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Review article

Encouraging regeneration in the central nervous system: Is there a role for olfactory ensheathing cells?

Josh King-Robson*

Peninsula Medical School, Knowledge Spa, Royal Cornwall Hospital Trust, Treliske, Truro TR1 3HD, United Kingdom

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ABSTRACT

The olfactory system holds a privileged position within the adult mammalian central nervous system; olfactory neurons undergo continual replacement and regeneration of synaptic contacts following injury, a feature shared by only a select few neuronal systems. The olfactory ensheathing cell, a glial cell found only in this system, is thought to play a central role in this regenerative process and has hence been the focus of numerous studies into promoting CNS regeneration following injury, in particular of the spinal cord.

In trials, olfactory ensheathing cells have achieved some of the most promising results yet in promoting CNS regeneration, including a degree of functional recovery in humans following CNS injury. Comparatively, numerous other strategies, both those involving cellular transplantation and those examining neutralisation of inhibitory factors of the CNS, have achieved limited success. A combinational strategy, with olfactory ensheathing cells at its centre, is arguably the best way forward in encouraging effective recovery following CNS injury.

This review examines the inhibitory environment of the CNS and the research to date on overcoming its effects on the regrowth of injured axons. The efficacy of therapies involving olfactory ensheathing cells, and the place of these therapies among the many other strategies being developed is examined.

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* Tel.: +44 7902163811.
E-mail address: josh.king-robson@students.pms.ac.uk

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Table 1
The glia and their respective roles.

	Cell	Role(s)
CNS	Astrocytes	Maintain blood–brain barrier Nutritive functions within CNS Regulate extracellular environment Provide structural support Aid in repair of breach following injury
	Oligodendrocytes	The myelinating cells of the CNS
	Microglia	(Inefficient) CNS phagocytes
PNS	Schwann cells	The myelinating cells of the PNS Aid in neuronal (Wallerian) regeneration
	Satellite cells	Encapsulate PNS neurons

Data compiled from: Yiu and He (2006), Raisman (2006), Bartolomei and Greer (2000), Kozlova (2008).

1. Introduction

While axons can regenerate under favourable circumstances in the injured peripheral nervous system (PNS), regeneration in the central nervous system (CNS) is negligible (Cajal, 1928). The effects of an injury to the CNS can therefore be devastating, with permanent paralysis and sensory loss distal to the lesion. The resulting paraplegia in 41.5% of patients and quadriplegia in 52.4% of patients (NSCISC, 2008) not only results in a decreased quality of life but also an increased risk of death from infection as a result of pressure sores, respiratory complications or urinary retention (Hartkopp et al., 1997).

Studies have shown that CNS axons will regenerate into a PNS nerve graft (Richardson et al., 1980), while regenerating PNS axons will not regrow across the root-cord transitional zone into the CNS (Cajal, 1928). This indicates that it is differences in the glial environment of the PNS and CNS (Table 1) that account for the failure of regeneration; the environment of the CNS is inhibitory to regeneration while the PNS environment supports it (Aguayo et al., 1981). Research in recent years has therefore focused on overcoming these differences, either by removing inhibitory factors from the CNS or introducing growth promoting factors present in the PNS. An area of particular excitement has been the use of glial cells of the olfactory system, olfactory ensheathing cells (OECs), to encourage axon growth. Research in this area has led to optimistic articles describing a "breakthrough" (Raisman, 2006) and "new horizons in SCI research" (Bartolomei and Greer, 2000). However, full functional recovery is yet to be achieved and the question remains as to what part OECs are to play among the plethora of prospective treatments under development.

2. Overcoming inhibition

The CNS has two major elements that inhibit axon regeneration following injury; the glial scar and myelin-associated inhibitors of axonal growth.

