Abstract

Cytokines encompass a diverse group of small proteins, typically ranging from 5-25 kDa (kilodaltons) and hold significant importance in cell signalling. These signalling molecules are released by cells in the form of proteins and profoundly influence cellular communication and interactions. Cytokines can exert their effects in various ways: autocrine action, paracrine action, and sometimes endocrine action. In inflammatory responses, cytokines come in two distinct types: pro-inflammatory and anti-inflammatory. Cytokines play a pivotal role in instigating and perpetuating pathological pain due to their direct activation of nociceptive sensory neurons. Furthermore, certain inflammatory cytokines contribute to the development of central sensitization, a process triggered by nerve injuries and inflammation. This review explores deep into our understanding of the role of cytokines in inflammation and their involvement in the mechanisms underlying pain signaling, shedding light on how these signaling molecules directly activate nociceptive sensory neurons. Furthermore, it unravels the contribution of specific inflammatory cytokines to central sensitization, a phenomenon triggered by nerve injuries and inflammation, which amplifies pain perception. Understanding the significance of cytokines is crucial for unravelling the underlying mechanisms behind their functions.

Categories: Endocrinology/Diabetes/Metabolism, Pain Management, Allergy/Immunology

Keywords: interleukin, pain, inflammation, chemokine, cytokine

Introduction And Background

1. Introduction

Many pathological pain states emerge and persist as a result of inflammatory reactions in the peripheral and central nervous systems [1]. Certain inflammatory cytokines have been linked to pain behaviours and the production of aberrant spontaneous activity from injured nerve fibres or compressed/inflamed dorsal root ganglion (DRG) neurons in the spinal cord, DRG, wounded nerve, and skin [2]. Small proteins (5-25 kDa) generated by cells called cytokines have a particular impact on how cells communicate and interact with one another. Based on either cell type that produces them or their act of action, the cytokine can also be defined in more specific terms including lymphokine (cytokines that produced by lymphocytes), monokine (cytokines that produced by monocytes), chemokine (cytokines with chemotactic properties), and interleukin (cytokines that produced by one leukocyte and acting on other leukocytes). Cytokines can influence the cells through the action of autocrine signaling (acts on same cell), paracrine signaling (acts on nearby cells) or, endocrine signaling (on cells far away). It is typical for different cell types to release the same cytokine or for one cytokine to function (via pleiotropy) on a variety of different cell types. Due to the redundancy in their activity, cytokines have the ability to activate distinct functions individually. They are frequently created in a cascade as one cytokine and encourages the production of subsequent cytokines by its target cells. Additionally, cytokines can have cooperative or competitive effects. Many different cell types create cytokines, although helper T cells and macrophages are the main producers by resident and recruited macrophages, mast cells, endothelial cells, and Schwann cells throughout healthy and pathological processes, peripheral nerve tissue can create cytokines. After a peripheral nerve is damaged, macrophages and Schwann cells conglomerate around the damaged area of the nerve and release specific growth factors and cytokines needed for nerve regeneration. Pro-inflammatory cytokines are increased by localized inflammatory irritation of the DRG, while anti-inflammatory cytokines are decreased [3]. Additionally, the herniated nucleus pulposus in the spinal cord can produce and release cytokines [4], the DRG soma [5], or the inflamed skin [6]. Additionally, cytokines can travel retrogradely from the periphery to the DRG and dorsal horn by axonal or non-axonal routes, where they can significantly impact neuronal activity [7] and therefore, contribute to the etiology of various pathological pain states.

Review
2. Cytokines in inflammation

There are a number of disorders whose etiology is aided by abnormal or excessive cytokine signalling [8]. For instance, increased IL-1 and IL-6 expression has been seen in a number of chronic inflammatory disorders and autoimmune diseases, including type 1 diabetes, rheumatic psoriasis, systemic sclerosis, lupus nephritis, and arthritis [9-13]. It is widely known that tumor necrosis factor (TNF) plays a direct role in the pathology of a number of systemic diseases and also influences disease pathology through more regional effects. Relevantly, suitable levels of TNF are also necessary to carry out crucial homeostatic processes, with their impacts on regular cell activity including cell proliferation, necrosis, and apoptosis [14]. TNF plays a crucial role in coordinating the inflammatory response, which encompasses both systemic and local responses, according to research [15]. TNF’s effects include activating the vascular system.

