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Role of inflammatory cytokines in peripheral nerve injury*☆●

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Abstract

Inflammatory events occurring in the distal part of an injured peripheral nerve have, nowadays, a great resonance. Investigating the timing of action of the several cytokines in the important stages of Wallerian degeneration helps to understand the regenerative process and design pharmacologic intervention that promotes and expedites recovery. The complex and synergistic action of inflammatory cytokines finally promotes axonal regeneration. Cytokines can be divided into pro- and anti-inflammatory cytokines that upregulate and downregulate, respectively, the production of inflammatory mediators. While pro-inflammatory cytokines are expressed in the first phase of Wallerian degeneration and promote the recruitment of macrophages, anti-inflammatory cytokines are expressed after this recruitment and downregulate the production of all cytokines, thus determining the end of the process. In this review, we describe the major inflammatory cytokines involved in Wallerian degeneration and the early phases of nerve regeneration. In particular, we focus on interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor-β, interleukin-10 and transforming growth factor-β.

Key Words

Pro-inflammatory cytokines; anti-inflammatory cytokines; inflammatory reaction; peripheral nervous system; nerve injury; wallerian degeneration; Schwann cells; macrophage; axonal regeneration; myelin

Research Highlights

(1) Inflammatory cytokines activated after nerve injury lead to a characteristic series of cellular and molecular events that facilitate axon regeneration and, eventually, re-innervation of target tissues.
(2) After peripheral nerve injury, pro- and anti-inflammatory cytokines are produced by both immune and non-immune cells resident in the distal part of the injured nerve or recruited from blood circulation. As surgically repaired nerves still do not give complete recovery of nerve function, better knowledge of these inflammatory events should provide new therapeutic perspectives that improve and accelerate peripheral nerve regeneration and functional recovery.

Abbreviations

WD, Wallerian degeneration; SCs, Schwann cells; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β; NCAM, Neural Cell Adhesion Molecule; SCIP, Suppressed cAMP-inducible POU-domain protein.

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INTRODUCTION

Peripheral nerve damage is a common injury; although the fibres retain a considerable regeneration potential in the adult, recovery is usually rather poor, especially in cases of large nerve defects. The clinical outcome of nerve lesions is far from satisfactory and functional recovery is seldom complete. It is necessary to understand more fully the biological mechanisms that underlie the complex sequence of events that follows nerve damage, but also to define the best strategies for optimizing post-traumatic nerve regeneration.

After peripheral nerve injuries, cellular and molecular events that occur in the distal part (Wallerian degeneration, WD) and stimulate axonal regeneration[1-3]. Axons in the distal part of the injured nerve remain intact for some days before granular disintegration of the cytoskeleton[4]. During the first 24 hours following injury and before the arrival of blood-derived macrophages, Schwann cells (SCs) control demyelination by degrading myelin basic protein[5].

Following the loss of contact of the glia with the axon and the activation of inflammatory events, myelin sheath disintegration, SC proliferation and rearrangement of the band of Büngner occur.

The breakdown of the blood-nerve barrier allows blood factors and cells that facilitate tissue repair to enter the nerve in the first 2 weeks. Permeability of the blood-nerve barrier increases again after 4 weeks in order to regain homeostasis after WD[6].

Immediately after nerve injury, the important phenomenon of macrophage recruitment occurs to aid debris elimination and tissue remodeling[7]. The rapid clearance of degenerated myelin activated by Schwann cells (SCs) and macrophages is a crucial step for successful nerve regeneration. In fact, during WD, SCs and macrophages phagocytize the degenerated myelin and moreover produce cytokines and neurotrophic factors necessary for axon regeneration. The inflammatory reaction is mainly due to macrophages. Signaling pathways between primary sensory neurons, SCs and immune cells are highly intertwined, and cytokines and chemokines are central components in this complex network[8].

Recent studies have been focused on inflammatory events occurring during WD[9-11]. There are several different factors produced by macrophages and SCs that play an important role during degeneration and regeneration of a peripheral nerve.

Activation of immune and immune-like glial cells in the injured nerve leads to the release of both pro- and anti-inflammatory cytokines[5]. Pro-inflammatory cytokines [*e.g*. interleukin (IL)-1, -2, -6 and tumor necrosis factor (TNF)] are expressed principally in the first phase of WD, promoting the recruitment of macrophages from 2 to 3 days after the injury, while anti-inflammatory cytokines [(*e.g.* IL-10 and transforming growth factor-β (TGF-β)] are expressed after macrophages recruitment[11] and have the role of attenuating the inflammatory process.

