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Review

The Physiological Role Of Cytokines In Inflammation And Immune Response

Vinjavarapu. L. Anusha[1*], G. Sudhakara rao[2], Manegar Akhleela[3], D. Lakshmi[4], M. Praharsha[5], K. Sofiya[6], B. Ramadevi[7], B. Navya[8], Ch. Anjaneya reddy[9]

[1]Associate Professor, Department of pharmacology, SIMS College of Pharmacy, Mangaldas Nagar, Guntur, Andhra Pradesh, India.
[2-9]Professor, Department of Pharmacology, MRM College College of Pharmacy, Chintapallyguda, Hyderabad, Telangana, India.

*Author for Correspondence: Vinjavarapu. L. Anusha
Email: gerapatisudhakararao@gmail.com

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Abstract

Cytokines are a category of signaling molecules that are used extensively in cellular communication. These are made up of large and diverse family of polypeptide regulators that are produced widely throughout the body by cells of diverse embryological origin. Cytokines participate in many physiological processes including the regulation of immune and inflammatory responses. Cytokines include chemokines, interferons, interleukins, lymphokines, tumor necrosis factor but generally not hormones or growth factors. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells.They act through receptors, and are especially important in the immune system, cytokines modulate the balance between humoral and cell-based immune responses and they regulate the maturation, growth, and responsiveness of particular cell populations. Cytokines are also serving as cell-signaling protein molecules used extensively in intercellular communication. Cytokines can be classified as proteins, peptides, or glycoproteins. Each cytokine has a matching cell-surface receptor; its activation leads to cascades of intracellular signaling that alter cell functions. This may include the up regulation and/or down regulation of several genes and their transcription factors, resulting in the production of other cytokines, an increase in the number of surface receptors for other molecules, or the suppression of their own effect by feedback inhibition.

Keywords: Cytokines, cell signaling, Immune response, Receptor, Diagnosis, Treatment.

INTRODUCTION

Definition

Cytokines are a category of signaling molecules that are used extensively in cellular communication. They are proteins, peptides, or glycoproteins. They are a broad and loose category of small proteins that are important in cell signaling. Cytokines are released by cells and affect the behavior of other cells, and sometimes releasing cell itself. Cytokines include chemokines, interferons, interleukins, lymphokines, tumor necrosis factor but generally not hormones or growth factors. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells.They act through receptors, and are especially important in the immune system, cytokines modulate the balance between humoral and cell-based immune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways. They are important in health and disease, specifically in host responses to infection, immune responses, inflammation, trauma, sepsis, cancer, and reproduction. Interleukin 2 (IL-2) triggers the immune system to produce T cells. IL-2's immunity-boosting properties have traditionally made it a promising treatment for several illnesses. Some cytokines chemically attracts specific cell[**1-6]**·

Cytokines are proteins produced by cells, and they serve as molecular messengers between cells. In arthritis, cytokines regulate various inflammatory responses. As part of the immune system, cytokines regulate the body's response to disease and infection, as well as mediate normal cellular processes in your body.

Cytokines are a broad and loose category of small proteins (~5–25 kDa) important in cell signaling. Due to their size, cytokines cannot cross the lipid bilayer of cells to enter the cytoplasm and therefore typically exert their functions by interacting with specific cytokine receptors on the target cell surface. Cytokines have been shown to be involved in autocrine, paracrine and endocrine signaling as immunomodulating agents. Cytokines include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors, but generally not hormones or growth factors (despite some overlap in the terminology). Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell. They act through cell surface receptors and are especially important in the immune system; cytokines modulate the balance between humoral and cell-based immune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways. They are different from hormones, which are also important cell signaling molecules. Hormones circulate in higher concentrations, and tend to be made by specific kinds of cells. Cytokines are important in health and disease, specifically in host immune responses to infection, inflammation, trauma, sepsis, cancer, and reproduction[7-10].

Cytokines participate in many physiological processes including the regulation of immune and inflammatory responses. These effector molecules are produced transiently and locally controlling the amplitude and duration of the response. A variety of experiments has shown that excessive or insufficient production may significantly contribute to the pathophysiology of a range of diseases. Particularly cytokines released by CD4+ T cells at the onset of an immune response are thought to be decisive for pathological or physiological consequences.

Cytokines contribute to the pathophysiology of autoimmune diseases, infectious diseases and allograft rejection (e.g., IL-1, IL-4, IL-6, IL-10, IL-12, TNF-alpha and IFN-alpha, -beta, -gamma). A central role for IFN-gamma in autoimmunity was suggested by blocking experiments in vivo using monoclonal antibodies and soluble forms of the IFN-gamma receptor (IFN-gamma SR). These agents ameliorated disease development in a variety of experimental autoimmune diseases in rodents. In a mouse model for the human disease Myasthenia gravis, IFN-alpha was found to reduce both the incidence and progression of the disease.

