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Review

Cytokine pathways regulating glial and leukocyte function after spinal cord and peripheral nerve injury

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ABSTRACT

Injury to the nervous system causes the almost immediate release of cytokines by glial cells and neurons. These cytokines orchestrate a complex array of responses leading to microgliosis, immune cell recruitment, astrogliosis, scarring, and the clearance of cellular debris, all steps that affect neuronal survival and repair. This review will focus on cytokines released after spinal cord and peripheral nerve injury and the primary signalling pathways triggered by these inflammatory mediators. Notably, the following cytokine families will be covered: IL-1, TNF, IL-6-like, TGF-β, and IL-10. Whether interfering with cytokine signalling could lead to novel therapies will also be discussed. Finally, the review will address whether manipulating the above-mentioned cytokine families and signalling pathways could exert distinct effects in the injured spinal cord *versus* peripheral nerve.

Contents

Introduction

Traumatic spinal cord injury (SCI) and peripheral nerve injury (PNI) cause damage to axons and their myelin sheaths. How axons respond to injury has been extensively studied for decades in a variety of organisms, ranging from invertebrates to non-human primates (Bradke et al., 2012). From these studies a main conclusion can be drawn: axonal regeneration is regulated by a multitude of intracellular and extracellular signals. Among which are several axon growth inhibitory molecules that have been found in myelin or associated with the scar (Burda and Sofroniew, 2014; Cregg et al., 2014; Schwab, 2010). Wallerian degeneration (WD) and clearance of inhibitory myelin debris are delayed in the

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injured CNS compared to the injured PNS, which could be one of the main reasons why CNS regeneration is generally so poor (David and Lacroix, 2005). In addition, immune cells that phagocytose myelin debris are potentially the source of neurotrophic factors and anti-inflammatory molecules that may support the regenerative and repair processes. In support of this are studies that showed that CNS axons can grow in transplanted peripheral nerve segments (Barrette et al., 2008; David and Aguayo, 1981).

Another direct consequence of SCI is the destruction of neurons and glia at the site of lesion, which has been referred to as the primary mechanical lesion. Long-standing evidence suggests that a second wave of cell death follows the primary mechanical insult, leading to apoptosis of oligodendrocytes (OLs) and neurons (Crowe et al., 1997; Liu et al., 1997). However, it is important to note that they are many other suspected causes of secondary damage in the injured spinal cord, including ischemia, vascular damage, glutamate excitotoxicity, ionic dysregulation, and inflammation (for reviews, see (David and Lacroix, 2005; Donnelly and Popovich, 2008)). The topic of inflammation has received the greatest attention because immune cells are the main producers of free radicals, proteases, eicosanoids and cytokines, all of which are molecules that have been shown to be both capable of inducing cell death and myelin damage and of being expressed in the injured spinal cord within minutes to days of mechanical impact (Bao and Liu, 2004; Hains et al., 2001; Liu et al., 1998, 2000; Noble et al., 2002; Pineau and Lacroix, 2007; Rice et al., 2007; Wells et al., 2003). This time course fits well with the timing of secondary damage, suggested to occur between 4 h and 14 d post-SCI (Blight, 1985; Liu et al., 1997). The concept of secondary cell damage is at the center of the preclinical development of potential neuroprotective therapies, with many studies reporting reduced lesion size and/or increased spared tissue as a result of treatment (reviewed extensively by (Kwon et al., 2011)). An outstanding question has been why neurons projecting through peripheral nerves do not seem to be as sensitive to these potentially cytotoxic molecules. Indeed, peripheral nerve and spinal cord lesion sites seem to contain the same inflammatory cells and molecules, but perhaps not at the same timing, duration and expression levels. This subject will be addressed in the last part of this review.

In the CNS, as in the PNS, glia can be activated by several different types of signals and modulators, among which cytokines and neurotransmission-related compounds are considered to play major regulatory roles (Hanisch and Kettenmann, 2007). For example, microglia respond within minutes to ATP released after laser-induced SCI by extending their processes in order to rapidly shield the site of injury (Davalos et al., 2005; Nimmerjahn et al., 2005) (Fig. 1). Depending on the repertoire of receptors activated, microglia can either promote neuronal survival and regeneration or contribute to neuronal death (Hanisch and Kettenmann, 2007; Ransohoff and Perry, 2009). Although they do not physically respond as quickly as microglia (Farrar et al., 2012), astrocytes, the main cellular component of the glial scar, increase their GFAP expression, become hypertrophic, proliferate and migrate around the lesion site in a process generally referred to as reactive astrogliosis (Sofroniew, 2009). Several different mediators of reactive astrogliosis exist, among which are cytokines of the IL-1, TNF, IL-6-like, TGF-β, and IL-10 families (reviewed by (Sofroniew, 2009)). Importantly, the glial scar has been shown to exert both beneficial and detrimental effects after SCI (Brambilla et al., 2005, 2009; Faulkner et al., 2004).

