An overview of cytokines; their current status & futuristic scope

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Abstract
The cytokines are biologically active proteinous substances secreted by monocytes, lymphocytes and other cell and are actively involved in innate immunity, acquired immunity and inflammation. The cytokines released by lymphocytes and monocytes are known as lymphokines and monokines respectively. Acting through specific receptors, these molecules are of utmost importance to the immune system, work by regulating growth, development, and maturation of various types of cells. In a number of complexes reactions of the body few cytokines increase or inhibit the action of other cytokines. They also play a very important role in our health and diseased state.

Keywords: Molecular cross talks, Inflammatory cytokines, Cytokine receptors.

Introduction
Cytokines are the molecules belonging to the diverse family of glycoproteins (wt. less than 30 kDa), whose function is to mount and coordinate an effective immune response, a mechanism by which lymphocytes, inflammatory cells and haematopoietic cells can communicate with each other. These low molecular weight molecules are secreted by white blood cells and various other cells in response of some stimulus.(1) Though their role in cell differentiation and directed migration is also well documented in the literature. For development of effective immune response, these agents influence both innate and adaptive immune responses. The two principal producers of cytokines are helper T cells and macrophages, although they can be transiently induced and secreted by virtually all nucleated cells.(2) A particular cytokine manifests its downstream effects through its high-affinity binding of its receptor expressed, at target cell surface. This action may occur in an autocrine, paracrine or endocrine manner.(3) If a particular cytokine exerts its effects through receptor binding on the same cell, it is called autocrine action. If the cytokine's receptors are present on the target cell which is in close proximity of the cytokine secreting cells, the action is called paracrine while the cytokine secreted may bind to target cell receptors available at distant part of the body exerting the endocrine action. Differentiation, proliferation and activation of the target cell are all biological effects which are mediated by cytokine stimulation.(3)

Cytokines even secreted by small number of cells, leads to proliferation of enormous no of cells. That's way they share many properties similar to hormones and growth factors.(4) These chemicals exhibit the properties of pleiotrophy (a given cytokine has different biological effects on different target cells), redundancy (many cytokines mediate similar functions), synergy (combined effect of 2 cytokines is more than the individual cytokine), antagonism (effect of one cytokine inhibits the other) and cascade induction (occurs when action of one cytokine on the cell induces the other's secretion which in turn may induce the other cytokine to secrete) in order to maintain and regulate cellular activity.(3,4) It is required in the body in picomolar concentration just like hormones and growth factors, but their action is very rarely endocrinal in nature, most of the time they behave in autocrine or paracrine manner.(1) A cytokine always work in an antigen independent nonspecific manner. The number of physiological responses mediated by cytokines are development of humoral and cellular immune response, induction of inflammatory response, regulation of hematopoiesis, control of cellular proliferation and differentiation etc.(5)

Cytokine Receptors: Because of their clinical relevance, the cytokine receptors have got so much attention in recent years. These receptors have remarkable characteristics, and have also been directly linked to certain debilitating immunodeficiency states. In this regard, and also because the redundancy and pleiotropy of cytokines are a consequence of their homologous receptors, it is necessary to have a proper classification of cytokine receptors.

A classification of cytokine receptors based on their three-dimensional structure provides several unique perspectives for attractive pharmacotherapeutic target, is as follows.

i. **Type I cytokine receptors**, Receptors of all the cytokines classified as hematopoitins belong to this class. The IL-2 receptor belongs to this group, whose γ-chain (common to several other cytokines) deficiency is directly responsible for the x-linked form of Severe Combined Immunodeficiency (X-SCID). 13 other members of this family are the interleukins and several colony stimulating factors and growth hormones. The members of this family

have conserved amino acid sequence consisting of 4 positionally conserved cysteine residues (CCCC) in the extracellular domain.[6]

ii. **Type II cytokine receptors**, whose members are receptors mainly for interferons. They possess the conserved CCCC motif but lack the WSXWS motif present in class 1 cytokine receptors. Both class I & II receptors include one subunit that binds specific cytokine molecules and another that mediate signal transduction.[6]

iii. **Immunoglobulin (Ig) superfamily**, receptors are the one which are, uniformly present in several cells and tissues of the vertebrate body. The receptors included are IL-1α & IL-β. Nearly 30 % identical in sequence, they are identical in functions even bind to the same receptor, and mediate the same responses. Most of the cytokine binding receptor belong to the same class.[7]

iv. **Tumor necrosis factor receptor family**, whose members share a cysteine-rich common extracellular binding domain, and includes several other non-cytokine ligands like receptors, CD40, CD27 and CD30, besides the ligands on which the family is named (TNF).[8]

v. **Chemokine receptors**, act as protein binders for HIV (CXCR4 and CCR5) and are G protein coupled receptors.[9]

vi. **TGF beta receptors** or Transforming growth factor beta (TGFβ) receptors are single passerine/threonine kinase receptors, exist in several different isoforms that can be homo- or heterodimeric. The number of ligands in the TGFβ superfamily are rationally more than the number of known receptors. This suggests the promiscuity lies between the ligand and receptor interactions. TGFβ is a growth factor and cytokine involved in paracrine signalling, found in many different tissue types, including brain, heart, kidney, liver, and testes. Cases of renal fibrosis, causing kidney disease, as well as diabetes, and ultimately end-stage renal disease have been reported due to over-expression of TGFβ.

