Cytokines, Inflammation and Pain

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Abstract

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). There are both pro-inflammatory cytokines and anti-inflammatory cytokines. There is significant evidence showing that certain cytokines/chemokines are involved in not only the initiation but also the persistence of pathologic pain by directly activating nociceptive sensory neurons. Certain inflammatory cytokines are also involved in nerve-injury/inflammation-induced central sensitization, and are related to the development of contralateral hyperalgesia/allodynia. The discussion presented in this chapter describes several key pro-inflammatory cytokines/chemokines and anti-inflammatory cytokines, their relation with pathological pain in animals and human patients, and possible underlying mechanisms.

Keywords

cytokine; inflammation; pain; hyperalgesia

1. Introduction

Inflammatory responses in the peripheral and central nervous systems play key roles in the development and persistence of many pathological pain states [1]. Certain inflammatory cytokines in spinal cord, dorsal root ganglion (DRG), injured nerve or skin are known to be associated with pain behaviors and with the generation of abnormal spontaneous activity from injured nerve fibers or compressed/inflamed DRG neurons.

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action).

It is common for different cell types to secrete the same cytokine or for a single cytokine to act on several different cell types (pleiotropy). Cytokines are redundant in their activity, meaning similar functions can be stimulated by different cytokines. They are often produced in a cascade, as one cytokine stimulates its target cells to make additional cytokines. Cytokines can also act synergistically or antagonistically (Figure 1).

Cytokines are made by many cell populations, but the predominant producers are helper T cells (Th) and macrophages. Cytokines may be produced in and by peripheral nerve tissue during physiological and pathological processes by resident and recruited macrophages, mast cells, endothelial cells, and Schwann cells. Following a peripheral nerve injury, macrophages and Schwann cells that gather around the injured site of the nerve secrete cytokines and specific growth factors required for nerve regeneration. Localized inflammatory irritation of the dorsal root ganglion (DRG) not only increases pro-inflammatory cytokines but also decreases anti-inflammatory cytokines [2]. Cytokines can also be synthesized and released from the herniated nucleus pulposus, synthesized inside the spinal cord [3], the DRG soma [4], or the inflamed skin [5]. Furthermore, cytokines may be transported in a retrograde fashion from the periphery, via axonal or non-axonal mechanisms, to the DRG and dorsal horn, where they can have profound effects on neuronal activity [6] and therefore contribute to the etiology of various pathological pain states.

2. Cytokines and pain

Pro-inflammatory cytokines

Proinflammatory cytokines are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions. There is abundant evidence that certain pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are involved in the process of pathological pain.

IL-1β is released primarily by monocytes and macrophages as well as by nonimmune cells, such as fibroblasts and endothelial cells, during cell injury, infection, invasion, and inflammation. Very recently, it was found that IL-1β is expressed in nociceptive DRG neurons [7]. IL-1β expression is enhanced following crush injury to peripheral nerve and after trauma in microglia and astrocytes in the central nervous system (CNS) [8]. IL-1β can produce hyperalgesia following either intraperitoneal, intracerebroventricular or intraplantar injection [9,10]. Moreover, IL-1β was found to increase the production of substance P and prostaglandin E_2 (PGE_2) in a number of neuronal and glial cells [11,12]. IL-1ra, a specific IL-1 receptor antagonist, competitively binds to the same receptor as IL-1β but does not transduce a cellular signal, thereby blocking IL-1β-mediated cellular changes. Administrations of IL-1ra and other anti-inflammatory cytokines have been demonstrated to prevent or attenuate cytokine-mediated inflammatory hyperalgesia [13] and nerve-injury induced mechanical allodynia [14].

IL-6 has been shown to play a central role in the neuronal reaction to nerve injury. Suppression of IL-6R by *in vivo* application of anti-IL-6R antibodies led to reduced regenerative effects [15]. IL-6 is also involved in microglial and astrocytic activation as well as in regulation of neuronal neuropeptides expression [16]. There is evidence that IL-6 contributes to the development of neuropathic pain behavior following a peripheral nerve injury [17,18]. For example, sciatic cryoneurolysis, a sympathetically-independent model of neuropathic pain involving repeatedly freezing and thawing a section of the sciatic nerve, results in increased IL-6 immunoreactivity in the spinal cord [3]. In addition, intrathecal infusion of IL-6 induces tactile allodynia and thermal hyperalgesia in intact and nerve-injured rats, respectively.

