Let's study Interleukins and Interferon

Interleukin and Interferon are types of Cytokines.

let's see what are Cytokines.

The term "cytokine" encompasses a wide range of low-weight molecular proteins that play different roles in regulating various aspects of the immune response such as its duration and intensity. Cytokines regulate the intensity and duration of the immune response by stimulating or inhibiting the activation, proliferation, and/or differentiation of various cells and by regulating their secretion of Abs or other cytokines.

Function of Cytokines

Cytokines generally function as intercellular messenger molecules that evoke particular biological activities after binding to a receptor on a responsive target cell. Although a variety of cells can secrete cytokines, the two principal producers are the Th cell and the macrophage.

The main biological activities of a number of cytokines include

- both cellular and humoral immune responses,
- induction of inflammatory responses,
- regulation of hematopoiesis,
- control of cellular proliferation and differentiation,
- and induction of wound healing.

Cytokine receptors

Cytokines exert their biological effects through specific receptors expressed on the membrane of responsive target cells. These receptors are expressed by many cell types as cytokines can affect a diverse array of cells.

There are 5 families of receptor proteins:

1) **Ig superfamily receptors** (IL1, M-CSF)
2) **hematopoietin receptor family** (class I cytokine receptor family) * most belong to this group (IL2,3,4,5,6,7,9,11,12,13,15, GM-CSF, G-CSF)
3) **interferon receptor family** (class II cytokine receptor family) (IFNα,β,γ)
4) **TNF receptor family** (TNFα,β Fas)
5) **chemokine receptor family** (IL8,rantes, MIP-1)

Cytokine antagonists

A number of proteins that inhibit the biological activity of cytokines have been identified. These proteins can act in either of two ways:

1) They bind directly to a cytokine receptor but fail to activate the cell or

2) They bind directly to the cytokine inhibiting its activity.

The best characterized inhibitor is the IL1 R antagonist IL1Ra which binds to the IL1 receptor but has no activity but blocks binding of IL1. Production of IL1Ra appears to play a role in regulating the intensity of the inflammatory response.

A second group of cytokine inhibitors are soluble cytokine receptors that are able to bind to the cytokine and neutralize its activity. Enzymatic cleavage of the extracellular domain of the receptor releases a fragment that retains its cytokine binding capabilities.

Why? Don't know but the presence of sIL2R (which is released following chronic T cell activation) has been used as a clinical marker of chronic T cell activation (autoimmunity, transplant rejection, AIDS).

Viruses have also been shown to produce cytokine binding proteins. These proteins bind cytokines (ie poxviruses have soluble TNF and IL1 binding proteins) and thus may prohibit or diminish the inflammatory effects of the cytokine thereby conferring upon the virus a selective advantage.

Important Points on Interleukin:

- IL-1
  - is produced by many different cell types, with relatively high concentrations being produced by macrophages, monocytes, Langerhans' cells of the skin, and other dendritic cells.
  - was formerly known as lymphocyte-activating factor (LAF).
  - augments the activity of many cell types, especially T cells.
  - is an endogenous pyrogen (EP).
  - induces an increase in acute phase reactants.
  - is a heat-stable and pH-stable peptide with a molecular weight of 17.5 kd.
  - occurs in two forms: IL-1ALPHA and IL-1BETA.

- IL-2
  - is produced by T cells and large granular lymphocytes (LGLs).
  - was formerly known as T-cell growth factor (TCGF).
  - augments proliferation of T and B cells.
  - enhances activity of T cells and natural killer (NK) cells.
  - is a heat-labile glycoprotein with a molecular weight of 15.5 kd.

- IFN-gamma
  - is produced by activated T cells and LGLs.
  - increases the expression of class II HLAs on B cells, macrophages, and other APCs.
  - has antiviral properties.
  - provides regulatory control in the immune response.
  - has a heat-labile glycoprotein with a molecular weight of 17 kd.

- IL-3
  - is produced by T cells.
  - enhances hematopoiesis.

