Review Article

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Cytokines & their physiologic and pharmacologic functions in inflammation: A review

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Abstract

Inflammation is mediated by a variety of soluble factors, including a group of secreted polypeptides known as cytokines. Inflammatory cytokines can be divided into two groups: those involved in acute inflammation and those responsible for chronic inflammation. This review describes the role played in acute inflammation by IL-1, TNF-α, IL- 6, IL-11, IL-8 and other chemokines, G-CSF, and GM-CSF. It also describes the involvement of cytokines in chronic inflammation. This latter group can be subdivided into cytokines mediating humoral responses such as IL-4, IL-5, IL-6, IL-7, and IL-13, and those mediating cellular responses such as IL-1, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, interferons, transforming growth factor-β, and tumor necrosis factor α and β. Some α cytokines, such as IL-1, significantly contribute to both acute and chronic inflammation. This review also summarizes features of the cell-surface receptors that mediate the inflammatory effects of the described cytokines. The anti-inflammatory cytokines are a series of immunoregulatory molecules that control the proinflammatory 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-6, IL-10, IL-11, and IL-13. Specific cytokine receptors for IL-1, tumor necrosis factor- α, and IL-18 also function as proinflammatory cytokine inhibitors. The nature of anti-inflammatory cytokines and soluble cytokine receptors is the focus of this review.

Key-Words: anti-inflammatory cytokines, Cytokines, Inflammation, Sepsis, Septic shock

Introduction

Inflammation, the response of tissue to injury, is characterized in the acute phase by increased blood flow & vascular permeability along with the accumulation of fluid, leukocytes, & inflammatory mediators such as cytokines. In the subacute / chronic phase (hereafter reffered to as the chronic phase), it is charactrised by the development of specific humoral & cellular immune responses to the pathogens present at the site of tissue injury.[1] The human immune response is regulated by a highly complex and intricate network of control elements. Under physiologic conditions, these cytokine inhibitors serve as immunomodulatory elements that limit the potentially injurious effects of sustained or excess inflammatory reactions.

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Under pathologic conditions, these anti-inflammatory mediators may either (1) provide insufficient control over proinflammatory activities in immune-mediated diseases or (2) overcompensate and inhibit the immune response, rendering the host at risk from systemic infection.[2,3] A dynamic and ever-shifting balance exists between proinflammatory cytokines and anti-inflammatory components of the human immune system.

The regulation of inflammation by these cytokines and cytokine inhibitors is complicated by the fact that the immune system has redundant pathwayswith multiple elements having similar physiologic effects. Furthermore, with the potential exception of interleukin (IL)-1 receptor antagonist (IL-1ra), all the anti-inflammatory cytokines have at least some proinflammatory properties as well. The net effect of any cytokine is dependent on the timing of cytokine release, the local milieu in which it acts, the presence of competing or synergistic elements, cytokine receptor density, and tissue responsiveness to each cytokine.[4]

This is what makes the study of cytokine biology so fascinating (and so frustrating as well!). Perturbations of this regulatory network of cytokines by genetic, environmental, or microbial elements may have highly deleterious consequences.[5–9] These inhibitory cytokines have already proven to be efficacious in a variety of clinical conditions marked by excess inflammation. Their potential therapeutic use in numerous other inflammatory states will also be described. The functional definition of an anti-inflammatory cytokine in this review is the ability of the cytokine to inhibit the synthesis of IL-1, tumor necrosis factor (TNF), and other major proinflammatory cytokines.

Cytokines involved in acute inflammation:

Several cytokines play key roles in mediating acute inflammatory reactions, namely IL-1, TNF-α , IL-6, IL-11, IL-8 & other chemokines, G-CSF, and GM-CSF. Of these, IL-1(α and β) & TNF are extremely potent inflammatory molecules: they are the primary cytokines that mediate acute inflammation induced in animals by intradermal injection of bacterial lipopolysaccharide.

Interleukin-1:

Their main cellular sources are mononuclear phagocytes, fibroblasts, keratinocytes, and T and B lymphocytes. Previous synonyms--endogenous pyrogen (EP), mononuclear cell factor, and lymphocyte-activating factor (LAF)--emphasize the role of IL-1 in inflammation. Both IL-1α and IL-1β can trigger fever by enhancing prostaglandin E_2 (PGE_2) synthesis by the vascular endothelium of the hypothalamus and can stimulate T cell proliferation. In addition, IL-1 elicits the release of histamine from mast cells at the site of inflammation. Histamine then triggers early vasodilation and increase of vascular permeability. The pro-inflammatory effects of IL-1 can be inhibited by IL-1 receptor antagonist (IL-1Ra), originally referred to as IL-1 inhibitor. IL-1Ra is produced by immune complex- or IL-4-stimulated macrophages and by TNF- or GM-CSF-stimulated neutrophils. It bears approximately 20-25% homology at the amino acid level to IL-1α and IL-1β. IL-1Ra inhibits IL-1 action by competing with IL-1 for binding to the IL-1 receptor (IL-1R).[10,11]