TNF-α, also known as cachectin, is another inflammatory cytokine that plays a well-established, key role in some pain models. TNF acts on several different signaling pathways through two cell surface receptors, TNFR1 and TNFR2 to regulate apoptotic pathways, NF-kB activation of inflammation, and activate stress-activated protein kinases (SAPKs). TNF-α receptors are present in both neurons and glia [19]. TNF-α has been shown to play important roles in both inflammatory and neuropathic hyperalgesia. Intraplantar injection of complete Freund's adjuvant in adult rats resulted in significant elevation in the levels of TNF-α, IL-1β, and nerve growth factor (NGF) in the inflamed paw. A single injection of anti-TNF-α antiserum before the CFA significantly delayed the onset of the resultant inflammatory hyperalgesia and reduced IL-1β but not NGF levels [20]. Intraplantar injection of TNF-α also produces mechanical [21] and thermal hyperalgesia [10]. It has been found that TNF-α injected into nerves induces Wallerian degeneration [20,22] and generates the transient display of behaviors and endoneurial pathologies found in experimentally painful nerve injury [23]. TNF binding protein (TNF-BP), an inhibitor of TNF, is a soluble form of a transmembrane TNF-receptor. When TNF-BP is administered systemically, the hyperalgesia normally observed after lipopolysaccharide (LPS) administration is completely eliminated [9]. Intrathecal administration of a combination of TNF-BP and IL-1 antagonist attenuated mechanical allodynia in rats with L_5 spinal nerve transection [24].

Chemokines

A variety of cytokines are known to induce chemotaxis. One particular subgroup of structurally related cytokines is known as chemokines. The term chemotactic cytokines (CHEMOtactic CytoKINES) usually refers to this. These factors represent a family of low molecular weight secreted proteins that primarily function in the activation and migration of leukocytes although some of them also possess a variety of other functions. Chemokines have conserved cysteine residues that allow them to be assigned to four groups: C-C chemokines (RANTES, monocyte chemoattractant protein or MCP-1, monocyte inflammatory protein or MIP-1α, and MIP-1β), C-X-C chemokines (IL-8 also called growth related oncogene or GRO/KC), C chemokines (lymphotactin), and CXXXC chemokines (fractalkine).

Various chemokines including MIP-1α, MCP-1 and GRO/KC are up-regulated not only in models of neuroinflammatory [2,25] and demylinating diseases, but also in various forms of CNS trauma [26] and in injured peripheral nerve [27]. Receptors for MCP-1, MIP-1α and GRO/KC are expressed on DRG neurons [28]. Interestingly, mice lacking the CCR2 receptor completely fail to develop mechanical allodynia in the partial sciatic injury model although pain sensitivity in uninjured animals is normal. In the same study, normal mice showed a sustained upregulation of the receptors in both DRG and peripheral nerve after the injury [29]. This suggests that the chemokines, including MCP-1 in particular, play very key roles in neuropathic pain as well as in neuroinflammatory conditions.

Anti-inflammatory cytokines

The anti-inflammatory cytokines are a series of immunoregulatory molecules that control the pro-inflammatory cytokine response. Cytokines act in concert with specific cytokine inhibitors and soluble cytokine receptors to regulate the human immune response. Their physiologic role in inflammation and pathologic role in systemic inflammatory states are increasingly recognized. Major anti-inflammatory cytokines include interleukin (IL)-1 receptor antagonist, IL-4, IL-10, IL-11, and IL-13. Leukemia inhibitory factor, interferon-alpha, IL-6, and transforming growth factor (TGF)-β are categorized as either anti-inflammatory or pro-inflammatory cytokines, under various circumstances. Specific cytokine receptors for IL-1, TNF-α, and IL-18 also function as inhibitors for pro-inflammatory cytokines.