Innate immune cells such as neutrophils and monocytes are rapidly recruited at sites of SCI (Beck et al., 2010; Fleming et al., 2006; Lee et al., 2011; Mawhinney et al., 2012; Pineau et al., 2010; Stirling and Yong, 2008; Thawer et al., 2013). Evidence suggests that these cells could play a key role in both secondary damage and tissue repair after traumatic neural injury (Barrette et al., 2008; Kigerl et al., 2009; Shechter et al., 2009; Stirling et al., 2009). The apparent contradictions between these studies may be due to the fact that different subsets of immune cells have divergent effects, resulting in either neurotoxicity or regeneration in the injured spinal cord (David and Kroner, 2011). The effects of cytokines on glia and leukocytes and the contribution of these cells to tissue damage, glial scarring and regeneration will be explored in more detail in the second part of this review. One important area of focus will be how cytokines govern immune cell recruitment, activation and polarization in the context of injury, as this could explain some of the controversies and paradoxical effects of neuroinflammation in SCI.

This review begins with an overview of the principal families of cytokines for which a role in the pathophysiology of spinal cord and peripheral nerve injury has been established.

Cytokines released after neural injury: production, receptor signalling pathways and immune responses

IL-1 family members

The role of interleukin (IL)-1 family cytokines in the initiation and regulation of inflammation during infection and injury is well established. The family contains 11 members, the best characterized of which are IL-1α, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-18, and IL-33 (Dinarello, 2009). IL-1α and IL-1β were the first two members of the family to be described. Despite the fact they share only 25–30% amino acid homology, they have a similar 3D structure and biological properties (Dinarello, 1991; Graves et al., 1990). Since they bind to the same receptor, IL-1 receptor type 1 (IL-1R1), with the same affinity and stimulate expression of similar downstream effectors, IL-1α and IL-1β have long been thought to trigger identical responses. However, Rothwell and colleagues have shown that the relative potencies of recombinant IL-1α and IL-1β vary depending on the context and the response being studied, thus suggesting that different mechanisms are likely to be involved in the various effects of IL-1 cytokines in the CNS (Andre et al., 2005; Anforth et al., 1998; Tsakiri et al., 2008). For example, the study by Anforth et al. showed that IL-1β is more effective than IL-1α at inducing fever when the cytokines are injected intracerebroventricularly (i.c.v.) (Anforth et al., 1998). Moreover, and in contrast to IL-1β, treatment with IL-1α failed to induce IL-6 production from glia and neurons, despite the fact that both forms of IL-1 were equally effective at increasing expression levels of chemokines such as CCL2/MCP-1, CXCL1/KC and IP-10 (Andre et al., 2005; Tsakiri et al., 2008), More recently, Rider et al. suggested that the precursor of IL-1α and mature IL-1β recruit different myeloid cells (neutrophils and macrophages, respectively) in response to hypoxia-induced cell death (Rider et al., 2011). It is therefore plausible that the two IL-1 cytokines signal through distinct signalling complexes and regulate expression of specific genes. Preliminary results in this direction, in which we compared the transcriptome of the injured spinal cord of IL-1α-knockout (KO), IL-1ß-KO and wild-type (WT) mice during the acute phase of SCI using Affymetrix GeneChip microarrays, indicate that a few genes appear to be specifically regulated by IL-1α (D. Bastien and S. Lacroix, unpublished observation).

Interleukin-1α (IL-1α). IL-1α and IL-1β are synthesized as 31-kDa precursor proteins. However, only the IL-1α precursor (pro-IL-1α) is able to bind to IL-1R1, which suggests that this form is biologically active (March et al., 1985; Mosley et al., 1987). Proteases such as calpain (Carruth et al., 1991; Kobayashi et al., 1990), and more recently granzyme B, elastase and chymase (Afonina et al., 2011), were shown to cleave pro-IL-1α and yield a 17-kDa form. Initially, that cleavage was thought to have no effect on the biological activities of the cytokine, but recent studies have shown that the 17-kDa mature form of IL-1α has enhanced immunological potency compared to the proform (Afonina et al., 2011; Zheng et al., 2013). Zheng et al. also identified the IL-1 receptor type 2 (IL-1R2) as a regulator of IL-1α cleavage, being able to bind IL-1α and prevent calpain from processing the precursor cytokine. Despite this, evidence has shown that the proform has the ability to recruit leukocytes following its release from hypoxic