IL-1ra

IL-1ra is produced by monocytes and macrophages and is released into the systemic circulation in >100-fold excess than either IL-1a or IL-1b after lipopolysaccharide (LPS) stimulation in human volunteers. The synthesis of IL-1ra and IL-1β are differentially regulated at their own promoter sites. Although bacterial LPS stimulates the synthesis of both IL-1β and IL-1ra, other stimuli cause differential release of IL-1ra and IL-1β. The anti-inflammatory cytokines IL-4, IL-6, IL-10, and IL-13 inhibit the synthesis of IL-1b, yet they stimulate the synthesis of IL-1ra. There is at least one important polymorphism in the genetic regulation of IL-1ra synthesis in human populations.[12] DNA polymorphisms at this site may determine the synthetic rate of IL-1ra and alter the host response to inflammatory stimuli. Excess IL-1ra synthesis in relationship to IL-1α or IL-1β synthesis has been shown to increase susceptibility to diverse human pathogens such as Lyme arthritis, tuberculosis, and a variety of other infectious diseases. [13-15] Conversely, inadequate local IL-1ra synthesis in the lung may predispose to severe acute lung injury and result in excess lethality in ARDS. Because IL-1 is such a prominent proinflammatory cytokine in a multitude of systemic inflammatory states, IL-1ra has been extensively studied in clinical trials as a specific IL-1 inhibitor. Despite convincing evidence that IL-1 plays an important role in the pathogenesis of bacterial sepsis, the results of IL-1ra therapy in large phase III clinical trials for severe sepsis have been disappointing. Nonetheless, IL-1ra continues to be a promising new treatment for the management of patients with refractory forms of rheumatoid arthritis .[16]

Interleukin-2:

IL-2 is a glycoprotein originally known as T cell growth factor (TCGF). It is secreted mainly by activated T helper cells. It acts as a growth factor/activator for T cells, NK cells, and B cells and promotes the development of lymphokine-activated killer (LAK) cells. It therefore plays a critical role in regulating both cellular and humoral chronic inflammatory responses. Binding of IL-2 to the IL-2 receptor on T lymphocytes leads to cell proliferation, increased lymphokine secretion, and enhanced expression of class II MHC molecules.

Interleukin-3:

IL-3, also called multi-CSF, is produced by activated T cells and mast cells. It stimulates eosinophils and B cell differentiation while it inhibits lymphokine-activated killer (LAK) cell activity[28]. IL-3 shares several biological activities with GM-CSF.[17]

Interleukin-4:

IL- 4 is produced by CD4+ (T_H) cells, mast cells, and basophils. It induces CD4+ T cells to differentiate into T_H2 cells while suppressing the development of T_H1 cells. It also acts as a B cell, T cell, and mast cell growth factor, it enhances class II MHC expression on B cells, and it promotes immunoglobulin class switching to IgG_1 and IgE. In fact, IL-4 is necessary for

IgE response induction, and its absence also leads to significantly lower levels of IgG1 in T cell-dependent immune responses.[18] The stimulatory effects of IL-4 on IgG1 and IgE production and on MHC class II induction are downregulated by IFN-γ, a cytokine whose functions are antagonized by IL-4 and vice versa. IL-4 also stimulates collagen [19] and IL-6 production [20] by human dermal fibroblasts, and may thus play a role in the pathogenesis of fibrotic diseases such as systemic sclerosis. In rheumatoid arthritis, on the other hand, IL-4 appears to exhibit some anti-inflammatory properties by inhibiting the production of several proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α, by synovial membranes of rheumatoid arthritis patients.[21] IL-4 is a highly pleiotropic cytokine that is able to influence Th cell differentiation. Early secretion of IL-4 leads to polarization of Th cell differentiation toward Th2-like cells. Th2-type cells secrete their own IL-4, and subsequent autocrine production of IL-4 supports cell proliferation. The Th2- cell secretion of IL-4 and IL-10 leads to the suppression of Th1 responses by down-regulating the production of macrophage-derived IL-12 and inhibiting the differentiation of Th1-type cells. IL-4 drives Th2 responses, mediates the recruitment and activation of mast cells, and stimulates the production of IgE antibodies via the differentiation of B cells into IgE-secreting cells.[22,23] IL-4 has marked inhibitory effects on the expression and release of the proinflammatory cytokines. It is able to block or suppress the monocyte-derived cytokines, including IL-1, TNF-α , IL-6, IL-8, and macrophage inflammatory protein (MIP)-1α.[24,25] It has also been shown to suppress macrophage cytotoxic activity, parasite killing, and macrophage-derived nitric oxide production.[26] In contrast to its inhibitory effects on the production of proinflammatory cytokines, it stimulates the synthesis of the cytokine inhibitor IL-1ra.[27] The immunologic effects of IL-4 in the presence of bacterial infection are complex and incompletely understood. IL-4 has been shown to enhance clearance of *Pseudomonas aeruginosa* from lung tissue in experimental models of Gram-negative bacterial pneumonia.[28] In Gram-positive bacterial infection models, IL-4 has been found to act as a growth factor for *Staphylococcus aureus*, resulting in systemic infection and increased lethality from bacterial sepsis. [29] IL-4 is able to affect a variety of structural cells. It can potentiate proliferation of vascular endothelium and skin fibroblasts yet decrease proliferation of adult human astrocytes and vascular smooth muscle cells.[30] In addition, IL-4 induces a potent cytotoxic response against tumors.[31,32] IL-4 may act by stabilizing disease and modifying tumor growth rates in addition to inducing tumor shrinkage and cell death without causing severe side effects, suggesting a possible adjuvant role for IL-4 in the treatment of malignant diseases.