In a human macrophage cell line, TNF-α exerted a stimulatory effect on viral replication and programmed cell death induced by HIV-1 which was potentiated by the simultaneous incubation with IFN-gamma. Upon transfection of human peripheral blood mono nuclear cells(PBLs) and CD4+ T cells with a retroviral vector encoding human IFN-beta, a notable reduction in reverse transcriptase activity after HIV-1 challenge was observed. Gp120 was also found to induce both IL-6 and TNF-alpha expression and to induce morphological changes reminiscent for apoptosis in primary astrocytes and in a re-aggregated human brain cell model, suggesting a role for these cytokines in the neuropathology of AIDS dementia[11-13].

Discovery

Interferon-alpha, an interferon type I, was identified in 1957 as a protein that interfered with viral replication. The activity of interferon-gamma (the sole member of the interferon type II class) was described in 1965; this was the first identified lymphocyte-derived mediator. Macrophage migration inhibitory factor (MIF) was identified

simultaneously in 1966 by Bloom and Bennett. In 1969 Dudley Dumonde proposed the term "lymphokine" to describe proteins secreted from lymphocytes and later, proteins derived from macrophages and monocytes in culture were called "monokines". It was understood that these proteins and others were part of a broader class of proteins involved in self-defense, and should be called "cytokines" [14-20].

Nomenclature

Cytokines are released by cells of the immune system, especially by monocytes and T lymphocytes, but they are also secreted by many cells in addition to those of the immune system, such as endothelial cells and fibroblasts. They used to different names depending on their origin, such as lymphokines (produced by lymphocytes), monokines (monocytes) or on their activity: chemokines, interleukins, interferon. The term "cytokine" has been used to refer to the immunomodulating agents, such as interleukins and interferons [21-23].

Classification

The classification based on the cell of origin or the function, their spectrum of activity, the category of activity they influence, the cells that are their targets, or on specific features of their ligand-receptor interaction, the knowledge of structural and functional aspects of cytokines has been extraordinarily developed, especially in the human and marine species. Classification According to Structure Structural homology has been able to partially distinguish between cytokines that do not demonstrate a considerable degree of redundancy so that they can be classified into four types. Structures of whose members have four bundles of α-helices. This family in turn is divided into three sub-families, the IL-2 subfamily, the interferon (INF) subfamily and the IL-10 subfamily. The first of these three subfamilies is the largest, and contains several non-immunological cytokines including erythropoietin (EPO) and thrombopoietin (THPO). IL-1 family, which primarily includes IL-1 and IL-18[24-32].

Classification According to Function A classification that proves more useful in clinical and experimental practice is dividing cytokines into those that enhance cellular immune responses, type 1 (IFN-γ, TNFα, etc.), and type 2 (TGF-β, IL-4, IL-10, IL-13, etc.), which favor antibody responses. A key focus of interest has been that cytokines in one of these two subsets tend to inhibit the effects of those in the other. Dysregulation of this tendency is under intensive study for its possible role in the pathogenesis of autoimmune disorders. Some cytokines are primarily lymphocyte growth factors; others function as proinflammatory or anti-inflammatory molecules whereas other cytokines polarize the immune response to antigen. Cytokines have become an important frontier in medicine in a vital place as diagnostic, prognostic and therapeutic agents in human disease [24].

Several inflammatory cytokines are induced by oxidative stress. The fact that cytokines themselves trigger the release of other cytokines and also lead to increased oxidative stress makes them important in chronic inflammation, as well as other immune responses, such as fever and acute phase proteins of the liver (IL-1,6,12, IFN-a). Interferon-γ (IFNγ), essential for defense against several intracellular microorganisms such as Mycobacterium tuberculosis, is also a major cytokine in the pathogenesis of several autoimmune diseases. IL-2 is needed for the generation of cytotoxic T-cells (CTL) and forms the basis for several vaccines but the same cytokine drives graft versus host disease and limits the success of bone marrow transplantation[33-38].

The cytokine receptors

The cytokine receptors are membrane glycoproteins consisting of several units. They have the role of internalization of the signal. Cytokines usually act locally, both in the cells producing them (autocrine activity) and in the cells next to it (paracrine activity). More rarely they have an effect on cells and tissues distant from the place where they are produced (endocrine activity). However, some cytokines, especially those with inflammatory effects such as IL-1 and TNF, have their effect after being transported through the blood to distant target cells. Several types of cytokines have been newly described, and some of them have been cloned. For example, in the human and murine species 36 cytokines have been cloned, although only 19 are available from the porcine species.