Among all the anti-inflammatory cytokines, IL-10 is a cytokine with potent anti-inflammatory properties, repressing the expression of inflammatory cytokines such as TNF-α, IL-6 and IL-1 by activated macrophages. In addition, IL-10 can up-regulate endogenous anti-cytokines and down-regulate pro-inflammatory cytokine receptors. Thus, it can counter-regulate production and function of pro-inflammatory cytokines at multiple levels. Acute administration of IL-10 protein has been well-documented to suppress the development of spinally-mediated pain facilitation in diverse animal models such as peripheral neuritis, spinal cord excitotoxic injury, and peripheral nerve injury [30]. Blocking spinal IL-10, on the other hand, has been found to prevent and even reverse established neuropathic pain behaviors [31]. Recent clinical studies also indicate that low blood levels of IL-10 and another anti-inflammatory cytokine, IL-4, could be key to chronic pain since low concentrations of these two cytokines were found in patients with chronic widespread pain [32].

The family of TGF-β comprises 5 different isoforms (TGF-β1 to -β5). TGF-β1 is found in meninges, choroid plexus, and peripheral ganglia and nerves [33]. It is known that TGF-β suppresses cytokine production by inhibiting macrophage and Th1 cell activity; counteracts IL-1, IL-2, IL-6, and TNF; and induces IL-1ra 6 [34]. Its mRNA is induced following axotomy and may be involved in a negative-feedback loop to limit the extent of glial activation [35]. TGF-β1 also antagonizes nitric oxide production in macrophages [36]. Nitric oxide has been strongly implicated in the final common pathway of neuropathic pain [37]. It is expected that by its anti-cytokine action, TGF-β1 or agents that induce its activity may be effective therapy for neuropathic pain.

3. Glial activation in CNS and PNS

In the CNS, there are two types of glial cells, microglia and astrocytes, which can be activated by excitatory neurotransmitters released from nearby neurons. These neurotransmitters include EAA, SP, PGEs, adenosine triphosphate (ATP), and nitric oxide. A novel neuron to glia signal is fractalkine, a protein expressed on the extracellular surface of neurons [38]. Fractalkine is tethered to the neuronal membrane by a mucin stalk. When the neuron is sufficiently activated, the stalk breaks, releasing fractalkine into the extracellular fluid. As immunocompetent cells, activated glia release several key pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 [39,40].

It has been well demonstrated that spinal glial activation is necessary for induction of the neuropathic pain state [30,41,42]. Spinal administration of glial activator, fractalkine, induces cutaneous hyperalgesia, whereas spinal administration of a fractalkine receptor antagonist blocks neuropathic pain [1]. Furthermore, blocking the activation of spinal cord glia with the inhibitor fluorocitrate blocks the pathological pain state in rats with peripheral sciatic nerve neuritis [42]. Recently, it was found that administration of a new glia-specific inhibitor, minocycline, blocked the development of neuropathic pain. Minocycline, a lipid-soluble tetracycline derivative with anti-inflammatory effects, inhibits an IL-1β-converting enzyme and inducible nitric oxide synthesis up-regulation. Minocycline also prevents glial cell proliferation and inhibits the activation of p38 MAPK [43].

Non-neuronal cells in the peripheral nervous system also react to nerve injury. In addition to hematogenous macrophage infiltration, the satellite glia that surround the somata of sensory neurons proliferate [44], elaborate processes [45], and become immunoreactive for glial fibrillary acidic protein (GFAP) [46].

4. Mechanisms underlying cytokines-mediated pathological pain

There is evidence that pro-inflammatory cytokines (e.g., IL-1β, TNF-α) [6,47,48] and chemokines (e.g., MCP-1) [25,28,49] may directly modulate neuronal activity in various

classes of neurons in the peripheral and central nervous system. In the peripheral nervous system, abnormal spontaneous activity can be evoked from nociceptive neurons by topical application of TNF-α to the peripheral axons *in vivo* [48], or to the somata of the DRG neurons *in vitro* [47]. Large, myelinated fast conducting Aβ neurons can also be excited by topical application of TNF-α to the DRG [47] or by an autologous HNP extract [50]. TNF-α can enhance the sensitivity of sensory neurons to the excitation produced by capsaicin and this enhancement likely is mediated by the neuronal production of prostaglandins [51]. It was found that TNF-α-induced neuronal excitation is mediated by cAMP-dependent protein kinase (PKA) pathway [47]. The p38 mitogen-activated protein kinase (MAPK) is also involved in TNF-α-induced cutaneous hypersensitivity to mechanical or thermal stimulation [4]. Results obtained from IL-6 knockout mice indicates that IL-6 plays a facilitating role in sympathetic sprouting induced by nerve injury and that its effect on pain behavior is indirectly mediated through sympathetic sprouting in the DRG [18]. Most recently, it is reported that localized inflammation of the DRG up-regulates a number of pro-inflammatory cytokines including IL-6 and induces abnormal sympathetic sprouting in the absence of peripheral nerve injury [2]. It suggests a possible correlation between inflammatory responses and sympathetic sprouting, which are two well-known mechanisms implicated in various chronic pain states.