Following CNS injury, scar formation occurs at the lesion site, largely due to the activation of astrocytes locally, resulting in their hypertrophy and hyperplasia; a process known as gliosis (Maxwell and Kruger, 1965; Latov et al., 1979; Miller et al., 1986). Gliosis destroys the precisely aligned astrocytic arrays and replaces them with a densely packed scar which is not conducive territory for regenerating axons (Fig. 1) (Cajal, 1928). Furthermore, activated astrocytes produce large amounts of chondroitin sulphate proteoglycans (CSPGs), a group of molecules known to be inhibitory to axon growth (McKeon et al., 1991, 1995). The scar is hence both a physical and a biochemical barrier to regeneration. However, reactive astrocytes at the lesion site also fulfil an essential protective function, repairing the blood–brain barrier following damage, preventing an inflammatory response and associated tissue damage (Janzer and Raff, 1987; Bush et al., 1999; Faulkner et al., 2004).

In addition to activated astrocytes, meningeal cells and Schwann cells have also been identified at CNS lesion sites (Zhang et al., 1997; Ramón-Cueto et al., 2000; Ruitenberg et al., 2003; López-Vales et al., 2006). Significantly, the glia limitans, the interface between the

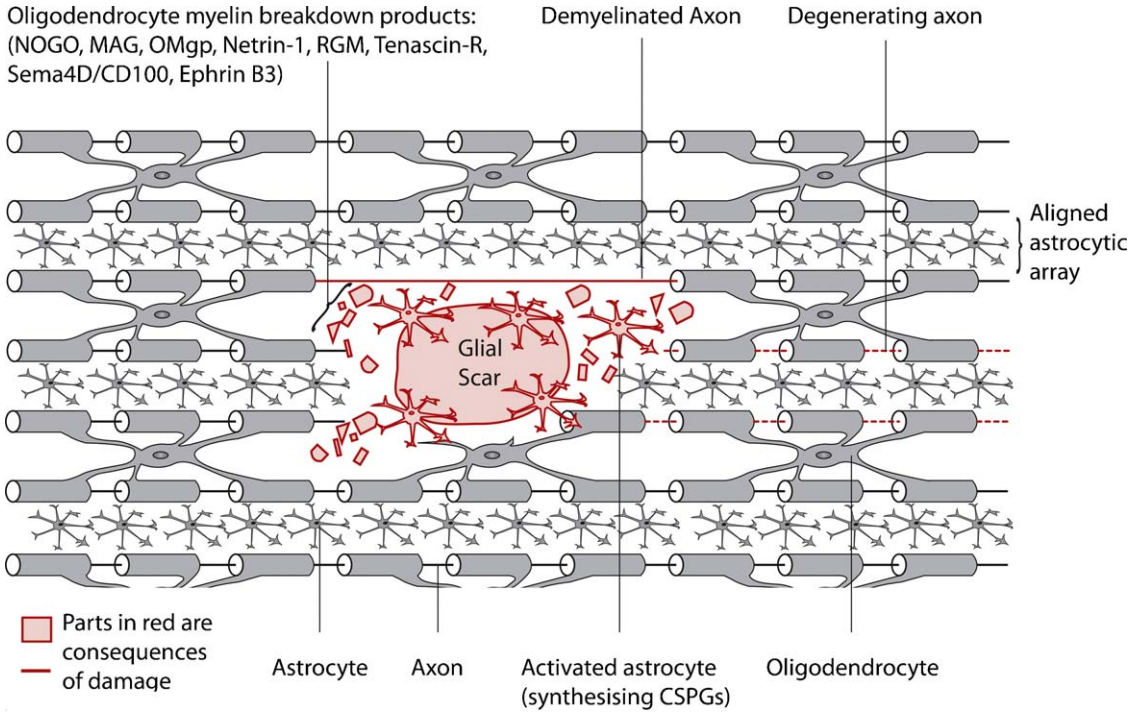

Fig. 1. The CNS injury site. Injury causes severing of axons, which degenerate distally, as well as demyelination of surrounding axons. The resultant myelin debris and glial scar both act to obstruct regeneration.
Adapted from Yiu and He (2006). CSPGs, chondroitin sulphate proteoglycans. See Table 2 for myelin breakdown product sources.