguayo@mcgill.ca
doi10.1038/nrn1974

Nerve regeneration revisited

Injury to the adult mammalian CNS can have devastating consequences. However, great strides have been made in our understanding of the barriers to regeneration and the mechanisms that enable restoration of function. Such advances have opened up a range of therapeutic avenues that are being explored, raising new hopes for the treatment of CNS injury.

The timing of this *Nature Reviews Neuroscience* focus issue on nerve regeneration coincides with the 100-year celebration of the awarding of the Nobel Prize to Santiago Ramón y Cajal, who was a leading figure in this field. Indeed, Cajal's book *Degeneration and Regeneration of the Nervous System* remains one of the most complete and accurate anatomical accounts of what happens when the nervous system is damaged.

Perhaps one of Cajal's most revealing comments on what enables the re-extension of cut axons was that it depends on "...external conditions, the presence or absence of auxiliary factors that are indispensable to the regenerative growth." These conditions, he added, influence the growth forces of the cell soma by alluring and guiding the leading tip of nerve fibres. He named this structure the 'growth cone' and considered it to be the nerve cell's sensor of its axonal environment. As indicated in the informative and well-balanced review by Yiu and He, new research, facilitated by the introduction of modern technologies, has revealed the identity and role of a good number of the growth promoting and inhibitory molecules that determine the axonal milieu conditions proposed by Cajal.

Cajal recognized how difficult it would be for the injured adult mammalian nervous system to heal by a process that involved replication of normal development. He compared the precision and orderly sequence in which neurons, axons and their connections are laid out in a small embryo with the adverse conditions imposed by a lesion that abruptly disrupts a mature CNS in which "...once development has ended, the founts of growth and regeneration ... dry up irrevocably". He also pointed out repeatedly that although axons in the PNS typically regenerate in large numbers, the course that they follow along a distal nerve stump is aberrant and seldom leads to their normal destination. Therefore, Cajal considered both axonal growth and appropriate guidance equally as important to the repair process, advancing the notion that "...if experimental neurology is some day to supply artificially the deficiencies in question ... it must give to the sprouts, by means of adequate alimentation, a

vigorous capacity for growth; and, place in front of the disoriented nerve cones ... specific orienting substances".

In their review, Harel and Strittmatter describe how much has been learnt in recent years about the genes and molecules responsible for the formation of normal neuronal circuits in the brain and spinal cord. Their account of the effects of relevant experimental manipulations of gene expression, cellular mechanisms and specific molecules in laboratory animals raises hopes that Cajal's proposed strategies for repair may indeed become feasible. Furthermore, in an Opinion article, Bradbury and McMahon discuss how certain functions might return even in the absence of restitution of the neural architecture acquired during normal development. It is indeed surprising how little is known of the minimal needs for growth and reconnection that are required for recovery of motor or sensory functions. It is clear, however, that a wide spectrum of compensatory and plastic mechanisms is involved in the spontaneous or treatment-related improvements that can occur after spinal cord injury. Harnessing this knowledge has already resulted in better regimes of clinical management.

During the past 50 years, improvements in medical and surgical care, the advent of rehabilitation programmes and new devices has drastically changed the prognosis of serious injuries to the spinal cord of humans from utter hopelessness, great suffering and early death to the expectation of long-term survival and a vastly improved quality of life. It is a sign of further progress that advances in neurobiology have now re-kindled hopes of translating new knowledge into ways to repair damaged neural tissues and help restore useful functions. The article by Thuret, Moon and Gage offers a comprehensive account of several efforts that have this aim. It is clear from their review that while there has never before been so much hope for significant breakthroughs, Cajal's anticipation of the formidable problems that still lie ahead is a cautionary message for us to heed.