- IL-4
  - is produced by T cells.
  - is mitogenic for B cells.
  - promotes a switch to IgE production.
  - stimulates mast cells.

- IL-5
  - is produced by T cells.
  - stimulates B-cell differentiation and maturation.
  - enhances IL-2 receptor expression.
  - enhances IgA synthesis.

- IL-6
  - is produced by B cells, T cells, monocytes, and fibroblasts.
  - induces acute phase reactants.
  - induces B-cell differentiation.

Table 7-1. Cytokines and Their Actions

Cytokine	Major Cell Source	Major Immunologic Action
IL-1	Macrophages Endothelial cells Dendritic cells Langerhans' cells	Stimulates IL-2 receptor emergence in T cells Enhances B-cell activation **Induces fever**, acute phase reactants, and IL-6 Increases nonspecific resistance Inhibited by an endogenous IL-1 receptor antagonist
IL-2	T_H1 cells	T-cell growth factor Activates NK and B cells
IL-3	T cells	**Stimulates hematopoiesis**
IL-4	T cells	Stimulates B-cell synthesis of IgE Down-regulation of IFN-gamma
IL-5	T cells	Stimulates growth and differentiation of eosinophils B-cell growth factor Enhances IgA synthesis
IL-6	Monocytes T cells Endothelial cells	Induces acute phase reactants, fever, and late B-cell differentiation
IL-7	Bone marrow	Stimulates pre-B and pre-T cells
IL-8	Monocytes Endothelial cells Lymphocytes Fibroblasts	**Chemotactic** factor for neutrophils and T cells
IL-9	T_H cells	T-cell mitogen
IL-10	T_H2 cells	Inhibits IFN-gamma synthesis by T_H1 cells Suppresses other cytokine synthesis
IL-11	Bone marrow	**Stimulates hematopoiesis** Enhances acute phase protein synthesis
IL-12	Macrophages B cells	Promotes T_H1 differentiation and IFN-GAMMA synthesis Stimulates NK cells and $CD8^+$ T cells to cytolysis Acts synergistically with IL-2
IL-13	T_H2 cells	Inhibits inflammatory cytokines (IL-1, IL-6, IL-8, IL-10, MCP)
IL-15	T cells	T-cell mitogen Enhances growth of intestinal epithelium
IL-16	$CD8^+$ T cells Eosinophils	Increases class II MHC, chemotaxis, and $CD4^+$ T-cell cytokines Decreases antigen-induced proliferation
IL-17	T cells	Increases the inflammatory response

IL-18	Activated macrophages	Increases IFN-GAMMA production and NK cell action
TNF-ALPHA	Macrophages T cells B cells Large granular lymphocytes	Cytotoxic for tumors Causes cachexia Mediates bacterial shock
TNF-BETA	T cells	Cytotoxic for tumors
Transforming growth factor BETA	Almost all normal cell types	Inhibits proliferation of both T and B cells Reduces cytokine receptors Potent chemotactic agent for leukocytes Mediates inflammation and tissue repair
IFN = interferon; Ig = immunoglobulin; IL = interleukin; MCP = macrophage chemotactic protein; MHC = major histocompatibility complex; NK = natural killer; TNF = tumor necrosis factor.		

Table - Interferons

Type	Characteristic
Alpha	At least 17 different subtypes Produced in B and null lymphocytes, macrophages, and epithelial cells Induced by viruses, bacteria, and tumor and foreign cells Inhibits viral replication
Beta	Only a single entity Produced in fibroblasts, macrophages, and epithelial cells Induced by viruses and bacterial products Inhibits viral replication
Gamma	Only a single entity Produced by T_H1 and NK cells Potent activator of macrophages Strong immunomodulating agent Inhibits IL-4 activation of mast cells and IgE synthesis

Ig = immunoglobulin; IL = interleukin; NK = natural killer; T_H = helper T cells.

MCQs

Q 1 -Which of the following substances enhances the switch from immunoglobulin G (IgG) to immunoglobulin E (IgE) production?