Interleukin-5:

IL-5, also known as B cell growth factor II (BCGFII) and T cell replacing factor (TRF), is produced by CD4+ T helper cells as well as NK cells. IL-5 is involved in eosinophil differentiation and activation and stimulation of immunoglobulin class switching to IgA. Other properties of IL-5 include increased activation of B cell proliferation, and enhancement of T cell cytotoxicity. The combined production of IL-4 and IL-5 by CD4+ T_H2 cells therefore results in IgE and IgA production and mast cell and eosinophil stimulation.

Interleukin-6:

Previous synonyms of IL-6 illustrate some of its biologic activities. They include interferon-β_2 (IFN-β_2), hybridoma/plasmacytoma growth factor, hepatocyte-stimulating factor, B cell stimulatory factor 2 (BSF-2), and B cell differentiation factor (BCDF). IL-6 is produced by a variety of cells including mononuclear phagocytes, T cells, and fibroblasts.[33,34] In addition to the stimulation of acute phase protein synthesis by the liver, IL-6 acts as a growth factor for mature B cells and induces their final maturation into antibody-producing plasma cells. It is involved in T cell activation and differentiation, and participates in the induction of IL-2 and IL-2 receptor expression. Some of the regulatory effects of IL-6 involve inhibition of TNF production, providing negative feedback for limiting the acute inflammatory response. Upregulation of IL-6 production has been observed in a variety of chronic inflammatory and autoimmune disorders such as thyroiditis, type I diabetes, rheumatoid arthritis[35,36] systemic sclerosis[37], mesangial proliferative glomerulonephritis and psoriasis, and neoplasms such as cardiac myxoma, renal cell carcinoma, multiple myeloma, lymphoma, and leukemia. IL-6 has long been regarded as a proinflammatory cytokine induced by LPS along with TNF-a and IL-1. IL-6 is often used as a marker for systemic activation of proinflammatory cytokines.[38] Like many other cytokines, IL-6 has both proinflammatory and anti-inflammatory properties. Although IL-6 is a potent inducer of the acute-phase protein response, it has anti-inflammatory properties as well.[39] Inasmuch as these peptide molecules use a common cellular receptor, they share many of the physiologic features attributable to IL-6. IL-6 down-regulates the synthesis of IL-1 and TNF.[40,41] IL-6 attenuates the synthesis of the proinflammatory

cytokines while having little effect on the synthesis of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β). IL-6 induces the synthesis of glucocorticoids[42] and promotes the synthesis of IL- 1ra and soluble TNF receptor release in human volunteers.[43] At the same time, IL-6 inhibits the production of proinflammatory cytokines such as GM-CSF, IFN-γ, and MIP-2. The net result of these immunologic effects place IL-6 among the anti-inflammatory cytokine group.

Interleukin-7:

IL-7 is a cytokine known as a pre-B cell growth factor, is a bone marrow and thymic stromal cell product. It stimulates the development of pre-B and pre-T cells and acts as a growth factor for B cells, T cells, and early thymocytes.[44]

Interleukin-8/chemokines:

IL-8 and other low molecular weight chemokines (*e.g.* platelet factor 4, macrophage inflammatory protein (MIP)-1α and β, MIP-2, monocyte chemoattractant protein-1 (MCP- 1/JE), RANTES) belong to a chemotactic cytokine family and are responsible for the chemotactic migration and activation of neutrophils and other cell types (such as monocytes, lymphocytes, basophils, and eosinophils) at sites of inflammation.[45,46] The two subsets of the chemokine family, "CXC" (or α), "C-C" (or β) are divided based on presence or absence of an amino acid between the first two of four conserved cysteines. A recent third subset, "C", has only two cysteines and to date only one member, IL-16, has been identified.[47] Chemokines have been implicated in inflammatory conditions from acute neutrophil-mediated conditions such as acute respiratory distress syndrome to allergic asthma, arthritis, psoriasis, and chronic inflammatory disorders. To date, at least 27 chemokines have been described. The product of many cell types, including mononuclear phagocytes, antigen-activated T cells, endothelial and epithelial cells, and even neutrophils, IL-8 was previously known as neutrophil chemotactic factor (NCF) and neutrophil activating protein (NAP- 1).[48] It is the most thoroughly studied chemokine and therefore serves as a prototype for discussing the biologic properties of this rapidly growing family of inflammatory mediators. Its main inflammatory impact lies in its chemotactic effects on neutrophils and its ability to stimulate granulocyte activity. In addition, IL-8, IL-1, and TNF are involved in neutrophil recruitment by upregulating cell-surface adhesion molecule expression (such as endothelial leukocyte adhesion molecule, ELAM-1, and intracellular adhesion molecule, ICAM-1), thereby enhancing neutrophil adherence to endothelial cells and facilitating their diapedesis through vessel walls. Thus, IL-8 mediates the recruitment and activation of neutrophils in inflamed tissue.[49] IL-8 can be detected in synovial fluid from patients with various inflammatory rheumatic diseases,[50] and mucosal levels of IL-8 are elevated in patients with active ulcerative colitis.[51] Other members of this cytokine family, such as NAP-2, RANTES, MCP-1, MCP-2, MCP-3, platelet factor 4, MIP-1α/β, and MIP-2, are also likely to play important roles in acute inflammation via their shared effects on cell migration. MCP-1 is a chemokine identified in supernatants of blood mononuclear cells. Its production in monocytes is enhanced by inflammatory cytokines. MIP-1α and MIP-1β induce monocyte and T lymphocyte migration. MIP-1α , MCP-1, and MIP-2 have been implicated in the pathogenesis of rheumatoid arthritis where they are believed to recruit mononuclear cells into the inflamed regions of the synovium.[52] Several other members of the IL-8/chemokine family have been identified but their biologic effects are as yet poorly defined. Two recently identified chemokines, eotaxin and IL-16, have some unique properties and are described below.