Cytokines action

The cytokines can act as:

- Mediators of the innate immunity (inflammation, chemotaxis, macrophage activation, NK cells) and adaptive immunity (humoral and cellular).
- Regulators of lymphocyte activation, proliferation and differentiation.
- Stimulators of the growth of hematopoietic stem cells [39-42].

Cytokines production and release

Cytokines production and release from innate immune cells are critical responses to inflammation and infection. Populations of white blood cells as circulating dendritic cells, monocytes, natural killer (NK) cells, neutrophils, eosinophils, basophils, tissue-resident mast cells and macrophages comprise innate immune cells. These cells control opportunistic invasion with a range of pathogens as viruses, bacteria, fungi and parasites.

Cytokine release can be directly evoked by immunoglobulin- or complement receptor-mediated signaling or by pathogens through a diverse array of cellular receptors, including pattern recognition receptors such as TLRs. The Gram-negative bacterial coat component lipopolysaccharide (LPS), the main culprit behind toxic shock syndrome and sepsis, is a highly potent trigger of cytokine secretion through TLR4. Most cytokines rely on membrane-bound and cytoplasmic cellular proteins, the so-called trafficking machinery, to mediate their transport through the cell. Cytokines are released by cells into the circulation or directly into tissues. The cytokines locate target immune cells and interact with receptors on the target immune cells by binding to them. The interaction triggers or stimulates specific responses by the target cells. Among the best studied of the trafficking machinery proteins in cytokine release are the membrane fusion proteins known as Soluble N-ethylmaleimide-sensitive factor activating protein receptor proteins (SNAREs). The SNAREs include subfamilies of vesicle associated membrane proteins (VAMPs) and syntaxins which are classified by the amino acid composition of their core SNARE domains as RSNAREs and Q-SNAREs, respectively. Typically, Q- and R-SNAREs on opposing target and vesicle membranes unite as a 4-helix coiled-coil bundle that winches tethered membranes together for fusion.

The mode of action of many of the cytokines involves typical signal transduction events such as protein phosphorylation. The role in other pathologic processes has provided insight into autoimmune and allergic diseases, as well as a variety of systemic disorders. Because of their broad spectrum of activity, cytokines have been used in a variety of therapeutic settings involving both infectious diseases and neoplasia.

Immunohistologic examination of mature peripheral blood neutrophils suggests that TGFα, TNF, IL-6, IL-12, and CXCL2/IL-8 are stored within peroxidase-negative organelles. Neutrophils produce a wide range of cytokines and chemokines. Basophils are another granulocyte that is important in the generation of cytokines, particularly IL-4 in allergic inflammation. Mast cells, which are important innate immune cells in allergy and inflammatory diseases that reside in tissues, secrete numerous cytokines and chemokines, many of which are stored as preformed mediators in their secretory granules. Cytokines are released during classical degranulation, shown by the rapid secretion of IL-4 and TNF during receptor-mediated exocytosis by cross-linking cell surface complexes of IgE and Ag [42-50].

Cytokine activities

- Cytokines are made by many cell populations, but the predominant producers are helper T cells (Th) and macrophages. Cytokines stimulate immune cell proliferation and differentiation. They include Interleukin 1 (IL-1), which activate T cells [86], IL-2, which stimulate the proliferation of antigen-activated T and B cells, IL-4, IL-5, and IL-6, which stimulate proliferation and differentiation of B cells, interferon gamma(IFN γ) which activates macrophages and IL-3, IL-7 and Granulocyte Monocyte Colony Stimulating Factor (GM-CSF), which stimulate hematopoiesis. Other groups of cytokines include interferons and chemokines. Interferons IFNα and IFNβ inhibit virus replication in infected cells, while IFNγ also stimulates antigen-presenting cell MHC expression [51-54].
- Chemokines attract leukocytes to infection sites. Chemokines have conserved cysteine residues that allow them to be assigned to four groups . The groups, with representative chemokines, are C-C chemokines (RANTES, MCP-1, MIP-1α, and MIP1β), C-X-C chemokines (IL-8), C chemokines (Lymphotactin), and CXXXC chemokines (Fractalkine). Some cytokines are predominantly inhibitory. For example, IL-10 and IL13 inhibit inflammatory cytokine production by macrophages [55-58].