Role of cytokines in innate immunity

Cytokines play a main role in the natural or innate immune response by means of immune mechanism which activates the NK (Natural Killer) cells and macrophages, leading to the release of cytokines; they are produced primarily in response to pathogen-associated molecular patterns (PAMPs).[10] The cytokines are able to identify viral nucleic acids like Type 1 IF leading to blockage of viral replication within the infected host cells.[11] These include:-

1. TNF-α: It acts on the endothelial cells to stimulate inflammation and coagulation pathway.
2. IL-1: It mediates acute inflammatory process by activating the coagulation pathway, stimulating the liver to produce acute phase proteins.
3. Chemokines: These enable the migration of leucocytes from blood to tissues at the site of inflammation. These trigger WBCs to release agents for extracellular killing e.g. IL-8, MIP-1a, MIP-1b etc.
4. IL-12: It stimulates the synthesis of IF-ϒ by T-lymphocytes and NK cells, destroys cytotoxic T-lymphocytes and NK cells and stimulates differentiation of naïve T4-lymphocytes into IF-ϒ producing TH-1 cells.
5. IL-6: Its function is to stimulate liver to produce acute phase proteins and also to boost up the proliferation of B lymphocytes and neutrophils.
6. IL-10: It is an inhibitor of activated macrophages and dendritic cells.
7. IL-15: It stimulates NK cells and T-8 lymphocytes proliferation.
8. IL-18: It stimulates production of IF-ϒ by NK cells and T lymphocytes.[10,11]

Role of cytokines in adaptive immunity

The cytokines involved in the adaptive immune response are produced primarily by T-lymphocytes that have recognized an antigen specific for that cell.[11]

1. IL-2: It helps in the proliferation of NK cells and T and B lymphocytes.
2. IL-4: It is the major stimulus for IgE antibody production.
3. IL-5: It acts as growth factor for eosinophils as a defence against the microorganisms.
4. IF-ϒ: It activates macrophages and stimulates the synthesis of TH1 cells and inhibits the proliferation of TH2 cells.
5. TGF-β: It inhibits the proliferation and effector function of T-lymphocytes, B-lymphocytes and macrophages.
6. Lymphotoxins: These help in the activation of neutrophils.
7. IL-13: It increases the production of IgE by B-lymphocytes, inhibits macrophages and increases mucus production.[10,11]

Cytokines in stimulating heamatopoisis

The cytokines involved in stimulating haematopoeisis are produced by bone marrow stromal cells which stimulate the growth and differentiation of immature leucocytes.[12]

1. CSF: It promotes the colonies production of different leucocytes in bone marrow. e.g. GM-CSF, G-CSF, M-CSF.
2. IL-3: It supports the growth of bone marrow stem cells.
3. IL-7: It plays a role in the survival and proliferation of immature B-lymphocytes and T-lymphocyte precursors.[12]

Cytokines in inflammation

The cytokines involved in inflammation are known as pro-inflammatory cytokines and are produced by activated macrophages.

1. IL-1β: It produces hyperalgesia followed by any painful stimuli[13,14] and also increases the production of substance P and PGE_2 in a number of neuronal and glial cells.[15,16]
2. IL-6: It helps in the neuronal reaction to nerve injury and also induces the neuropathic pain followed by any peripheral nerve injury.[10,11]
3. TNF-α: It acts on different signaling pathways through two cell surface receptors, TNFR1 and TNFR2 to regulate apoptosis. It also contributes in inflammation and neuropathic hyperalgesia.[11]
4. Chemokines: Certain chemokines like MIP 1α, MCP-1 and GRO/KC are upregulated in various forms in CNS trauma[13] and in injured peripheral nerve.[17,18]
5. Lymphotoxins: These are the mediator of acute inflammatory responses.

Endogenous cytokines in health and disease

The cytokines are often involved in the developmental process during embryogenesis.[19,20] These help in immune response and they can be pathological in trauma, inflammation and sepsis [21]. There are certain adverse effects of cytokines like schizophrenia, major depression,[22] Alzheimer's disease,[23] cancer[24] etc.

Current status and futuristic scope of cytokines

Although cytokines have a wide range of medicinal applications but they are not in much use currently. They are used in the recombinant DNA technology[3] like the Bone Morphogenic Protein (BMP) is used to treat bone related conditions, Erythropoietin (EPO) is used to treat anaemia, G-CSF is used to treat neutropenia and fungal infections in cancer patients. IL-α is used to treat Hepatitis C and multiple sclerosis, IL-2 to treat cancer, IL-11 in thrombocytopenia in cancer patients, IL-ϒ to treat granulomatous disease and osteoporosis.[20] The cytokines are also useful in the diagnostic field. Their rise in the plasma levels indicate the presence of inflammatory process involved in the autoimmune diseases such as Rheumatoid Arthritis.[25] In the similar way, rise in the levels of IL-7 indicates homeostasis in HIV-infected patients.[26] Thus, cytokines play a vast useful but unrecognizable role in various fields of medical sciences. Therefore it's a high time to give them a recognizable hand. Thus, it is necessary to make them accessible at the doorstep of every needy person and quite affordable so that every needy person can easily avail them. There is a high need of them in the near future; therefore researches should be done in this field to explore more about them and their versatile uses.

Conclusion

Encompassing a broad range of molecules, the cytokines are essentially important for molecular cross talks among various immune and non-immune cells. There huge number of cytokines are presently known, and it is likely that in near future more and more of these molecule types will be searched. In present scenario, considerable research has been done in the direction to define in vivo characteristics and functions of these peptide molecules. These studies have cleared our vision about a number of diseases contributed by dysregulation of cytokines or their signalling pathway. Even few cytokines are in successful therapeutic use. Still a long way to go to have many cytokine and anti-cytokine therapies be available reasonably in the service of mankind.

Conflict of Interest: None

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