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Review

Non-mammalian model systems for studying neuro-immune interactions after spinal cord injury

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ABSTRACT

Mammals exhibit poor recovery after injury to the spinal cord, where the loss of neurons and neuronal connections can be functionally devastating. In contrast, it has long been appreciated that many non-mammalian vertebrate species exhibit significant spontaneous functional recovery after spinal cord injury (SCI). Identifying the biological responses that support an organism's inability or ability to recover function after SCI is an important scientific and medical question. While recent advances have been made in understanding the responses to SCI in mammals, we remain without an effective clinical therapy for SCI. A comparative biological approach to understanding responses to SCI in non-mammalian vertebrates will yield important insights into mechanisms that promote recovery after SCI. Presently, mechanistic studies aimed at elucidating responses, both intrinsic and extrinsic to neurons, that result in different regenerative capacities after SCI across vertebrates are just in their early stages. There are several inhibitory mechanisms proposed to impede recovery from SCI in mammals, including reactive gliosis and scarring, myelin associated proteins, and a suboptimal immune response. One hypothesis to explain the robust regenerative capacity of several non-mammalian vertebrates is a lack of some or all of these inhibitory signals. This review presents the current knowledge of immune responses to SCI in several non-mammalian species that achieve anatomical and functional recovery after SCI. This subject is of growing interest, as studies increasingly show both beneficial and detrimental roles of the immune response following SCI in mammals. A long-term goal of biomedical research in all experimental models of SCI is to understand how to promote functional recovery after SCI in humans. Therefore, understanding immune responses to SCI in non-mammalian vertebrates that achieve functional recovery spontaneously may identify novel strategies to modulate immune responses in less regenerative species and promote recovery after SCI.
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Contents

Introduction

SCI was once thought to be incurable, because of a lack of plasticity and regeneration in the adult mammalian central nervous system (CNS). However, studies performed over the past two decades have

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demonstrated both neurogenesis and considerable plasticity of the adult vertebrate CNS, stimulating studies of biological responses to SCI (Thuret et al., 2006). Based on the premise that neuronal function relies on fundamental pathways conserved across species, neurobiology has a long tradition of addressing basic biological questions by exploiting the advantageous experimental or natural traits of a variety of organisms including sea slug, squid, frog, chicken, and songbirds (Alvarez-Buylla and Nottebohm, 1988; Castellucci et al., 1980; Cohen et al., 1954; Fatt and Katz, 1951; Hodgkin and Huxley, 1939; Kupfermann and Kandel, 1969; Marder, 2002). Similarly, the ability to promote successful recovery after SCI will likely derive from identification of biological processes that determine both success and failure to regenerate axons, in species where regenerative capacity ranges from limited to robust.

Studies in mammals, which exhibit poor spontaneous recovery after SCI, have focused primarily on identifying factors both intrinsic and extrinsic to neurons that inhibit axon regeneration, *e.g.* Buchli and Schwab (2005), Giger et al. (2010), and Gonzenbach and Schwab (2008). These inhibitory mechanisms include reactive gliosis and a glial scar that contains chondroitin sulfate proteoglycans (CSPGs) and the presence of myelin and myelin-associated proteins (Filbin, 2003; Pernet and Schwab, 2012; Silver and Miller, 2004). Another extrinsic factor studied in the context of mammalian SCI is the immune response, as inflammation has been widely shown to exacerbate neuronal loss and induce secondary damage acutely after SCI (Bartholdi and Schwab, 1997; Klusman and Schwab, 1997; Schnell et al., 1997; Streit et al., 1998). One of the long-considered hypotheses to explain the differential regenerative capacity among vertebrates is that species able to accomplish spontaneous recovery after SCI have less inhibitory extrinsic factors present near the injury zone, including an acute immune response that is weaker or distinct from that observed in mammals (Tanaka and Ferretti, 2009). Increasingly, elements of the immune response are also recognized to benefit axonal regeneration after SCI in mammals, reviewed in Benowitz and Popovich (2011) and Gensel et al. (2012). Therefore, studies of immune responses to SCI in regenerating vertebrates will enhance the ability to promote an optimal immune response in mammals, in order to prevent loss of neurons and promote recovery. This approach is clinically relevant, as the immune response is routinely manipulated in a variety of clinical settings. For example, FDA-approved antibodies or drugs that target pro-inflammatory cytokines are routinely used in patients with rheumatoid arthritis, Crohn's disease, diabetes (types I and II) and multiple sclerosis (Dinarello et al., 2012). In mouse models of SCI, treatment with three different FDA-approved TNF inhibitors improved biochemical, histological and functional outcomes after SCI (Genovese et al., 2006, 2008a, 2008b). Based on the clinical success of monoclonal antibodies and other biologic therapies, a pipeline of therapeutic small molecules targeting pro-inflammatory mediators is in development (Dinarello et al., 2012; Kopf et al., 2010). Therefore, understanding beneficial and detrimental aspects of the immune response to SCI across a variety of species may offer clinically relevant insights. Here, I review data from a growing number of studies that investigated immune responses to SCI in non-mammalian model organisms including the jawless (lamprey) and jawed vertebrates, including teleosts (zebrafish), amphibians (salamander and frog), and reptiles (turtle) (Fig. 1).

