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Myelin-associated inhibitors in axonal growth after CNS injury

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There are multiple barriers to axonal growth after CNS injury. Myelin-associated inhibitors represent one group of barriers extrinsic to the injured neurons. Nogo, MAG and OMgp are three prototypical myelin inhibitors that signal through multiple neuronal receptors to exert growth inhibition. Targeting myelin inhibition alone modulates the compensatory sprouting of uninjured axons but the effect on the regeneration of injured axons is limited. Meanwhile, modulating sprouting, a naturally occurring repair mechanism, may be a more attainable therapeutic goal for promoting functional repair after CNS injury in the near term.

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Introduction

It is notorious that after injury of the adult mammalian central nervous system (CNS), damaged axons cannot regenerate to a significant extent, leading to major functional impairments in patients of spinal cord injury (SCI). Because the peripheral nervous system (PNS) has a remarkable ability to regenerate axons, extensive efforts have been focusing on understanding the differences between the PNS and the CNS. The key observation that CNS axons can regenerate in a PNS environment [1] prompted the notion that the environment in the PNS, but not the CNS, is conducive to axon regeneration. One major distinction between the CNS and the PNS is the origin of the myelin and its composition. This led to the hypothesis that CNS myelin is inhibitory to axon regeneration. The production of the IN-1 antibody against an inhibitory activity from CNS myelin [2], the identification of Nogo [3], other myelin-associated inhibitors (MAIs) and their receptors, and the many *in vitro* and *in vivo* studies since have contributed much to our understanding of the molecular regulation of axonal growth after CNS injury. It is now widely recognized that both neuron-intrinsic and extrinsic mechanisms contribute to the lack of CNS axon regeneration. Here we discuss the role of the prototypical myelin inhibitors in the context of recent development in the field of axon growth and repair after CNS injury.

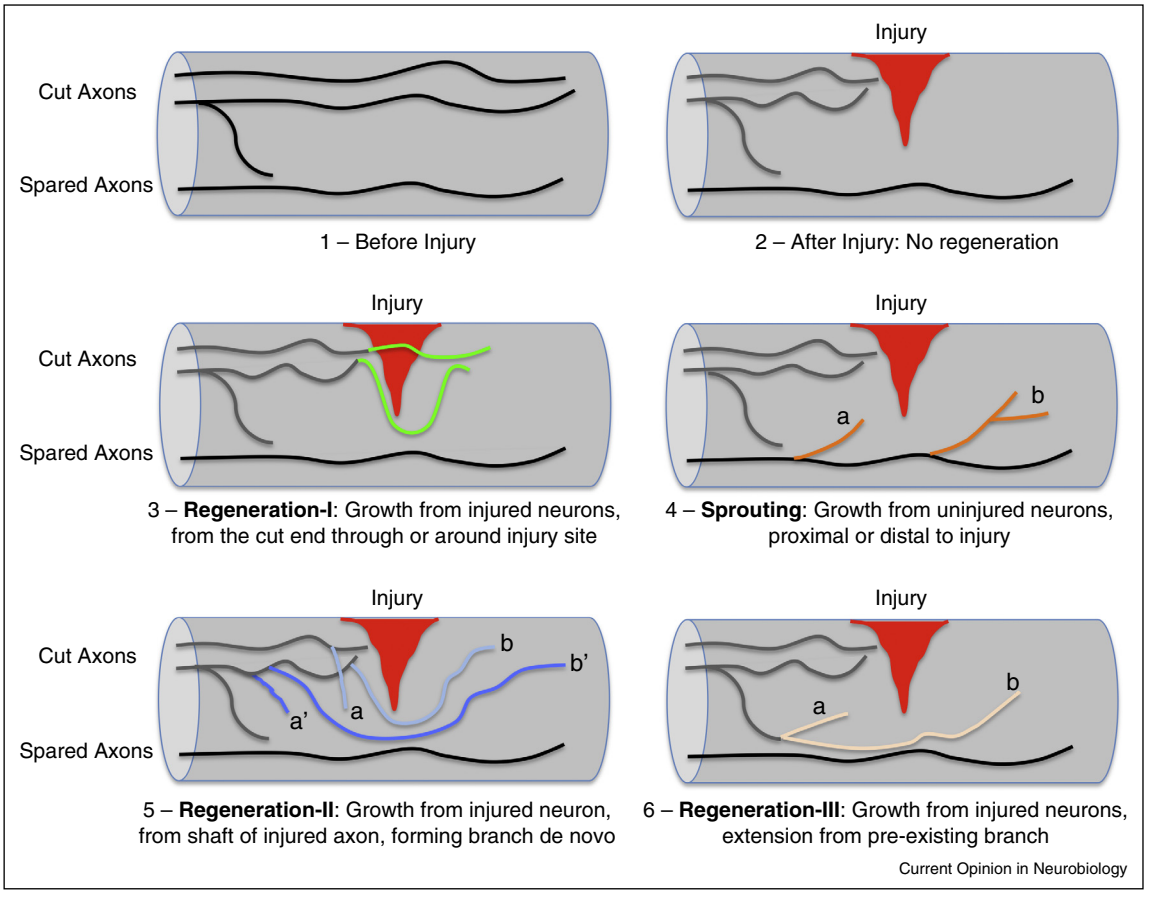
Definition of regeneration and sprouting