Interleukin-9:

IL-9 is another cytokine produced by CD4+ T helper (T_H2) cells as well as some B lymphomas first described in the mouse, IL-9 was known as mast cell growth-enhancing activity (MEA) and murine Tcell growth factor P40.[53] Its production is IL-4 and IL-10, and thus IL-2-dependent. IL-9 is regulatory in nature in that it inhibits lymphokine production by IFN-γ-producing CD4+ T cells and enhances the growth of CD8+ T cells.[54] In addition, IL-9 promotes the production of immunoglobulins by B cells and the proliferation of mast cells.[55]

Interleukin-10:

IL-10 is also referred to as B cell-derived T cell growth factor and cytokine synthesis inhibitory factor (CSIF) because it inhibits IFN-γ production by activated T cells. IL-10 is produced by a variety of cell types, including CD4+ T cells, activated CD8+ T cells, and activated B cells.[56] Its effects include reduction of antigen-specific T cell proliferation, inhibition of IL- 2-induced IFN-γ production by NK cells, and inhibition of IL-4 and IFN-γ induced MHC class II expression on monocytes.[56] Since IL-10 can be produced by T_H2 cells and inhibits T_H1 function by preventing T_H1 cytokine production (such as IFN-γ), IL-10 is considered a T cell cross-regulatory factor and has thus been referred to as an "anticytokine".[57] IL-10 also acts as a co-differentiation factor for cytotoxic T cells and a co-factor for T cell growth. Human IL-10

(hIL-10) shares 84% identity at the amino acid level with a homolog, viral IL-10 (vIL-10), which is encoded by the Epstein-Barr virus.[58] vIL-10 shares with hIL-10 inhibitory effects on cytokine production and stimulatory effects on B cell growth.[59] IL-10 is the most important anti-inflammatory cytokine found within the human immune response. It is a potent inhibitor of Th1 cytokines, including both IL-2 and IFN-γ. This activity accounts for its initial designation as cytokine synthesis inhibition factor.[60,61] In addition to its activity as a Th2 lymphocyte cytokine, IL-10 is also a potent deactivator of monocyte/macrophage proinflammatory cytokine synthesis.[62,63] IL-10 is primarily synthesized by CD41 Th2 cells, monocytes, and B cells. After engaging its high-affinity 110-kd cellular receptor, IL-10 inhibits monocyte/macrophage-derived TNF-α, IL-1, IL-6, IL-8, IL-12, granulocyte colony-stimulating factor, MIP-1α, and MIP-2α.[64-65] IL-10 inhibits cell surface expression of major histocompatibility complex class II molecules, B7 accessory molecules, and the LPS recognition and signaling molecule CD14. It also inhibits cytokine production by neutrophils and natural killer cells. IL-10 inhibits nuclear factor kB (NF-κβ) nuclear translocation after LPS stimulation and promotes degradation of messenger RNA for the proinflammatory cytokines. In addition to these activities, IL-10 attenuates surface expression of TNF receptors and promotes the shedding of TNF receptors into the systemic circulation.[66-67]IL-10 is readily measurable in the circulation in patients with systemic illnesses and a variety of inflammatory states.[68,69] IL-10 is present in sufficient concentrations to have a physiologic impact on host responses to systemic inflammation. It has been determined that patients who preferentially express high levels of IL-10 and reduced levels of TNF-α are more likely to die from meningococcemia[70,71]and a variety of other community acquired infections.[72] Physiologically inadequate IL-10 responses after systemic injury may have detrimental consequences as well. Low lung concentrations of IL-10 in patients with acute lung injury indicate that ARDS is more likely to develop. The administration of IL-10 in experimental animal models of endotoxemia improves survival. Human volunteers given IL-10 after endotoxin challenge suffer fewer systemic symptoms, neutrophil responses, and cytokine production than placebo-treated control subjects.[73] Moreover, mice who have genetic deletions of the IL-10 gene are more susceptible to endotoxin-induced shock than normal mice.[74] IL-10 generally protects the host from systemic inflammation after toxin-induced injury, but renders the host susceptible to lethality from overwhelming infection in a variety of experimental studies.[75,76] This observation should be kept in mind when administering anti-inflammatory cytokines in clinical medicine. The IL-10 knockout mouse spontaneously develops a chronic inflammatory enteritis that mimics inflammatory bowel disease in humans.[77-80] This indicates that endogenous concentrations of IL-10 are important in limiting the inflammatory response to gut-associated bacteria. For this reason, IL-10 is in clinical trials as an anti-inflammatory therapy for inflammatory bowel disease among other potential indications.