This review focused on the role of the inflammatory cytokines in WD and in the early phases of regeneration of a peripheral nerve.

TNF-α

TNF-α is a pro-inflammatory cytokine expressed as a 26-kDa transmembrane protein that can be cleaved to release a 17-kDa soluble form. It is widely considered as the prototypical pro-inflammatory cytokine because it regulates inflammatory responses after injury to the peripheral or central nervous system[12-14], initiating the activation cascade of other cytokines and growth factors[15]. TNF-α exerts its action *via* its receptors, TNF-α receptor 1 (TNF-R1) and the lower affinity TNFR2[16], which are expressed in both glia and neurons[17]. TNF-R1 contains an intracellular “death domain” and is responsible for controlling the neuronal death. TNF-R2 contributes to neuroprotection due to his relation to T-cell development and the proliferation[12,13,16-18].

In the peripheral nervous system, the endogenous TNF-α released by SCs, resident macrophages and mast cells occurs after nerve damage. Immediately after peripheral nerve injury, TNF-α expression increases in the site of lesion[19-20] leading to a massive recruitment of macrophages[21-22]. Recruitment is probably mediated by metalloproteinase[23], or through the upregulation of adhesion molecules or cytokines[21].

Shubayev’s group, after performing sciatic crush lesions in TNF-α and matrix metallopeptidase 9 (MMP-9) knockout mice, found fewer macrophages in the distal parts of the injury[23]. Furthermore, MMP-9 produced by SCs and endoneurial macrophages after TNF-α activation promote blood nerve barrier degradation and demyelination[23-24].

Macrophages activated during WD phagocytose degenerating myelin, collaborate in the reorganization of the endoneurial space, and help remodel the extracellular matrix[10,25]. Infiltrating blood-derived cells also release additional TNF-α, resulting in a second peak 3–5 days after injury[26].

The role of TNF-α in peripheral nerve injury has been

thoroughly investigated both *in vivo* and *in vitro* by many groups. Liefner and collegues[21] demonstrated in a transected sciatic nerve of TNF-α deficient mice that poor macrophage recruitment results in delayed myelin removal. Also Uncini and collegues[27] have demonstrated the role of TNF-α in blood-nerve barrier degradation; in fact they showed that the injection of TNF-α in an injured sciatic nerve of the rat resulted in the damage of the blood-nerve barrier and an inflammatory infiltration of the vessel walls, thus supporting the hypothesis of a direct chemotactic effect of TNF-α. Interestingly, two *in vitro* studies revealed the direct effect of TNF-α on SCs[20,28], showing that TNF-α decreases SC proliferation in a dose-dependent manner without affecting SCs viability.

IL-1

Another very important pro-inflammatory cytokine involved in the peripheral nerve injury process is the IL-1. IL-1, the product of a member of a superfamily of related genes, some of which generate proteins not involved in inflammation[29], causes the accumulation of arachidonic acid metabolites, upregulates inducible nitric oxide synthase, and sustains nitric oxide production. It is a polypeptide produced in 2 molecular forms, IL-1α and IL-1β; despite only a 26% amino acid homology, both forms can determine a wide variety of biological responses. *In vitro*, IL-1 activates T and B lymphocytes and induces a variety of lymphokines, interferons, and other cytokines, particularly TNF, for the induction of inflammatory changes, such as prostaglandin synthesis, activation of endothelial cells, and bone resorption. They are both synthesized as 31 kDa precursors, the processing of these molecules to their final mature form requiring a specific protease. Pro IL-1α remains in the cytosol in association with cytoskeletal structures, *e.g.* microtubules[30]. When the cells die, the pro-protein is released and can be processed by extracellular proteases, but can also be cleaved by the activation of calcium-dependent, membrane associated cysteine proteases called calpains[31]. Following synthesis, pro IL-1β remains in the cytosol and is only partially active. Its active form is secreted from the cell after the cleavage by ICE, the IL-1β converting enzyme[32-33].