The literature on MAIs in axonal repair is abundant, mostly aimed at addressing the key question: can the manipulation of the MAIs and their receptors promote axon regeneration *in vivo*? The short answer is: yes and no. Indeed, the answer depends on the definition of regeneration. There are many different terms used to describe axon growth after injury: regeneration, sprouting, regenerative sprouting, or even axonal plasticity. Use of inaccurate or ambiguous terminology has been a major issue in the field, leading to confusion and disagreement. This is partly due to the continuous evolution of scientific concepts and partly to the limitations of the experimental tools available at any given time.

To allow for a meaningful discussion, here we provide one way to define regeneration and sprouting. In this definition, whether any axonal growth after injury is regeneration or sprouting depends solely on whether or not a neuron has been injured in the first place. Regeneration is axonal growth from injured neurons, while sprouting is axonal growth from uninjured neurons (Figure 1). Under this definition, there are three typical scenarios for regeneration. First, regeneration can originate from the cut end (or tip) of injured axons (Figure 1.3), which is the most classic type of regeneration. In the literature regenerating axons often have to grow beyond (either through or around) the injury site and towards their original targets to be considered significant or relevant. However, this may not be necessary if neurons proximal to the injury can relay information from regenerated axons [4]. Second, regeneration can originate from the shaft of injured axons, forming new branches *de novo* (Figure 1.5). In this scenario, regeneration can initiate close to the injury site or at a distance, and the growth can cover a short or long distance (Figure 1.5). Third, regeneration can be extension from pre-existing, non-injured axonal branches of injured neurons (Figure 1.6). By contrast, as axonal growth from uninjured neurons, sprouting generally occurs as a compensatory response to injury of other neurons. Just as regeneration, sprouting may also initiate at different locations (proximal or distal, close or distant) relative to the injury site, and the growth can also be for short or long distances (Figure 1.4).

It should be noted that even though regeneration and sprouting can be strictly defined conceptually, it is not

Figure 1



Axon regeneration *versus* axon sprouting after injury in the spinal cord. (1) Axons in the non-injured spinal cord. (2) After a partial injury, injured axons normally do not regenerate. (3) Regeneration scenario I: injured axons grow from the cut end (i.e. injured axonal tip), through or around the injury site. This is the typical definition of regeneration. (4) Sprouting is any new axonal growth from uninjured neurons. This occurs in response to injury of other neurons. It can occur proximal (a) or distal (b) to the injury site. (5) Regeneration scenario II: axonal growth from the shaft of injured axons, forming new branches *de novo.* The growth can originate close to the injury site (a, b) or at a distance (a′, b′); it can be for a short (a, a′) or long (b, b′) distance. (6) Regeneration scenario III: axonal extension from pre-existing branches of injured neurons. It can be for a short (a) or long (b) distance. The common theme for all scenarios of regeneration here is that axonal growth is from injured neurons.

always technically straightforward to distinguish the different types of axonal growth depicted in Figure 1. For instance, axonal growth represented in Figure 1.5 (a, a′) and 1.6 (a) are often collectively referred to as 'regenerative sprouting' in the literature. Note that in all these three cases, growth is from injured neurons, thus the term 'regenerative sprouting' contradicts with the definition of sprouting as growth from uninjured neurons and could be confusing. It is therefore always advisable to describe in great detail the axon growth phenotype one observes in spinal cord injury models.

Distinguishing regeneration from sprouting based on the injury status of the neurons will be useful in investigating the molecular mechanisms because injured and uninjured neurons are likely to be differentially regulated in their axon growth abilities [5]. Using more defined terms to describe axonal growth also has important bearing on clinical applications. A treatment that promotes sprouting but not regeneration can be efficacious for anatomically incomplete but not complete injuries. Targeting the appropriate cohort of patients would be crucial for the success of clinical trials.

Multiple ligands and multiple receptors involved in axon growth inhibition

There are three prototypical MAIs: Nogo, MAG and OMgp, all of which have potent inhibitory activity on neurite growth *in vitro*. These MAIs signal through multiple neuronal receptors and co-receptors to effect cytoskeleton rearrangement and neurite inhibition through a signaling pathway involving Rho and Rho-associated kinase (ROCK) (Figure 2). There are other potential MAIs expressed by myelin and oligodendrocytes. Here we focus on the prototypical myelin inhibitors and their receptors.