Interleukin-11:

IL-11is produced by bone marrow stromal cells and by some fibroblasts. It is a functional homologue of IL-6 and can replace IL-6 for the proliferation of certain plasmacytoma cell lines and in the induction of acute phase protein secretion in the liver.[81] Additional IL-11 activities include stimulation of T cell-dependent B cell immunoglobulin secretion, increased platelet production, and induction of IL-6 expression by CD4+ T cells. IL-11 shares many properties of IL-6, including the common use of the gp130 receptor ligand complex as a signal transduction pathway. IL-11 binds to its own unique receptor and then complexes with gp130 cell membranes of target cells.[82] IL-11 was initially described as a hematopoietic growth factor with particular activity in the stimulation of thrombopoiesis. IL-11 has recently been approved for clinical use as a platelet restorative agent after chemotherapy-induced bone marrow suppression.[83] It has become clear that IL-11 has important immunoregulatory activities separate from its hematopoietic growth factor potential. IL-11 has been shown to attenuate IL-1 and TNF synthesis from macrophages by up-regulating inhibitory NF-kB (inhibitory NF-κβ) synthesis in monocyte/macrophage cell lines. Inhibitory NF-kB prevents NF-kB from translocating to the nucleus where NF-kB functions as a transcriptional activator for the proinflammatory cytokines.[84] IL-11 has also been shown to inhibit the synthesis of IFN-γ and IL-2 by CD41 T cells. IL-11 functions as a Th2-type cytokine, with induction of IL-4 and inhibition of Th1-type cytokines.[85] IL-11 does not induce the synthesis of IL-10 or TGF-β. This indicates that IL-11 is a direct inhibitor of Th1 lymphocytes and does not act indirectly through induction of IL-10. IL-11 is rarely measurable in the systemic circulation but has been detected and is physiologically active in localized areas of inflammation, such as inflammatory arthritis or inflammatory bowel disease.[86] IL-11 is currently in clinical trials as an immunomodulator for a number of potential clinical indications.

Interleukin-12:
IL-12, previously known as natural killer cell stimulatory factor (NKSF) and cytotoxic lymphocyte maturation factor (CLMF), was originally isolated from Epstein-Barr virus transformed B cells. Its biological activities include enhancement of cytotoxic T cells and lymphokine activated killer (LAK) cell generation and activation, increased natural killer (NK) cell cytotoxicity, induction of activated T cell and NK cell proliferation, induction of IFN-γ production by NK cells and T cells, and inhibition of IgE synthesis by IL-4-stimulated lymphocytes via IFN-γ-dependent and independent mechanisms.[87,88] IL-12 is secreted by activated B cells, macrophages, and other antigen-presenting cells (APCs), but its production is inhibited by IL-4 and IL-10. In addition, the stimulatory effect of IL-12 on T_H1 development is antagonized by IL-4, a cytokine which promotes T_H2 cell development. Therefore, IL-12 plays an important role in cell-mediated inflammation and also contributes to the regulation of immunoglobulin production.

Interleukin-13:
IL-13 exhibits anti-inflammatory activities by inhibiting the production of inflammatory cytokines, such as IL-1β, TNF-α, IL-8, and IL-6, by human peripheral blood monocytes induced with lipopolysaccharide. Inhibition of inflammatory cytokine production is also a characteristic of two other cytokines produced by T_H2 lymphocytes, namely IL-4 and IL-10. In addition, IL- 13 enhances monocyte and B lymphocyte differentiation and proliferation, increases CD23 expression, and induces IgG4 and IgE class switching.[89] IL-13, a potent *in vitro* modulator of human monocytes and B-cell function, is secreted by activated T lymphocytes.[90,91] IL-13and IL-4 share a common cellular receptor (IL-4 type 1 receptor), and this accounts for many of the similarities between these two anti-inflammatory cytokines.[92] IL-4 and IL-13 share only 20% to 25% primary amino acid homology, but the major a-helical regions that are essential for their activity are highly homologous. The principal functional difference between IL-4 and IL-13 lies in their effects on T cells. IL-4 is a dominant mediator of Th2 cell differentiation, proliferation, and activity, whereas IL-13 has minimal effects on T-cell function. IL-13 can down-regulate the production of TNF, IL-1, IL-8, and MIP-1α by monocytes and has profound effects on expression of surface molecules on both monocytes and macrophages. IL-13 upregulates cell surface expression of b_2 integrins and major histocompatibility complex (MHC) class II antigens and down-regulates CD14 and Fcγ receptor expression. IL-13 inhibits NF-kB activation in macrophages and protects against LPS-induced lethality in animal models.[93,94] IL-13 suppresses lung inflammatory injury after the deposition of IgG immune complexes.[95-97] Exogenous administration of anti-inflammatory cytokines into the lungs of rats after IgG immune complex deposition reveals that the greatest inhibitory activity is observed by IL-13 and IL-10, followed by IL-4 and IL-6. The potential role of IL-13 in clinical medicine remains to be defined.[98]

Interleukin-14:
A product of malignant B and T cells as well as normal T cells, B-cell growth factor (BCGF). Like IL-4, IL-14 has been shown to induce B cell proliferation. However, IL-14 inhibits immunoglobulin secretion. It has been suggested to play an important role in the aggressive form of B-cell type non-Hodgkin's lymphoma.

Interleukin-15:
IL-15 is a cytokine of a T cell stimulatory activity produced by activated monocytes, epithelial cells, and fibroblasts. IL-15 shares many biologic properties with IL-2 and mediates its activity via a multi-subunit high affinity receptor comprised of a unique alpha chain and the beta and gamma chains of the IL-2R. IL-15 is produced by a large variety of cells including T lymphocytes and monocytes. It stimulates T lymphocyte and NK cell proliferation. It enhances B cell expansion and immunoglobulin production.[99] It is also a T lymphocyte chemoattractant. IL-15 may be responsible for the recruitment and activation of T lymphocytes in the synovium of patients with rheumatoid arthritis where its levels have been found to be elevated.[100]