Two IL-1 receptors and one accessory protein (IL-1 R-AcP) have been identified. They comprise 3 IgG-like domains, and share a significant homology to each other[30,34]. While the type I receptor (IL-IRI) transduces a signal, the type II receptor (IL-1RII) binds IL-1, but does not exhibit signal transduction; in fact, the receptor IL-1RII acts as a suppressor of signaling mediated by IL-1 and -3[30]. When IL-1 binds to IL-IRI, a complex is formed that then binds to the IL-1R accessory protein (IL-1R-AcP), resulting in high affinity binding[34]. It is like a heterodimerization of the cytosolic domains of IL-1RI and IL-1R-AcP that can trigger IL-1 signal transduction.

In the intact peripheral nervous system, IL-1α mRNA is constitutively expressed, but IL-1α protein is not synthesized. Due to nerve injury, IL-1α is rapidly upregulated by SCs that have lost their close contact with interrupted axons. This upregulation occurs both at mRNA and protein levels 5 to 6 hours following damage[11]. The fundamental role of IL-1α in this type of injury is to induce the fibroblasts located on site to produce IL-6 and granulocyte macrophage-colony stimulating factor; the production of these molecules is detectable from 2 to 5 hours after injury.

Regarding SCs, IL-1β expression during WD is detected 5–10 hours after injury and the delayed expression might be due to SC-derived TNF-α. Interestingly, the highest levels of TNF-α and IL-1β protein secretion were detected 1 day after the injury, thus before macrophage recruitment; in fact, it has been reported that the administration of a function-blocking antibody against IL-1β into the injured mouse sciatic nerve halts, with a reduction in the recruitment of macrophages and retarded myelin phagocytosis[35].

It is well known that IL-1α, IL-1β and TNF-α determine the first peak of nerve growth factor mRNA within hours after nerve injury in fibroblasts, but not in SCs[11]; moreover, they participate in WD by first upregulating the production of additional inflammatory cytokines and thereafter the production of anti-inflammatory cytokines[25].

IL-6

IL-6 is a glycoprotein belonging to the neurokines family with pro-inflammatory activity, crucial in the acute inflammatory phase of the reaction. It enhances T-cell activation, and acts as a neurotrophic factor for cholinergic and dopaminergic neurons[36]. IL-6 plays a role in neuroprotection[37-38] and modulation of pain, binding a non-signaling α-receptor (IL-6R, also known as CD126), which, after dimerization with gp130, leads to activation of receptor-associated kinases JAK1, JAK2, and Tyk2. In turn, these lead to phosphorylation of proximal tyrosine residues within the intracellular portion of gp130, with subsequent control of STAT1 and STAT3 activity[10,39-40].

Increased synthesis and release of cytokines, including

IL-6, can directly modulate neuronal activity through the synthesis of neuropeptide transmitters. Furthermore, IL-6 is a key component of the nervous system's injury response. Previous studies have shown that IL-6 plays a role in axon regeneration after peripheral nerve injury and also makes an important contribution in the overall cellular response[41]. IL-6 level is elevated both in neurons and non-neuronal cells, and can increase gene expression of regeneration associated genes (RAGs) in neurons and promote neurite growth together with some neurotrophic factors, such as nerve growth factor[9]. Resident macrophages and fibroblasts of injured peripheral nerves are the major producers of IL6[42]. SC-derived IL-6 increases within 3 hours of nerve lesion and is required for immune cell chemotaxis within 2–5 hours after the injury, with IL-6 secreted by macrophages becoming detectable[11]. IL-6 produced by resident fibroblast is induced by TNF-α and IL-1 produced by SCs.

Several studies show that the expression of IL-6 and IL-6 receptor α-subunit (IL-6Rα) is upregulated in dorsal root ganglion neurons after axonal injury and elongation. However, the biological actions of IL-6 signaling on SCs have not been fully elucidated[43].

IL-10

IL-10 is a 18.5 kDa large immunoregulatory anti-inflammatory cytokine secreted by a variety of cells, including monocytes, macrophages, dendritic cells, T cells, B cells, granulocytes, epithelial cells, and mast cells[44]. The principal routine function of IL-10 may be limited and ultimately terminates inflammatory responses[45]. In fact, IL-10 limits secretion of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6; it deactivates macrophages, inhibits secretion of Th1 cytokines such as IL-2 and interferon-gamma, and controls differentiation and proliferation of macrophages, T cells, and B cells. While keeping pro-inflammatory events under control, it protects against excessive immune responses and tissue damage.