Expression of lipid mediators that encourage tissue oedema and leukocyte adhesion molecules that increase immune cell infiltration by endothelial cells. For instance, TNF is responsible for the early activation of chemokine expression and lymphocyte infiltration in response to microbial infection [16].

Large trials have demonstrated the effectiveness of anti-TNF medication in inflammatory disorders. Understanding TNF’s primary role in causing synovial inflammation was crucial because it the creation of TNF–blockers, which have emerged as very powerful treatments [17]. In inflammatory disorders, also higher levels of specific chemokines and their receptors have been reported in tissue specimen. In the synovial fluid of people suffering from several inflammatory rheumatic disorders, IL-8 can be found [18]. IL-8 levels in the mucosa are higher in patients with active ulcerative colitis [19] correlate with the recruitment of monocytes and T lymphocytes into synovial tissues in rheumatoid arthritis patients [20,21]. Additionally, B cell synovial cytokine generation and activity have been linked to CCR5, CCR6, CCR7, CXCR3, CXCR4, and CXCR5 [22].

Complex regional pain syndrome (CRPS) is known to cause an imbalance between proinflammatory and anti-inflammatory cytokines, according to clinical investigations [23] resulting in a shift towards a proinflammatory cytokine profile [24]. The serum, cerebral fluid, and skin blister fluid of CRPS patients had higher levels of proinflammatory cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor (TNF). Similar results have been obtained in animal research, by the considerable elevation of proinflammatory mediators and chemokines in the plantar, spinal dorsal horn (SDH), and dorsal root ganglion (DRG) of rats in the chronic post-ischemia pain (CPIP) model of CRPS [25-27].

3. Cytokines

3.1 Pro-inflammatory cytokines

Proinflammatory cytokines play a role in the stimulation of inflammatory responses and are mostly generated by activated macrophages. Numerous studies have demonstrated the role of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 in the pathogenesis of pathological pain. Crohn’s disease (CD), ulcerative colitis (UC), and other inflammatory bowel illnesses (IBD) are characterized by persistent, self-destructive inflammation of the digestive tract [28].

A major contributing factor to asthma is inflammation, which is facilitated by the chemokine CCL11 (eotaxin) and its receptor, CCR3 [29]. Bronchoalveolar lavage and biopsy samples from asthmatic patients showed elevated chemokine levels [30,31] including IL-8, CXCL10, CCL2, CCL3, CCL5, CCL7, CCL11, CCL13, and IL-24. Additionally, chemokine stimulation of AHR and cellular emigration have been connected to asthma in mouse models in airway inflammation via CCL2, CCL5, CCL11, CXCL10, and CXCL12 [32].

During cell injury, infection, invasion, and inflammation, IL-1 is largely secreted by monocytes and macrophages as well as by non-immune cells such as fibroblasts and endothelial cells. Recently, it was discovered that nociceptive DRG neurons express IL-1 [33]. It has been demonstrated that IL-6 is crucial for the neuronal response to nerve damage. Reduced regeneration effects were seen when anti-IL-6R antibodies were used to inhibit IL-6R in vivo [34]. IL-6 also controls the expression of neuronal neuropetides and activates microglia and astrocytes [35]. There is proof that IL-6 has a role in the neuropathic pain behaviour that develops after a peripheral nerve lesion [4,56]. For instance, sciatic cryoneurolysis, a model of neuropathic pain in which a portion of the sciatic nerve is repeatedly frozen and thawed, causes an increase in IL-6 immuno-reactivity in the spinal cord [4]. Additionally, undamaged, and nerve-damaged rats, both experience tactile allodynia and heat hyperalgesia after intrathecal injection of IL-6, respectively.