In summary, proinflammatory cytokines are involved in the development of inflammatory and neuropathic pain. Just as specific cytokines and their neutralizing antibodies have been introduced into clinical trials for the treatment of stroke, Alzheimer's disease, autoimmune diseases, wound healing, and amyotrophic lateral sclerosis, one could utilize local or systemic delivery of anti-inflammatory cytokines or inflammatory cytokine antagonists for the treatment of chronic pain. These specific cytokines or antagonists would act to disrupt the hyperexcitability cycle taking place in the sensory neurons, providing a new, non-opioid therapeutic approach for the treatment of pathological pain due to inflammation or peripheral nerve injury.

Acknowledgments

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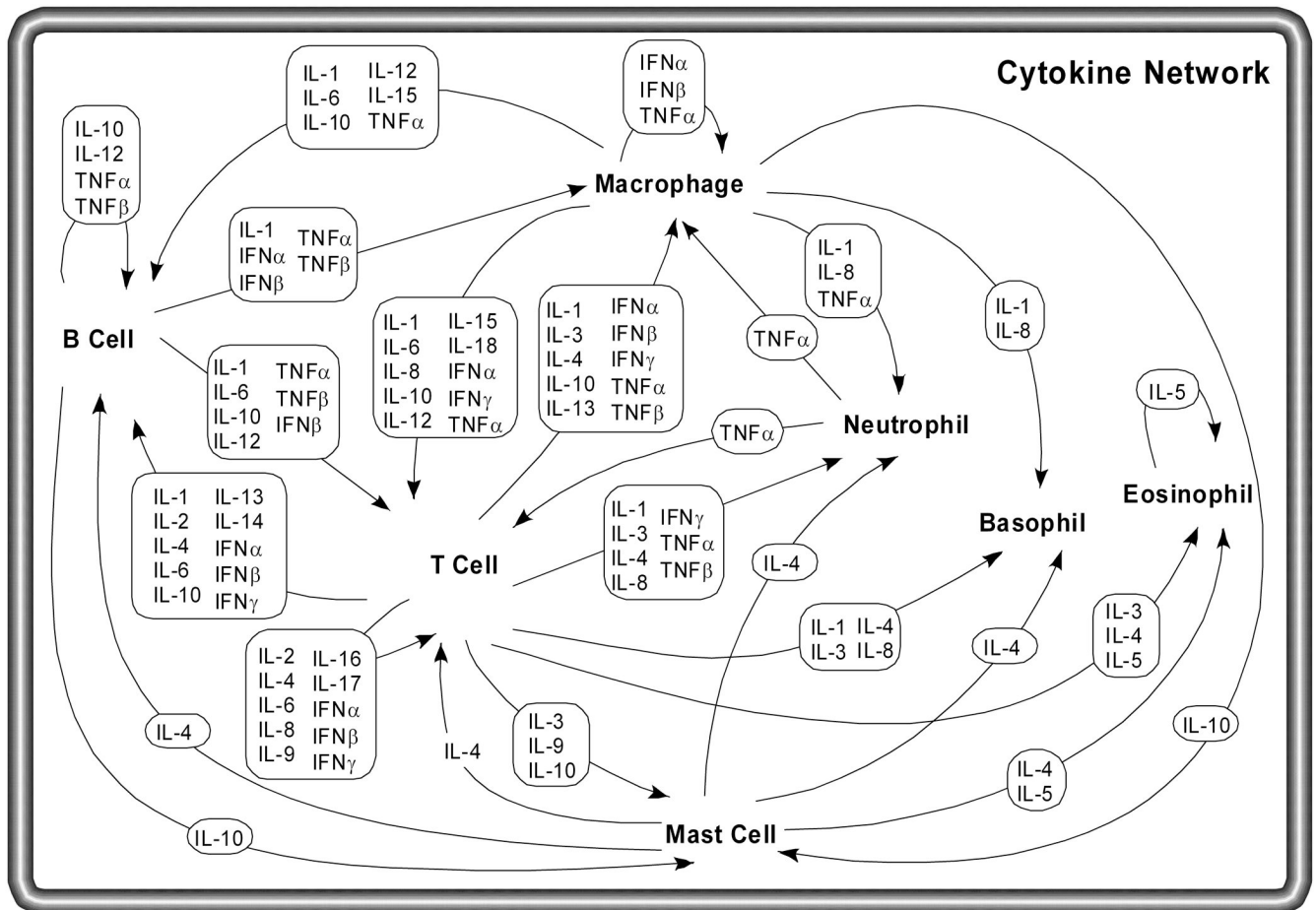
Figure 1.
Cytokine network. Several different cell types coordinate their efforts as part of the immune
system, including B cells, T cells, macrophages, mast cells, neutrophils, basophils and
eosinophils. Each of these cell types has a distinct role in the immune system, and
communicates with other immune cells using secreted cytokines. Macrophages phagocytose
foreign bodies and are antigen-presenting cells, using cytokines to stimulate specific antigen
dependent responses by B and T cells and non-specific responses by other cell types. T cells
secrete a variety of factors to coordinate and stimulate immune responses to specific antigen,
such as the role of helper T cells in B cell activation in response to antigen. The proliferation
and activation of eosinophils, neutrophils and basophils respond to cytokines as well.