Interleukin-16:
IL-16 was originally identified as a chemotactic factor known as lymphocyte chemoattractant factor or lymphotactin. It is the only member of the "C" family of chemokines. IL-16 is an unusual cytokine in that preformed IL-16 is stored in CD8+ lymphocytes and is secreted upon stimulation with histamine or serotonin.[101] It induces chemotaxis of CD4+ T lymphocytes [102,103] and is believed to initiate T-cell mediated inflammation in asthma.[104]

Interleukin-17:
IL-17 is a product of activated T lymphocytes and its biologic activities include stimulation of IL-6 and IL-8 production and enhanced ICAM-1 expression on human foreskin fibroblasts.[105]

Tumor necrosis factor:

Tumor necrosis factors-(TNF) α and β are cytokines that bind to common receptors on the surface of target cells and exhibit several common biological activities. TNF-α, or cachectin, exists as a trimer [131] and is one of the products of activated macrophages/monocytes, fibroblasts, mast cells, and some T and natural killer (NK) cells.[106,107] TNF-α and IL-1 share several pro-inflammatory properties. Like IL-1, TNF- α can induce fever, either directly via stimulation of PGE_2 synthesis by the vascular endothelium of the hypothalamus, or indirectly by inducing release of IL-1. Both cytokines can stimulate the production of collagenase and PGE_2 by synovial cells and thus are believed to contribute to joint damage in inflammatory conditions such as rheumatoid arthritis. TNF-α also shares an important inflammatory property with IL-6 and IL-11, *i.e.* the induction of acute phase reactant protein production by the liver. TNF-α and IL-1 further exert secondary inflammatory effects by stimulating IL-6 synthesis in several cell types. IL-6 then mediates its own effects and those of TNF- α and IL-1 in inducing fever and the acute phase response, thereby perpetuating the inflammatory response through a cascade of cytokines with overlapping properties. TNF-α, also known as lymphotoxin, is produced by activated T and B lymphocytes. It binds to the same high affinity receptors as TNF-α. Its properties are similar to those of TNF-α and include the induction of apoptosis (programmed cell death) in many types of transformed, virally infected, and tumor cells, and the stimulation of several PMN effector functions.[108] Although in general the effects of cytokines are exerted locally at the site of their production (autocrine and paracrine), TNF- α and TNF-β , as well as IL-1 and IL-6, have major systemic (endocrine) effects when either produced acutely in large amounts, as in the case of bacterial sepsis, or chronically in lesser amounts, as in the case of chronic infections. During sepsis with Gram negative organisms, lipopolysaccharides (endotoxin) released from bacteria trigger the widespread production of TNF-α (and subsequently IL-1 and IL-6) by macrophages. The systemic release of these cytokines has been shown to be responsible for the fever and hypotension that characterize septic shock. In an analogous fashion, the production of large amounts of TNF-α by T lymphocytes in response to "superantigens" such as staphylococcal toxic shock syndrome toxin and enterotoxins are responsible for many of the systemic manifestations (fever, hypotension) of infections with toxin-producing Gram positive organisms.[109,110] In addition, the chronic production of TNF is believed to be responsible for the metabolic alterations which result in the cachexia associated with chronic parasitic infections and some cancers.

Eotaxin:

Eotaxin is a specific chemoattractant for eosinophils. It is produced by cytokine-stimulated epithelial and endothelial cells as well as IL-3- stimulated eosinophils. Eotaxin is implicated in inflammatory bowel disease where its mRNA levels are markedly elevated, especially in ulcerative colitis.[111]

Colony stimulating factors:

Colony stimulating factors (CSF) are named according to the target cell type whose colony formation in soft agar cultures of bone marrow they induce.[112] Of the CSF's, granulocyte-CSF (G-CSF) and granulocyte macrophage-CSF (GM-CSF) participate in acute inflammation. G-CSF was cloned in 1986 and its gene was mapped to chromosome 17.[113] Monocytes, T cells, fibroblasts and endothelial cells activated by macrophage products such as IL-1 or TNF, can produce G-CSF and GM-CSF. Both CSF's can stimulate neutrophils, while GM-CSF can also activate effector functions of eosinophils and mononuclear phagocytes. An example of the pathophysiologic role of GM-CSF is the airway inflammation accompanying asthma, where the implicated cytokines include IL-3, IL-5, and GM-CSF which perpetuate eosinophil activation and survival. In this scenario, the source of GM-CSF may be the alveolar macrophages which are reported to produce two to threefold higher levels of GM-CSF than control macrophages. Another possible source for all three cytokines are T cells present in the airways. Additional cytokines such IL-4, IL-13 (both stimulatory) and IFN-γ (inhibitory) may be involved in the control of IgE synthesis, while IL-1 and TNF-α may contribute to the airway inflammation by upregulation of endothelial adhesion molecule expression.[114]

Transforming growth factor - β:

The transforming growth factor- β (TGF-β) family of cytokines includes three isoforms, TGF-β1, β2, and β3 which are encoded by separate genes yet bind to the same high affinity receptor. It is produced by T cells, platelets, and monocytes. TGF-β inhibits T cell and NK cell proliferation and activation and may play an important role in inflammation. At a site of injury, TGF-β stored in platelets is released upon degranulation. TGF-β then attracts monocytes and other leukocytes to the site, thus participating in the initial step of chronic inflammation. TGF- β then positively regulates its own production and the production and deposition of extracellular matrix components as well as the expression of integrins

resulting in enhanced cell adhesion. It also inhibits collagenase production, and if expression is prolonged, it may result in progressive fibrosis analogous to unregulated tissue repair. Conditions in which a role for TGF-β has been suggested include mesangial proliferative glomerulonephritis and diabetic nephropathy in rats, pulmonary fibrosis, and systemic sclerosis. Another example of the role played by TGF-β in inflammation is collagen-induced arthritis in rats. In this model, TNF-α and TGF-β, when injected into the rat ankle joint, accelerate disease onset.[115] TGF-β is synthesized as an inactive precursor and requires activation before exerting its effect. There are three isoforms of TGF-β (designated TGF-β_{1-3}) expressed in mammalian species. TGF-β is an important regulator of cell proliferation, differentiation, and formulation of the extracellular matrix. *In vitro*, it inhibits growth of ectodermally derived cells. TGF-β induces squamous cell differentiation of human bronchial epithelial cells.[116] TGF-β has been shown to inhibit alveolar type II cell proliferation and to decrease the expression of surfactant protein A in human lung explant cultures and in a human lung adenocarcinoma cell line. TGF-β appears to contribute to the fibroproliferative phase of acute lung injury from a variety of injurious agents. It plays a role in regulating the extracellular matrix by decreasing degradation of matrix proteins through a reduction in protease synthesis and an increase in the synthesis of protease inhibitors. Like many cytokines, TGF-β has both pro- and anti-inflammatory effects. It functions as a biological switch, antagonizing or modifying the action of other cytokines or growth factors. The presence of other cytokines may modulate the cellular response to TGF-β, and the effect may differ depending on the activation state of the cell. TGF-β is capable of converting an active site of inflammation into one dominated by resolution and repair. TGF-β often exhibits effects with immune-enhancing activity in local tissues and immune-suppressive activity in the systemic circulation. TGF-β1 suppresses the proliferation and differentiation of T cells and B cells and limits IL-2, IFN-γ, and TNF production. TGF-β_1 acts as a monocyte/ macrophage deactivator in a manner similar to IL- 10. However, TGF-β is less potent an inhibitor than IL-10 and has little or no effect on IL-1 production. The severe and uncontrolled inflammatory reactions observed in the TGF-β_1 knockout mouse attests to the physiologic role of TGF-β as an endogenous anti-inflammatory cytokine.[117]

Interferons:

The interferons are a group of cytokines originally identified by and named for their anti-viral activity.[118] Type I interferons include IFN-α, an 18-20 kDa product of leukocytes, and IFN-β, a product of fibroblasts. They exhibit anti-viral as well as anti-proliferative properties and upregulate MHC class I expression. Type II interferon, immune interferon or IFN-γ, is a homodimer produced by activated T cells and NK cells. IFN-γ is known to enhance MHC class I and II expression on nucleated cells and to stimulate many of the effector functions of mononuclear phagocytes. While IFN-α and –β bind to a common receptor, IFN- γ recognizes a distinct and specific cell surface receptor. IFN-γ has been implicated in the pathogenesis of a variety of autoimmune and chronic inflammatory conditions[119] including murine models of systemic lupus erythematosus,[148] Type I diabetes mellitus,[120] adjuvant-induced arthritis,[121] and experimental cerebral malaria.[122] Based on experiments with IFN-γ knock-out mice, one of its primary functions *in vivo* appears to be the activation of macrophages to kill intracellular pathogens such as Mycobacteria.[123]

IFN- γ-inducing factor:

An IFN-γ-inducing activity was identified in murine Kupffer cells and activated macrophages and referred to as IFN-γ-inducing factor (IGIF).[124] IGIF induces IFN-γ production more potently than does IL- 12 and is involved in the development of T_H1 cells.

Pharmacologic role of Anti-inflammatory Cytokines and Cytokine Inhibitors:

A complex network of cytokines is generated in response to a systemic immune challenge. Microbial pathogens may actually use components of the cytokine network to their own advantage. A number of DNA viruses synthesize soluble TNF receptor and IL-1 receptors.[126,127] Epstein-Barr virus mediates the synthesis of viral IL-10 in infected human B cells.[128] These viral-induced anticytokine strategies appear to assist the virus in the promotion of viral replication and evasion of host-derived clearance mechanisms. Several bacterial pathogens have the capacity to alter host cell cytokine synthesis, degrade proinflammatory cytokines, or use cytokine receptors as portals of entry for cellular invasion.[129] Administration of inhibitors of proinflammatory cytokines (antibodies, soluble receptors, and anti-inflammatory cytokines) in experimental models generally provides an advantage in systemic toxicity models such as endotoxin challenge studies. However, in localized infection models, inhibitors of the proinflammatory cytokine