There is evidence showing that IL-10 is involved in nerve healing process after injury. In this context, previous studies have shown that IL-10 plays an important role during nerve regeneration; in particular, the administration of a low dose of IL-10 to a site of sciatic nerve injury reduces scar formation (which is considered one of the main problems in nerve repair), and permits better regeneration of damaged axons that leads to greater myelination[46-47].

Some studies have shown that the effect of IL-10 applied at the repair site is dependent upon the concentration used, with no beneficial effects at high concentration while there was that enhanced regeneration of the nerve at a low concentration[47].

The production and secretion of the anti-inflammatory cytokine IL-10 is induced by resident fibroblasts within 5 hours of injury, but levels are low and ineffective because nerve-resident fibroblasts are poor producers, like SCs. To overcome this deficiency, recruited macrophages produce and secrete IL-10; protein levels increase, peaking at day 7 concomitant with the timing and magnitude of macrophage recruitment. IL-10 then gradually downregulates the production of cytokines, bringing the cytokine network of normal WD to a conclusion 2–3 weeks after injury[11].

OTHERS

In the last part of this review, we wish to focus also on cytokines that remain poorly studied with regard to their role in peripheral nerve degeneration and regeneration.

TGF-β family comprises three isoforms in mammals: TGF-β1, -β2 and -β3. Moreover, the TGF-β superfamily has a huge number of homologous proteins[48]. Potentially, every cell in the body, including hematopoietic, endothelial, epithelial, neuronal and connective-tissue cells, produces TGF-β and has receptors for it.

TGF-β-related proteins are synthesized as precursor proteins with an amino-terminal residue for identification of the signal target and a varying pro-domain that assists in folding, dimerization and regulation of factor activity[49]. As to the other components, TGF-β1, an anti-inflammatory cytokine, is one that is a secreted signalling molecule mediating many essential events of normal growth and development[50].

TGF-β1 can bind at least three proteins located in the cell surface: type I, type II, and type III receptors, of 53, 70–85 and 200–400 kDa, respectively[51]. Type I and type II receptors are the best binding molecules to transduce signalling pathway. TGF- β1 is the major isoform expressed in SCs, and this rate of expression is modulated by interaction with axons[52]. These authors also found that TGF-β1 has mitogen effects on isolated rat SCs, increasing the expression levels of markers of premyelination, neural cell adhesionmolecule, suppressed cAMP-inducible POU-domain protein, and inhibiting forskolin-induced transition to a myelinating phenotype. In agreement with these early observations, co-culture of axon and SC revealed that administration of TGF-β1 inhibits myelination and the correct formation of the basal lamina[52-53].

TGF-β1 expression and its effects on proliferation are strongly strengthened by the increased protein level immediately after peripheral nerve injury[54-55] and the following downregulation, *i.e.* once the nerve fibers have grown back into the distal stump, thus allowing subsequent ensheathment and myelination.

IL-2 is a 15.5 kDa pro-inflammatory cytokine composed of 133 amino acids[56] that has multiple functions in the inflammatory response, including activation of immune cell effectors and stimulation of the number of white blood cells on the endothelial surface of skeletal muscle. In addition, it is a potent inducer of the proliferation, differentiation, development, survival, memory and regulatory functions of T-lymphocytes[57]. IL-2 exerts its biological activity by binding to the high-affinity IL-2 receptor (IL-2R). Soluble IL-2R is part of a membrane receptor localized on the cell surface of different lymphoid cell lines, including activated T and natural killer cells, monocytes, eosinophils[58].

The IL-2R consists of 3 subunits, the α-chain (also known as CD25), the β-chain (CD122) and the γ-chain (CD132). A major function of IL-2 is to promote proliferation and expansion of $CD4^+$ and $CD8^+$ T cells as well as inducing the production of other cytokines[59]. Previous studies have shown that IL-2 in also present in nervous system; endogenous IL-2 and IL-2Ra occur in different regions of the adult rat brain, such as the frontal cortex, hippocampal formation, hypothalamus and cerebellum. Although the cellular origin of brain IL-2 is unclear, evidence shows that the glial cells, including astroglial and microglial cells, are the possible sources.