Tumor necrosis factor (TNF-α) was first discovered as an endotoxin-induced serum factor responsible for the necrosis of specific tumors in-vivo and in-vitro in the 1970s. The term “tumor necrosis factor” was first applied to two molecules, TNFα monocyte-derived tumour necrosis factor and TNFα lymphocyte-derived tumour necrosis factor [37]. Subsequently, TNFα was isolated [8] and it’s gene cloned [38]. It is a potent
inflammatory mediator that is central to the inflammatory action of the innate immune system, including induction of cytokine production, activation or expression of adhesion molecules, and growth stimulation [39-42]. It stimulates the proliferation of normal cells, exerts cytolytic or cytostatic activity against tumour cells, and causes inflammatory, antiviral, and immune-regulatory effects [43]. TNFα has also been shown to perform a number of additional functions linked with lipid metabolism, coagulation, insulin resistance, and endothelial function. Indeed, it has been shown to be one of the most important and pleiotropic cytokine mediating inflammatory and immune responses.

TNFα is the prototypic member of the TNF superfamily of type II transmembrane proteins that includes 30 receptors and 19 associated ligands with diverse functions in cell differentiation, inflammation, immunity and apoptosis [44]. TNFα is synthesized as a transmembrane precursor protein (mTNFα) with a molecular mass of 26 kDa [45], after which it is transported via the rough endoplasmic reticulum (RER), Golgi complex and the recycling endosome to the cell surface [45]. The monomers of TNFα associate at the plasma membrane as non-covalent trimers [14,46] prior to being cleaved by the metalloprotease, TNFα converting enzyme (TACE or ADAM17) [47]. Following TACE cleavage, the membrane stub is proteolytically processed by the signal peptide peptidases (SPPLs) SPPL2a and SPPL2b [39]. This cleavage produces an intracellular domain (ICD) that translocate to the nucleus and induces pro-inflammatory cytokine signalling, particularly the expression of IL-12 [39]. Thus, the precursor TNFα molecule is subjected to multiple cleavage events to release potent modulators of inflammation.

3.2 Anti-inflammatory cytokines

A group of immunoregulatory molecules known as anti-inflammatory cytokines regulate the pro-inflammatory cytokine response. To control the human immune response, cytokines work in conjunction with certain cytokine inhibitors and soluble cytokine receptors. More and more people are becoming aware of their pathologic and physiological roles in systemic inflammatory conditions. The interleukin (IL)-1 receptor antagonist, IL-4, IL-10, IL-11, and IL-13 are important anti-inflammatory cytokines. Depending on the situation, the cytokines leukemia inhibitory factor, interferon-alpha, IL-6, and transforming growth factor (TGF)-β are either anti-inflammatory or pro-inflammatory. Pro-inflammatory cytokines are inhibited by specific cytokine receptors for IL-1, TNFα, and IL-18.

One of the most effective anti-inflammatory cytokines is IL-10, which inhibits the expression of pro-inflammatory cytokines by activated macrophages such TNFα, IL-6, and IL-1 [48]. On the other hand, blocking spinal IL-10 has been discovered to diminished and even reverse established neuropathic pain behaviours [49]. Recent clinical studies further suggest that low blood levels of the anti-inflammatory cytokines IL-10 and IL-4, which were discovered in low amounts in individuals with chronic widespread pain, may be crucial to chronic pain [50].
FIGURE 1: Cytokine in response to body injury, inflammation, and pain

