Behavioural Brain Research 192 (2008) 114–123

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Plastic responses to spinal cord injury

Olivier Raineteau*

Department of Clinical Neurosciences, University of Cambridge, Robinson Way, Cambridge CB2 2PY, UK

ARTICLE INFO

Article history:
Received 12 November 2007
Received in revised form 12 February 2008
Accepted 13 February 2008
Available online 17 February 2008

Keywords:
Reactive astrocytes
Neural precursor cells
Fate acquisition
Anatomical plasticity
Neuronal sprouting

ABSTRACT

The commonly accepted view of a highly rigid, hardwired central nervous system has evolved considerably over the past few decades. The adult central nervous system is now known to be capable of significant functional reorganization, frequently referred to as plasticity, in order to adapt to a changing environment or to a change in the CNS hardware itself, for example after trauma. Focusing on the motor system, I will discuss the cellular responses that occur after spinal cord injury and that illustrate distinct plastic events occurring at the lesion site as well as at other levels of the neuraxis. These plastic responses are not restricted to neuronal cells and to the formation of new circuitries, but can also be illustrated by the change of morphology, fate and biochemical properties of non-neuronal cells (i.e. astrocytes and neural precursor cells). These cellular responses interact with one another and contribute, together, to the tissue remodeling and to the sparing or recovery of some motor functions. Understanding these cellular responses as well as their interrelations is necessary to find appropriate approaches to manipulate one with no detrimental effects to the others. This is a prerequisite for the development of new and effective therapeutic strategies for the treatment of patients with CNS injuries.

1. Introduction

The commonly accepted view of a highly rigid, hardwired central nervous system has evolved considerably over the past few decades. The adult central nervous system (CNS) is now considered a tissue in which adaptive events, although limited, are continuously occurring throughout the life of an individual. These adaptive changes, which are frequently referred to as plasticity, can be observed either in health or after trauma: to adapt to a changing environment or to a change in the CNS hardware itself, respectively. This dramatic change of view has been made possible by the constant improvement of techniques that allow one to label defined cell populations and to analyze anatomical changes of neuronal circuits and their functional significance.

Few neuroscientists had anticipated the importance of plasticity for CNS repair following an injury. Most scientists that did so were those that had made repeated observation of patients showing some degree of spontaneous recovery over extended periods of time after CNS injuries. These observations suggested "adjustments" or "re-wiring" of neurons and circuits that had been spared by the trauma. The late Professor Jacques Paillard was one of these neuroscientists, as illustrated by his seminal paper, published in French in 1975 and translated in this special issue (this issue). His definition of the concept of plasticity reads *"the term plasticity is only appropriate in terms of the ability of a system to achieve novel functions, either by transforming its internal connectivity or by changing the elements of which it is made"*. His definition anticipates two levels of plasticity: (1) the "transformation of internal connectivity", that is to say the formation of new neuronal circuits; and (2) the "change of elements of which it is made" that can be partly interpreted as the capacity of the CNS tissue to incorporate new cells. In light of modern neuroscience, these elements can be defined as being neuronal, but also non-neuronal, i.e., glial cells that are now viewed as active participants in the functioning of neuronal networks. Moreover, these elements may be spared after a trauma, or may be generated *de novo*.

Three independent but highly inter-related cellular responses contribute to CNS plasticity and to functional recovery after injury (Fig. 1):

(1) Alteration in cellular morphology and biochemical properties. This is best illustrated by reactive astrocytes that participate in the rapid wounding of the injured CNS.
(2) Change of fate of resident neural precursor cells. Accumulating evidence indicates that endogenous precursor cells proliferate and differentiate in response to injury and may partly compensate for the major cell loss observed acutely after the lesion.

* Current address: Brain Research Institute, University of Zurich/ETH, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland. Tel.: +41 446353288; fax: +41 446353303.
E-mail address: Raineteau@hifo.uzh.ch.