(A) Interleukin (IL)-1

(B) IL-2

(C) IL-3

(D) IL-4

ANS - D. Interleukin-4 (IL-4) is the major interleukin involved in the shift to immunoglobulin E (IgE) production and concomitant stimulation of mast cells. IL-4 is therefore important in the inception and maintenance of type I hypersensitivity reactions.

Q 2 - Which of the following substances is produced by macrophages and macrophage-like cells?

(A) Interleukin (IL)-1

(B) IL-2

(C) IL-3

(D) IL-4

ANS - A. Macrophage and macrophage-like cells produce interleukin (IL)-1. (All the other interleukins listed are T-cell products.) Macrophages are also known to produce tumor necrosis factor (TNF)-Î² and several other monokines. Some researchers believe that IL-6 and IL-8 are produced by both T cells and macrophages.

Q 3 - Which of the following substances is a potent stimulator of hematopoiesis?

(A) Interleukin (IL)-1

(B) IL-2

(C) IL-3

(D) IL-4

ANS - C. Interleukin-3 (IL-3) is the major hematopoiesis stimulator of the interleukins listed.

Q 4 - Which of the following substances is an endogenous pyrogen?

(A) Interleukin (IL)-1

(B) IL-2

(C) IL-3

(D) IL-4

ANS - A. Interleukin-1 (IL-1), or endogenous pyrogen, is a cytokine released from antigen-presenting cells and enhances T-cell responses.

Q 5 - A 26-year-old woman presents with nonspecific symptoms including fever, malaise, and increasing respiratory problems. A chest x-ray reveals enlarged hilar lymph nodes, while laboratory tests find her serum calcium level to be elevated. A transbronchial biopsy reveals scattered chronic inflammatory cells, reactive epithelial changes, and several non-caseating granulomas. The pathomechanism involved in the formation of these non-caseating granulomas involves the activation of macrophages to form epithelial cells by the action of which substance?

a. Gamma-interferon

b. Leukotriene C4

c. Interleukin-2

d. Interleukin-5

The answer is a. (Kumar, pp 215–218.)

Type IV hypersensitivity reactions do not involve antibody formation, but instead are mediated by T cells (cell-mediated hypersensitivity). There are two subtypes of type IV hypersensitivity reactions -

One involves CD4 cells also called delayed-type hypersensitivity (DTH). Examples tuberculin skin test (Mantoux reaction), granulomatous inflammation, poison ivy reactions and contact dermatitis (often the result of sensitivity to nickel)

The other of which involves CD8 cells called cell-mediated cytotoxicity.

The formation of granulomas (with epithelioid cells) is another example of a type IV hypersensitivity reaction. The pathomechanisms involved in the formation of granulomas is as follows. Upon first exposure to the antigen in

DTH reactions, macrophages ingest the antigen and process it in association with class II antigens (HLA-D) to helper T cells (CD4), which differentiate into CD4 TH1 cells based on the actions of interleukin-12 secreted by macrophages and

dendritic cells. Upon reexposure to the antigen, these CD4 TH1 cells are activated and secrete biologically active factors (the lymphokines). Specifically, TH1 cells secrete gamma-interferon, interleukin 2, and TNF-alpha.

Gamma-interferon is the main cytokine that is responsible for DTH reactions. It activates macrophages (epithelioid cells) and forms granulomas (caseating or noncaseating). Interleukin 2 activates other CD4 cells, while TNF-alpha causes endothelial cells to increase production of prostacyclin and ELAM-1. Note that type I hypersensitivity reactions involve IgE antibodies, secreted from plasma cells, that attach to the surface of mast cells and basophils. Initially an allergen binds to antigen-presenting cells, which then stimulate TH2 cells to secrete IL-4, IL-5, and IL-6. IL-5 stimulates the production of eosinophils, while IL-4 stimulates B cells to transform into plasma cells and produce IgE. The activation of mast cells and basophils causes them to secrete many substances, such as histamine. Finally, leukotrienes C4, D4, and E4 increase vascular permeability and cause vasoconstriction and bronchospasm.