Cytokines work in a complex and interconnected manner to regulate the inflammatory and pain response. Understanding the role of these cytokines has led to the development of therapies targeting specific cytokines to manage conditions associated with inflammation and pain, such as rheumatoid arthritis and chronic pain disorders.
<table>
<thead>
<tr>
<th>S. No</th>
<th>Cytokine</th>
<th>Function in Inflammation and Pain</th>
<th>References</th>
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<tbody>
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<td><strong>Pro-inflammatory Signalling</strong></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>Interleukin-1 (IL-1)</td>
<td>Initiates and amplifies inflammation, mediates pain response</td>
<td>[51]</td>
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<tr>
<td>2</td>
<td>Tumor Necrosis Factor-alpha (TNF-α)</td>
<td>Promotes inflammation and contributes to pain sensation</td>
<td>[52]</td>
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<td>3</td>
<td>Interleukin-6 (IL-6)</td>
<td>Regulates acute-phase response, involved in pain perception</td>
<td>[53]</td>
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<tr>
<td>4</td>
<td>Interleukin-17 (IL-17)</td>
<td>Promotes inflammation and tissue damage, linked to chronic pain</td>
<td>[54]</td>
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<tr>
<td>5</td>
<td>Interferon-gamma (IFN-γ)</td>
<td>Modulates immune responses, can influence pain perception</td>
<td>[55]</td>
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<tr>
<td>6</td>
<td>Interleukin-8 (IL-8)</td>
<td>Chemotactic factor, recruits neutrophils to the site of inflammation</td>
<td>[56]</td>
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<tr>
<td>7</td>
<td>Interleukin-9 (IL-9)</td>
<td>Promotes inflammation, may contribute to pain in certain conditions</td>
<td>[57]</td>
</tr>
<tr>
<td>8</td>
<td>Interferon-gamma (IFN-γ)</td>
<td>Modulates immune responses, can influence pain perception</td>
<td>[58]</td>
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<tr>
<td>9</td>
<td>Transforming Growth Factor (TGF-β)</td>
<td>Regulates tissue repair and fibrosis in chronic inflammation</td>
<td>[59]</td>
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<tr>
<td>10</td>
<td>(GM-CSF)</td>
<td>Stimulates immune cell production, involved in inflammatory responses</td>
<td>[60]</td>
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<tr>
<td>11</td>
<td>Interleukin-12 (IL-12)</td>
<td>Enhances Th1 cell immune responses, may affect pain perception</td>
<td>[61]</td>
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<tr>
<td><strong>Anti-inflammatory Signalling</strong></td>
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<tr>
<td>1</td>
<td>Interleukin-10 (IL-10)</td>
<td>Anti-inflammatory cytokine, inhibits inflammation and pain</td>
<td>[62]</td>
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<tr>
<td>2</td>
<td>Interleukin-4 (IL-4)</td>
<td>Anti-inflammatory, may reduce pain by inhibiting inflammation</td>
<td>[63]</td>
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<tr>
<td>3</td>
<td>Interleukin-13 (IL-13)</td>
<td>Anti-inflammatory, involved in tissue repair, may alleviate pain</td>
<td>[64]</td>
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</table>

**TABLE 1: Cytokine and its important function**

Cytokines are primarily responsible for initiating and maintaining inflammatory responses in the body and involved in a variety of immunological processes, such as immune cell activation, immune response regulation, and tissue damage brought on by inflammation.

The TGF-β family consists of 5 distinct isoforms i.e. TGF-β1 to TGF-β5. Meninges, the choroid plexus, peripheral ganglia, and nerves all contain TGF-1 [50]. It is well known that TGF-β inhibits macrophage, Th1 cell activity, IL-1, IL-2, IL-6, TNF production, and promotes IL-1ra [64]. Following axotomy, its mRNA is stimulated, and it may be utilized in a negative feedback loop to regulate the degree of glial activation [65]. Nitric oxide generation is also inhibited by TGF-β1 in macrophages [66]. Strong evidence points to nitric oxide as the ultimate common mechanism of neuropathic pain [67]. It is anticipated that TGF-β1 or substances that stimulate it may be a viable treatment for neuropathic pain due to their anti-cytokine impact.

4. Glia cells role in inflammation

Gial cells are widely dispersed throughout the nervous system and play a critical role in the emergence of neuroinflammation by interacting with neurons, immune cells, and blood vessels [68-70]. They have many neuropeptide and neurotransmitter receptors that can be triggered by the by-products of neurogenic inflammation. Glial mediators that control pain sensitivity are released because of this activation [71]. As watchdogs of neuronal activity, microglia are innate immune cells found in the brain and spinal cord. They can control and monitor neuronal activity by generating prostaglandin (PG) E2, TNF-α, IL-1β, and neurotrophins that sensitize primary pain-mediated interneurons and primary nociceptive neurons [71,72]. The majority of the TNF-α in the spinal cord was produced by microglia, according to single-cell sequencing analyses [73]. Astrocytes aid in the transmission of pain signals from the spinal cord by controlling microglial activity and neuronal synaptic transmission in chronic pain. Additionally, through mechanisms including synapse formation regulation, astrocytes in the superior central nervous system govern anxiety and aversion to chronic pain [74]. Gap junctions between astrocytes and neurons can be formed, directly modifying neuronal activity. In animals with peripheral nerve damage, astrocytes are stimulated by glutamate, ATP, and cytokines (TNF-α, IL-1β, and IL-6) generated by microglia or afferent neurons [75]. There are two subtypes of reactive astrocytes: toxic A1 astrocytes and neuroprotective A2 astrocytes [76]. While A2 astrocytes have neuroprotective benefits, A1 astrocytes rapidly kill neurons and oligodendroglia [77,78].
5. Cytokines-mediated pathological pain