Cytokine receptors

Cytokines act on their target cells by binding specific membrane receptors. The receptors and their corresponding cytokines have been divided into several families based on their structure and activities. Hematopoietin family receptors are dimers or trimers with conserved cysteines in their extracellular domains and a conserved TrpSer-X-Trp-Ser sequence. Interferon family receptors have the conserved cysteine residues but not the Trp-Ser-X-Trp-Ser sequence, and include the receptors for IFNα, IFNβ, and IFNγ.

Tumor Necrosis Factor family receptors have four extracellular domains; they include receptors for soluble TNFα and TNFβ as well as membrane-bound CD40 and Fas (which signals the cell to undergo apoptosis).

Chemokine family receptors have seven transmembrane helices and interact with G protein. This family includes receptors for IL-8, MIP-1 and RANTES. Chemokine receptors CCR5 and CXCR4 are used by HIV to preferentially enter either macrophages or T cells. Hematopoietin cytokine receptors have two subunits, one cytokine-

specific and one signal transducing. An example is the GM-CSF subfamily, where a unique α subunit specifically binds either GM-CSF, IL-3, or IL-5 with low affinity and a shared β subunit signal transducer also increases cytokine-binding affinity.

Cytokine binding promotes dimerization of the α and β subunits, which then associate with cytoplasmic tyrosine kinases to phosphorylate proteins which activate mRNA transcription. GM-CSF and IL-3 act on hematopoietic stem cells and progenitor cells and activate monocytes. With IL-5, they also stimulate eosinophil proliferation and basophil degranulation. All three receptors phosphorylate the same cytoplasmic protein. Antagonistic GMCSF and IL-3 activities can be explained by their competition for limited amounts of β subunit.

The IL-2R subfamilies of receptors for IL-2, IL-4, IL-7, IL-9, and IL-15 have a common signaltransducing γ chain. Each has a unique cytokine-specific α chain. IL-2 and IL-15 are trimers, and share an IL-2R β chain. Monomeric IL-2R α has low affinity for IL-2, dimeric IL-2R αβ has intermediate affinity, and trimeric IL-2R αβγ binds IL-2 with high affinity. IL-2Rα chain (Tac) is expressed by activated but not resting T cells. Resting T cells and NK cells constitutively express low numbers of IL-2R βγ . Antigen activation stimulates T cell expression of high affinity [59-60].

Functions of cytokines

- Cytokines play a variety of regulatory roles in both host defense and normal and abnormal homeostatic mechanisms. They may be produced by diverse cell types and exert their function on a variety of cells. Their effects (which may be suppressive or enhancing) are on cellular proliferation, differentiation, activation, and motility.
- In addition, cytokines can exert cytodestructive effects on infectious agents or tumor cells, either directly or by activating cells with cytodestructive potential. Any given cytokine may have many different biologic effects.
- The mode of action of many of the cytokines involves typical signal transduction events such as protein phosphorylation, and a specific biologic reaction. Nevertheless, elucidation of their role in other pathologic processes has provided insight into autoimmune and allergic diseases, as well as a variety of systemic disorders. Because of their broad spectrum of activity, cytokines have been used in a variety of therapeutic settings involving both infectious diseases and neoplasia [61].

Role of cytokines in health and diseases

Roles of Cytokines in Health Cytokines and innate immune system

The immune system is a complex network designed to protect the host from both external (such as bacteria and viruses) and internal threats (such as malignant transformation). Cytokines are important mediators of immune responses that allow integration of the behavior of cells in time and geographical location as the immune responses are generated. The immune system is organized into innate and adaptive immune responses, with adaptive immunity further subdivided into two branches, humoral and cell-mediated immunity.

Innate immunity is immediate and rapid. Innate defense mechanisms include neutrophils and macrophages, which, among other functions, can ingest and destroy pathogens. While often effective in protecting the host, innate immunity is associated with damage to host tissue in the context of providing defense. It is also amnestic in that the inciting agent is not specifically recognized by a unique structure and there is no creation of a memory to that agent such that future responses are more efficient.

Adaptive immunity is slower in its response to threats. However, it provides two main features that innate immunity lacks: specific antigen recognition and memory that allows rapid recall of original antigen exposure. Host defense is generally provided in two major arms of the adaptive response. Resistance to Trypanosoma cruzi infections is critically dependent on cytokine-mediated activation of cell-mediated immune effector mechanisms. The role of IL-10, TNF-α, IFN-γ and IL-12 in controlling T. cruzi replication by the innate and specific immune systems.In addition, IL-12 synthesized by infected or LPS-stimulated macrophages, in addition to other actions, stimulates cytokine synthesis by both NK and T helper cells and promotes the activation and expansion of these lymphocyte subpopulations. Reciprocal regulatory interactions among cytokines secreted by the innate and acquired immune systems ultimately control the activation of each system and its cytokine-mediated effector functions. White blood cells and certain other cells of the immune system produce cytokines when an antigen is detected. There are many different cytokines, which affect different parts of the immune system:

- Some cytokines stimulate activity. They stimulate certain white blood cells to become more effective killers and to attract other white blood cells to a trouble spot.Other cytokines inhibit activity, helping end an immune response.
- Some cytokines, called interferons, interfere with the reproduction (replication) of viruses
- Cytokines also participate in acquired immunity.