system may be detrimental to the host and precipitate overwhelming infection with excess mortality. This is particularly true in the absence of appropriate antimicrobial therapy against the invading microbial pathogen. The dichotomous nature of anti-inflammatory cytokine responses in experimental systems is commonly observed in cytokine biology. Inadequate concentrations of anti-inflammatory cytokines result in excess inflammation, yet excess anti-inflammatory cytokine concentrations disrupt clearance mechanisms of microbial pathogens in the host. Nonetheless, these anti-inflammatory agents must be present in far greater concentrations than those of proinflammatory cytokines to inhibit their actions. Systemic concentrations of soluble cytokine inhibitors IL-1ra and IL-10 indicate that they are of sufficient magnitude to at least partially inhibit proinflammatory cytokine action.[130] These results suggest that there may well be a pharmacologic role for anti-inflammatory cytokines and soluble cytokine receptors in the face of systemic inflammation. Recent evidence indicates that individuals differ in their susceptibility to systemic infection and inflammatory states on the basis of their cytokine profiles and genetic background. Patients and first-degree relatives of patients with meningococcemia are more likely to have fatal infections if they have high ratios of IL-10 to TNF-α. Similarly, patients with high ratios of TNF to soluble TNF receptors are at increased risk of having lethal meningococcal infections. These studies make it clear that alterations in cytokine networks can have a significant impact on the human host response to a variety of infectious agents and inflammatory states. Despite complexities inherent in the human immune response, therapeutic intervention with specific cytokine inhibitors or anti-inflammatory cytokines has already been shown to have significant clinical benefits.[131] Several of these agents are already approved for clinical use, and others are undergoing extensive clinical trials for a variety of inflammatory disease states. The ability to rapidly assess the state of the human immune response and regulate this response in the presence of a variety of human disease states has been the goal of immunologists for the past century. Advances in human genetics and immunobiology now provide an opportunity to capitalize on recent discoveries in basic immunology and cytokine biology. It is likely that anti-inflammatory cytokines and specific cytokine inhibitors will increasingly find their way into standard clinical practice as we enter the next millennium.

Receptor of inflammatory cytokines:

Cytokines elicit their responses by binding to specific high affinity cell-surface receptors on target cells and initiating a series of intracellular signal transduction pathways. The receptors of several cytokines and growth factors are homologous within their extracellular domains. These receptors have been grouped into families, the largest of which is the hematopoietin receptor superfamily which includes one or multiple chains of the receptors for erythropoietin, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, v-*mpl* oncogene, GM-CSF, G-CSF, prolactin, and growth hormone. The receptors in this family share a common structure of four conserved cysteine residues in the amino-terminal portion of the ligand-binding domain, as well as a conserved stretch of amino acids (WSXWS = Trp-Ser-X-Trp-Ser; X representing a nonconserved residue) proximal to the membrane-spanning region. The receptors also share fibronectin type III domains.[132] Of the above-mentioned members of the erythropoietin receptor family, one of the best characterized is the IL-2 receptor (IL-2R). It consists of three polypeptide chains: IL-2Rβ (p70) and IL-2Rγ (p64), which are expressed on resting T cells, and IL- 2Rα (p55; T cell activation antigen or Tac), which is expressed upon T cell activation. Association of these subunits yields a high affinity receptor for IL-2.[133,134] In addition, Tac (IL-2Rα) is shed from cells in a soluble form, but it has low affinity for IL-2. Another member of the erythropoietin receptor family, IL-6 receptor (IL-6R), consists of an 80 kDa ligand-binding molecule and a 130 kDa nonligand binding signal-transducing subunit (gp130). Both molecules exhibit the structures shared by members of the hematopoietin receptor superfamily.[135] Such a bimolecular complex is also described for IL- 3R, IL-5R, and GM-CSFR. One of the biologic consequences of these receptor complexes is that although cytokines bind to specific receptors, some may share common pathways in eliciting the target cell's response as a result of shared receptor components. As an example, IL-6, IL-11, leukemia inhibitory factor (LIF), and oncostatin M recognize different cellular receptors (by virtue of unique ligand-binding subunits), but share the same signaltransducing receptor subunit (gp130) and similar biological activities. These cytokines may therefore exert their effects via common signal transduction pathways. A group of receptors distantly related to the erythropoietin receptor family consists of the receptors for type I (α and β) and type II (γ) interferons.[136] Receptors in this class share a homologous binding domain of about 210 amino acids and four cysteine

pairs divided equally between the amino and carboxy terminal. Another group of related receptors includes the two receptors for TNF, the receptor for nerve growth factor (NGF), a transmembrane protein, FAS (Apo-1 or CD95), involved in the apoptosis of activated T lymphocytes,[137] and CD40, a cell surface receptor important in B cell growth and isotype switching.[138] The TNF receptors are 55 kDa (TR55) and 75 kDa (TR75) proteins that bind TNF-α and β equally. Their extracellular domains share 28% identity. There is growing evidence that the two receptors may mediate different cellular responses to TNF,[139,140] although there may be crosstalk between the receptors, perhaps at the level of the signalling pathways to which they are coupled. The chemokine receptors are members of the G protein-coupled receptor (GPCR) superfamily and include IL-8R-A, an IL-8-specific receptor, IL- 8R-B, a receptor recognized by IL-8, and other chemokines of the CXC subset. Recently, receptors for the CC subset of chemokines have been identified. They include CC-CKR-1, CC-CKR-2, CCCKR- 3,and CC-CKR-4 and CC-CKR-5.[141] A recently described receptor, the Duffy blood group antigen receptor for chemokines (DARC), binds both CXC and CC chemokines. In addition, the identification of new 'orphan' chemokine receptors, for which no ligands have been identified, has been reported.[142] Recently, five groups reported that CCCKR- 5 is a co-receptor for certain strains of HIV-1.[143] A 32-bp deletion in *CKR5* is reported to delay progression to AIDS in infected individuals and may be responsible for the antibody-negative status of individuals exposed to HIV-1.[144-164]

Conclusion

In conclusion, cytokines are key modulators of inflammation. They participate in acute and chronic inflammation in a complex network of interactions. Several cytokines exhibit some redundancy in function and share overlapping properties as well as subunits of their cell surface receptors. Better understanding of the pathways regulated by cytokines will allow the identification and/or development of agents for improved modulation of the inflammatory response for the treatment of autoimmune, infectious, and neoplastic diseases.

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