There is proof that pro-inflammatory cytokines, such as TNF-α and IL-1 [7,79,80] and chemokines (e.g., MCP-1) [81] may directly regulate the activity of several kinds of peripheral and central nervous system neurons. Topical administration of TNF-α to the peripheral axons in-vivo or to the somata of the DRG neurons in vitro might induce aberrant spontaneous activity from nociceptive neurons in the peripheral nervous system (PNS) [79]. TNF-α applied topically to the DRG can also stimulate large, myelinated rapid conducting neurons [79] or by an autologous HNP extract. TNF-α may increase the sensitivity of sensory neurons to the excitation caused by capsaicin, and this increase is probably mediated via prostaglandins generated by the neurons [29].

Peripheral nerve terminals that are sensitive to pain have receptors and ion channels that can pick up inflammatory mediators. When nociceptors in the DRG are activated, nociceptive action potentials spread to their cell bodies, where they are then sent to the spinal cord and brain for processing. A variety of cytokines are increased after peripheral nerve injury [82] which can activate and sensitize C fibers [82], increasing neurogenic inflammation as a result. The modulation of nociceptor activation and pain sensitivity is greatly aided by those inflammatory cytokines [83]. An overview of their role in neuro-inflammation and Complex Regional Pain Syndrome (CRPS) is given in this section.

Conclusions

6. Conclusion

The first cytokine was first characterized about 60 years ago. Since then, more than 300 cytokines, chemokines, and growth factors have been identified, each with a unique role in the immune system as well as the functioning of all other organ systems in the body. Despite this, our knowledge of how these parameters, acting alone or in combination with other factors, affect homeostatic and inflammatory events is still mainly in its infancy. Along with the use of proinflammatory cytokine antagonists (such glucocorticoids, thalidomide, and pentoxiphylline) and local or systemic anti-inflammatory cytokines or cytokine antagonists for chronic pain. The hyperexcitability loop of sensory neurons may be broken by those antagonists or anti-inflammatory cytokines, encouraging the development of a novel non-opioid treatment strategy for pathologic pain brought on by inflammation or peripheral nerve damage.

Appendices

kDa: Kilodalton

DRG: Dorsal Root Ganglion

IL-1: Interleukin-1

IL-6: Interleukin-6

TNF: Tumor Necrosis Factor

IL-8: Interleukin-8

CCR5, CCR6, CCR7: Chemokine Receptor 5, 6, 7,

CXCR3, CXCR4, and CXCR5: C-X-C Motif Chemokine Receptor 3, 4, and 5

CRPS: Complex Regional Pain Syndrome

SDH: Spinal Dorsal Horn

CPIP: Chronic Postsurgical Pain

CD: Crohn’s Disease

UC: Ulcerative Colitis

IBD: Inflammatory Bowel Disease

CCL11: C-C Motif Chemokine Ligand 11
CCL2, CCL5, CCL7, CCL11, CCL13, and IL-24: Chemokine Ligand 2, 5, 7, 11, 13, and Interleukin-24
CXCL10, and CXCL12: C-X-C Motif Chemokine Ligand 10, and 12
IL-6R: Interleukin-6 Receptor
TNFα: Tumor Necrosis Factor-Alpha
TACE or ADAM17: Tumor Necrosis Factor-Alpha Converting Enzyme or A Disintegrin and Metalloproteinase
TACE: Tumor Necrosis Factor-Alpha Converting Enzyme
SPPLs: Signal Peptide Peptidases
SPPL2a: Signal Peptide Peptidase-Like 2a
SPPL2b: Signal Peptide Peptidase-Like 2b
IL-12: Interleukin-12
TGF-β: Transforming Growth Factor-Beta
(GM-CSF): Granulocyte-Macrophage Colony-Stimulating Factor
TGF-β1: Transforming Growth Factor-Beta 1
TGF-β5: Transforming Growth Factor-Beta 5
PG: Prostaglandin
A2 astrocytes: Type A2 Astrocytes
MCP-1: Monocyte Chemoattractant Protein-1

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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