- Cytokines released from innate immune cells play key roles in the regulation of the immune response.
- These intercellular messengers are the source of soluble regulatory signals that initiate and constrain inflammatory responses to pathogens and injury. These include: Monokines, cytokines produced by mononuclear phagocytic cells.
- Lymphokines, cytokines produced by activated lymphocytes, especially The cells.
- Interleukins, cytokines that act as mediators between leukocytes.
- Cytokines are a group of proteins produced by different cells, especially cells of the immune system, either as a response to an immune stimulus or as an intercellular signal after a certain stimulation. Cytokines have a multitude of different biological effects and are very important both in the innate and in the adaptive immune response.
- Cytokines bind to specific receptors on target cells with high affinity and the cells that respond to a cytokine are either: 1) the same cell that secreted cytokine (autocrine); 2) a nearby cell (paracrine) or 3) a distant cell reached through the circulation (endocrine). Cellular responses to cytokines are generally slow (hours) because they require new mRNA and protein synthesis1, IL-10, IL-12, type I interferons (IFN-α and IFN-β), IFN-γ, and chemokines [62-64].

Types of cytokines

1. Lymphokines, made by lymphocytes, attract immune cells such as macrophages
2. **Monokines,** made by monocytes, attract neutrophils
3. **Chemokines** are associated with chemotactic actions
4. **Interleukins** are made by one leukocyte but act on other leukocytes, mediating communication between cells. Specific interleukins can have a major impact on cell-cell communication.

1. **Lymphokines**:

Produced by lymphocytes, a type of white blood cell.

2. **Monokines**:

Produced by monocytes, a type of white blood cell

3. **Chemokines**:

Chemokines direct immune cells toward places in the body where they can fight infection

4. **Interleukins**:

Interleukins get their name from “inter” which means between and “leukocyte,” which is another name for a white blood cell. Originally, scientists thought that leukocytes alone released interleukins and only relayed messages to other leukocytes. But the cells other than leukocytes release these proteins. Also, interleukins can relay messages between cells that are not leukocytes.

5. **Interferons**:

Interferons signal cells to put up their defenses against viruses invading body. In this way, interferons “interfere” in the process that allows viruses to replicate, or make more viruses once they have invaded a healthy cell.

6. **Tumor necrosis factor (TNF)**:

TNF helps regulate inflammation in your body. TNF also signals to immune cells that kill tumor cells.

7. **Colony-stimulating factors (CSF)**:

CSF signals hematopoietic stem cells to develop into specific cell types. Hematopoietic stem cells (HSC) are precursor cells that give rise to all blood cell types: white blood cells, red blood cells and platelets. These changes take place during a process called hematopoiesis. For example, granulocyte-colony stimulating factor (G-CSF) signals an HSC to become a white blood cell called a neutrophil. Neutrophils help fight infection.

Functions

Cytokines as signal:

- **Cell activation**: Cytokines can give signal to cells where to move and what action can do. For example, cytokines can direct immune cells toward an infection site so the cells can fight microbes there. They can heighten or lessen the processes associated with inflammation.
- **Cell differentiation**: Cytokines can promote immature cells to develop into a specific type of cell. For example, cytokines can modify into an immature cell to mature into a white blood cell capable of fighting infection.
- **Cell proliferation**: Cytokines can give signal to a cell to make more cells as like it. For example, cytokines give signal to a white blood cell to make more white blood cells to fight infection.
- Stimulate the production of blood cell.
- Aid in the development, maintenance, and repair of tissues.

- Regulate the immune system.
- Drive inflammation through interferons, interleukins, and tumor necrosis factor-alpha (TNF-α)1.[65].

CONCLUSION

Cytokines can be classified as proteins, peptides, or glycoproteins. Each cytokine has a matching cell-surface receptor; its activation leads to cascades of intracellular signaling that alter cell functions. This may include the up regulation and/or down regulation of several genes and their transcription factors, resulting in the production of other cytokines, an increase in the number of surface receptors for other molecules, or the suppression of their own effect by feedback inhibition.

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