Evidence has also been found that IL-2 plays multiple roles in the central nervous system. It has trophic functions on both neurons and glia. For example, IL-2, a neurotrophic factor for sympathetic neurons, has been reported to enhance the proliferation and differentiation of oligodendrocytes. Furthermore, IL-2 can modulate neurotransmitter release and affect electrical activity. It is also involved in responses to central nervous system trauma and spontaneous regeneration. Recent studies demonstrated that IL-2 might also play a role in spatial learning and memory[60]. In dorsal root ganglia neurons, IL-2 plays an important role in the modulation of neural and neuroendocrine function; furthermore, there is evidence to show that IL-2 has an antinociceptive (analgesic) effect in dorsal root ganglia by binding to opioid receptors[61].

OVERVIEW

During WD, the orchestrated action of pro-, and anti-inflammatory cytokines regulates the main cellular and molecular events that stimulate axonal regrowth from proximal stumps and support axonal regeneration. Immediately after peripheral nerve damage, SCs, that have lost their contact with axons, and resident macrophages produce TNF-α, IL-1α and -β. These cytokines induce resident fibroblasts to produce IL-6[25]. Concomitantly, IL-6 is expressed by SCs in the early phases of WD; like the other cytokines, it is required for immune cell chemotaxis[25,59]. Following the activation of these cytokines, metalloproteinase, whose action is very important for damaged tissue remodeling, is responsible for basal lamina degradation, favoring destruction of the blood-nerve barrier and the infiltration of circulating macrophages[62]. Recruited cells (macrophages and T cells) produce inflammatory cytokines, and notably IL-10 which attenuates the inflammatory process by inhibiting cytokine production of activated macrophages, monocytes and other cell types[45,63]. Initial production of pro-inflammatory cytokines at the site of a peripheral nerve lesion is important in influencing the long-term behavioral outcome of nerve injury. IL-10 may accomplish this by downregulating the inflammatory response of the nerve to injury[63].

TGF-β1 expressed by SCs contributes to the maintenance of the immature phenotype of the cells themselves by stimulating their proliferation and inhibiting the myelination of axons. Only when nerve fibers have grown back during nerve regeneration into the distal stump is TGF-β1 downregulated and myelination is allowed. SC-derived IL-2 promotes proliferation of T cells, has trophic functions on both neurons and glia, and induces production of other cytokines.

Of relevance is the involvement of vitamins in nerve regeneration and their interaction with the inflammatory cytokines in the inflammatory response. Chabas and collegues[64] found that vitamin D potentiates axon regeneration, increasing axogenesis and axon diameter, and improving the responses of sensory neurons to metabolites, *e.g*. KCl and lactic acid.

In vitro studies have demonstrated that vitamin D suppresses pro-inflammatory cytokines and increases anti-inflammatory cytokines[65]. Experimental evidence shows that vitamin D can suppress the release of TNF-α and effectively upregulates the synthesis of anti-inflammatory IL-10[66-67]. Vitamin D reduces the inflammatory milieu and might serve as a new anti-inflammatory agent in future treatment of the disorder.

CONCLUSION

Peripheral nerve injury leads to a characteristic series of

cellular and molecular events necessary for axon regeneration and re-innervation of target tissues[68]. Inflammatory reaction is one of the crucial events, being important for the orchestration of all the processes that occur during WD.

In this review, the more studied cytokines involved in WD and the early phases of regeneration of a peripheral nerve have been outlined (TNF-α, IL-1, IL-6, IL-10). Attention has also been focused on two cytokines (TGF-α and IL-2) that are poorly described in the literature on peripheral nerve injury to date, which could make them of greater interest in the future.

After peripheral nerve injury, pro- and anti-inflammatory cytokines are produced by both immune and non-immune cells that are resident in the distal part of the injured nerve or recruited from blood circulation. Although nowadays even the most severe nerve injury can be surgically repaired, complete recovery of nerve function does not occur and clinical results remain unsatisfactory. Future research could therefore address the issues to give better knowledge of inflammatory events that might help develop new therapeutic measures that improve and accelerate peripheral nerve regeneration, stimulating the endogenous anti-inflammatory reaction and decreasing pro-inflammatory processes. It is expected that a complete functional recovery could be achieved by coupling surgical repair with a pharmacological approach targeted to the specific molecules that trigger the inflammatory reaction[69-70].

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