0166-4328/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2008.02.017

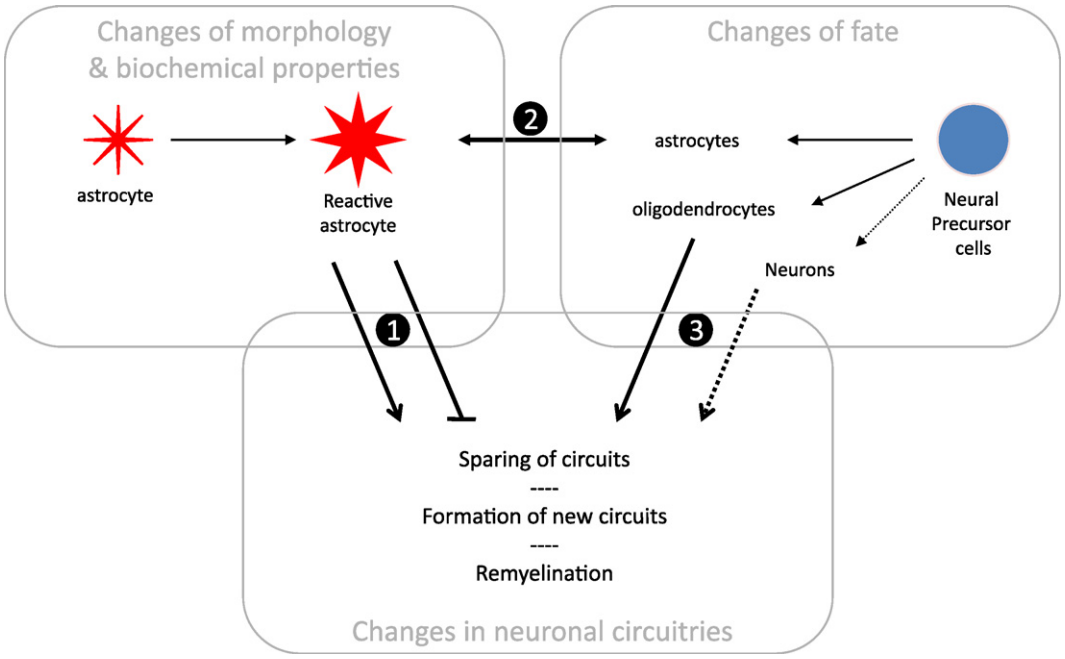

Fig. 1. Inter-relation of cellular changes occurring after spinal cord injury: Plasticity after SCI can be illustrated by three cellular events: (i) change of cell morphology and biochemical properties, e.g., astrocytic reactivity; (ii) change of cell fate, e.g., neural precursor cell differentiation; (iii) change in neuronal circuitries, e.g., formation of new circuits and/or remyelination of the spared ones. These distinct cellular events interact at multiple levels. (1) Reactive astrocytes limit tissue inflammation and are therefore important for the sparing of neuronal circuitries, but secrete molecules that inhibit their anatomical reorganisation. (2) Neural precursor cells may contribute to the formation of the glial scar, and at the same time reactive astrocytes may favour their astrocytic differentiation. (3) Newly generated oligodendrocytes (and possibly neurons) may participate to the formation of new functional neuronal circuitries by re-myelinating spared or newly formed axons. Plasticity of intraspinal neurons may permit the functional integration of newly generated neurons whenever this aim will be achieved.

(3) Change of connectivity of neurons. Significant anatomical reorganization occurs or can be experimentally induced in the motor system after injury, leading to the formation of new neuronal circuits that compensate for those lost.

These cellular responses have been well characterized in animal models of spinal cord injuries (SCI), and will be the focus of this review. As it is impossible to cover in details such a wide range of topics in a single review, my aim is here to give an overview emphasizing the multiple levels of interactions in-between these distinct but highly interrelated cellular events. References to more detailed reviews are given where appropriate.

2. Plasticity in non-neuronal cells following spinal cord injury

2.1. Wounding the injured spinal cord: astrocyte reactivity

Following spinal cord injury, a rapid cellular and transcriptional response evolves at the injury site. This highly orchestrated tissue remodeling process presents a transcriptional signature resembling the one observed during cutaneous wound healing [8,106,114]. As part of this remodeling process, the formation of a dense scar tissue (the "glial scar") is a ubiquitous cellular response that develops in the first 2 weeks after CNS injury. Astrocytes show limited proliferation but migrate and accumulate at the lesion site, thereby constituting a major cellular component of the glial scar. They become hypertrophic and upregulate the expression of structural proteins such as the intermediate filaments GFAP, vimentin and nestin, and are often referred to as "reactive astrocytes" [9]. Reactive astrocytes have long been considered to play a mostly negative role in tissue repair. In addition to contributing to the formation of a physical barrier, they express a class of molecules called proteoglycans that consist of carbohydrates linked to a core protein and that accumulate at and around the site of injury [42,75]. One group of these extracellular matrix molecules (the chondroitin sulfate proteoglycans or CSPGs), has been implicated in axonal regenerative failure after injury both *in vitro* [76] and *in vivo* [26].

More recently, important functions of reactive astrocytes in protecting the injured CNS tissue have been demonstrated. By using an elegant combinational technique of viral infection of mammalian astrocytes and gancyclovir delivery, Faulkner et al. [37] produced a targeted depletion of a subpopulation of reactive astrocytes that undergo proliferation after SCI. This cell ablation technique is believed to be highly selective to the GFAP-expressing cells, sparing neighboring GFAP-negative ones [56], and is regarded as non-inflammatory *in vivo* [38]. Interestingly, this selective ablation resulted in a worsening of motor deficits and a large increase in secondary damages, that is to say the death of oligodendrocytes and neurons occurring in the days following a trauma. The secondary injury was shown to result from a failure of the blood–brain-barrier (BBB) to repair, resulting in a long-lasting tissue inflammation.

In order to reduce the inhibitory properties of astrocytes for CNS repair, while preserving their role in repairing the BBB, experiments have aimed at modulating astrocyte reactivity. Thus, whereas glial scar formation appears normal in mice lacking the structural proteins GFAP or vimentin, double knock-out animals showed reduced astroglial reactivity that resulted in an improved functional recovery after SCI [78,117]. It should, however, be noted that these double-knockout mice have a modified expression of some cell adhesion molecules, such as laminin and N-cadherin, that might contribute to the observed axonal sprouting [77,94]. A prime target to modulate the astrocytic response to injury is the protein STAT3 (signal transducer and activator of transcription 3), a signaling molecule that mediates certain aspects of astrogliosis downstream