Table 1

Selected cytokines and their primary activities

Cytokines	Principal Source	Primary Activity
GM-CSF	Th cells	Growth and differentiation of monocytes and dendritic cells
IL-1α	Macrophages and other antigen	Costimulation of APCs and T cells, inflammation and fever, acute phase
IL-β	presenting cells (APCs)	response,
		hematopoiesis
IL-2	Activated Th1 cells, NK cells	Proliferation of B cells and activated T cells, NK functions
IL-3	Activated T cells	Growth of hematopoietic progenitor cells
IL-4	Activated T cells	B cell proliferation, eosinophil and mast cell growth and function, IgE and class II MHC
		expression on B cells, inhibition of monokine production
IL-5	Th2 and mast cells	Eosinophil growth and function
IL-6	Activated Th2 cells, APCs, other somatic cells	Acute phase response, B cell proliferation, thrombopoiesis, synergistic with IL-1 and TNF on
		T cells
IL-7	Thymic and marrow stromal cells	T and B lymphopoiesis
IL-8	macrophages, somatic cells	Chemoattractant for neutrophils and T cells
IL-9	T cells	Hematopoietic and thymopoietic effects
IL-10	Activated Th2 cells, CD8+ T and B cells, macrophages	Inhibits cytokine production, promotes B cell proliferation and antibody production,
		suppresses cellular immunity, mast cell growth
IL-11	Atromal cells	Synergistic hematopoietic and thrombopoietic effects
IL-12	B cells, macrophages	Proliferation of NK cells, IFN production, promotes cell-mediated immune functions
IL-13	Th2 cells	IL-4-like activities
IL-18	Macrophages	potent inducer of interferon-+ by T cells and NK cells
IFN-α	Macrophages, neutrophils and	Antiviral effects, induction of class I MHC on all somatic cells, activation of
IFN-β	some somatic cells	NK cells and
		macrophages
IFN-γ	Activated Th1 and NK cells	Induces of class I MHC on all somatic cells, induces class II MHC on APCs and somatic
		cells, activates macrophages, neutrophils, NK cells, promotes cell-mediated immunity,
		antiviral effects
MIP-1α	Macrophages	Chemotaxis
MIP-1β	Lymphocytes	Chemotaxis
TGF-β	T cells, monocytes	Chemotaxis, IL-1 synthesis, IgA synthesis, inhibit proliferation
TNF-α	macrophages, mast cells, NK cells, sensory neurons	Cell death, inflammation, pain
TNF-β	Th1 and Tc cells	phagocytosis, NO production, cell death