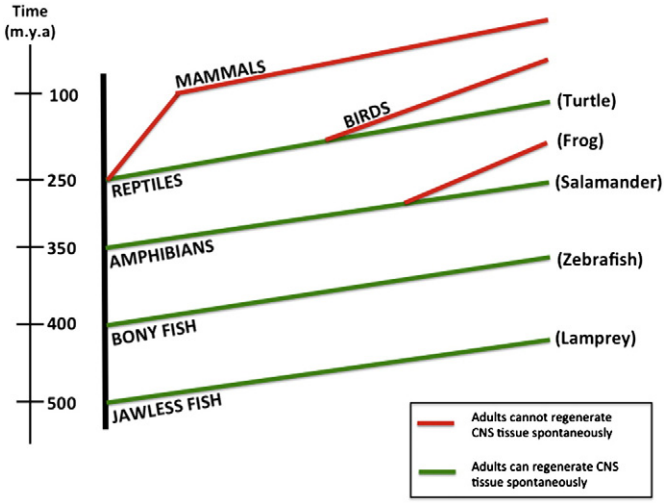

Fig. 1. Phylogenetic tree illustrates evolutionary relationships of multiple vertebrate species and their differential capacity to regenerate CNS tissue after injury. The dimensions of the timeline are not drawn to scale.

Immune responses to SCI in mammals

In mammals, immune responses are thought to contribute to deleterious outcomes, including neuronal death, inhibition of axon regeneration, and poor functional recovery of motor and sensory systems. Microglia, the resident immune cells of the CNS, are among the first cells to respond in mammalian experimental models of SCI (Adrian et al., 1978; David and Kroner, 2011; Popovich et al., 1993; Spitzbarth et al., 2011). Within minutes to days, microglia, together with neutrophils, macrophages and lymphocytes recruited from the periphery, are activated and accumulate at the lesion site (Carlson et al., 1998; Detloff et al., 2008; Fitch and Silver, 1997; Fitch et al., 1999; Gensel et al., 2011; Horn et al., 2008; Kigerl and Popovich, 2009; Popovich and Hickey, 2001; Popovich et al., 1993, 1997, 2002, 2003; Schnell et al., 1997). Resident and invading immune cells release pro-inflammatory mediators, including cytokines that rapidly amplify the local immune response (Alexander and Popovich, 2009; Bartholdi and Schwab, 1995, 1997; Bethea et al., 1998; Brambilla et al., 2005; Fitch et al., 1999; Herbomel et al., 2001; Kigerl and Popovich, 2009; Klusman and Schwab, 1997; Schnell et al., 1999; Streit et al., 1998). Astrocytes promote scarring at the lesion site and synthesize CSPGs, which are inhibitory to neuronal regeneration (Bradbury and Carter, 2011; Bradbury et al., 2002; Garcia-Alias et al., 2009; Rudge and Silver, 1990; Rudge et al., 1989; Silver and Miller, 2004; Smith et al., 1986, 1990; Snow et al., 1990). At the lesion site, the molecular interactions between astrocytes and infiltrating immune cells are not well understood. After SCI in mice, reactive astrocytes expressing the transcription factor STAT3 + confined inflammatory cells at the lesion epicenter, while deletion of STAT3 from astrocytes was pro-inflammatory, resulting in a broader distribution of inflammatory cells around the injury site and decreased neuronal viability (Herrmann et al., 2008; Okada et al., 2006; Wanner et al., 2013). *In vitro* co-culturing of macrophages with resting STAT3 + astrocytes activated the astrocytes to reorient their processes and surround the inflammatory cells (Wanner et al., 2013). A subpopulation of neural stem cell-derived astrocytes recruited to the injury was shown to restrict the size of the lesion, by being neuroprotective (Goritz et al., 2011; Wanner et al., 2013). Surprisingly, the removal of these ependymal-derived astrocytes decreased the numbers of immune cells in the injured spinal cord (Sabelstrom et al., 2013). These studies suggest complex and heterogeneous interactions between neuronal, immune and other non-neuronal cells at the lesion site, that together contribute to recovery after SCI in mammals.

Additional interactions of the nervous and immune systems may also be relevant in mammalian SCI. For example, the vagus nerve, which is part of the autonomic nervous system, has efferent connections to immune organs, which regulate immune functions, such as cytokine production (Olofsson et al., 2012). Autonomic dysreflexia, which occurs when the autonomic nervous system is interrupted and can be life-threatening in SCI patients, caused immune depression in mice and in a human SCI subject (Zhang et al., 2013) (and see Zhang et al., 2014b–in this issue). At the molecular level, classic immune molecules, such as major histocompatibility complex class I (MHCI), are now known to play a role in normal CNS synapse remodeling and plasticity (Corriveau et al., 1998), while the complement cascade participates in

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