Cytokines

Cytokines are low-molecular weight regulatory proteins or glycoproteins secreted by white blood cells and various other cells in the body in response to a number of stimuli. These proteins assist in regulating the development of immune effector cells, and some cytokines possess direct effector functions of their own**.**

Properties of Cytokines

Cytokines bind to specific receptors on the membrane of target cells, triggering signal-transduction pathways that ultimately alter gene expression in the target cells (Figure 1). The susceptibility of the target cell to a particular cytokine is determined by the presence of specific membrane receptors. In general, the cytokines and their receptors exhibit very high affinity for each other, with dissociation constants ranging from 10^{-10} to 10^{-12} M. Because their affinities are so high, cytokines can mediate biological effects at picomolar concentrations**.**

A particular cytokine may bind to receptors on the membrane of the same cell that secreted it, exerting **autocrine** action; it may bind to receptors on a target cell in close proximity to the producer cell, exerting **paracrine** action; in a few cases, it may bind to target cells in distant parts of the body, exerting **endocrine** action (Figure 2). 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 the secretion of antibodies or other cytokines. Binding of a given cytokine to responsive target cells generally stimulates increased expression of cytokine receptors and secretion of other cytokines, which affect other target cells in turn**.**

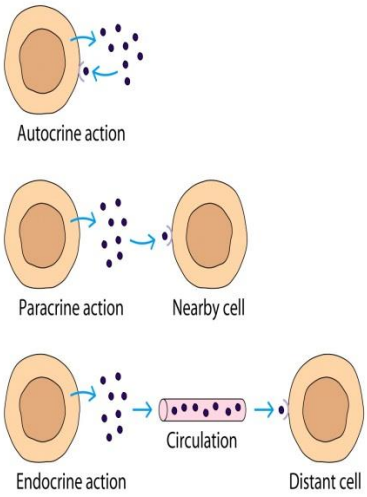

Figure 2

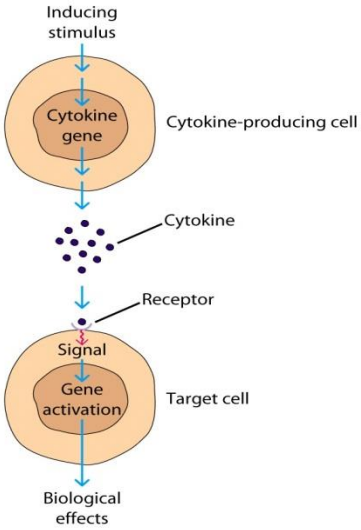

figure 1

Cytokines activity:

1- **Pleiotropy:** this occur when a given cytokine that has different biological effects on different target cells
2- **Redundancy:** Two or more cytokines that mediate similar functions are said to be redundant; redundancy makes it difficult to ascribe a particular activity to a single cytokine
3- **Synergy:** Cytokine synergism occurs when the combined effect of two cytokines on cellular activity is greater than the additive effects of the individual cytokines.

4- **Antagonism**: In some cases, cytokines exhibit antagonism; that is, the effects of one cytokine inhibit or offset the effects of another cytokine**.**
5- **cascade induction**: Cascade induction occurs when the action of one cytokine on a target cell induces that cell to produce one or more other cytokines, which in turn may induce other target cells to produce other cytokines.

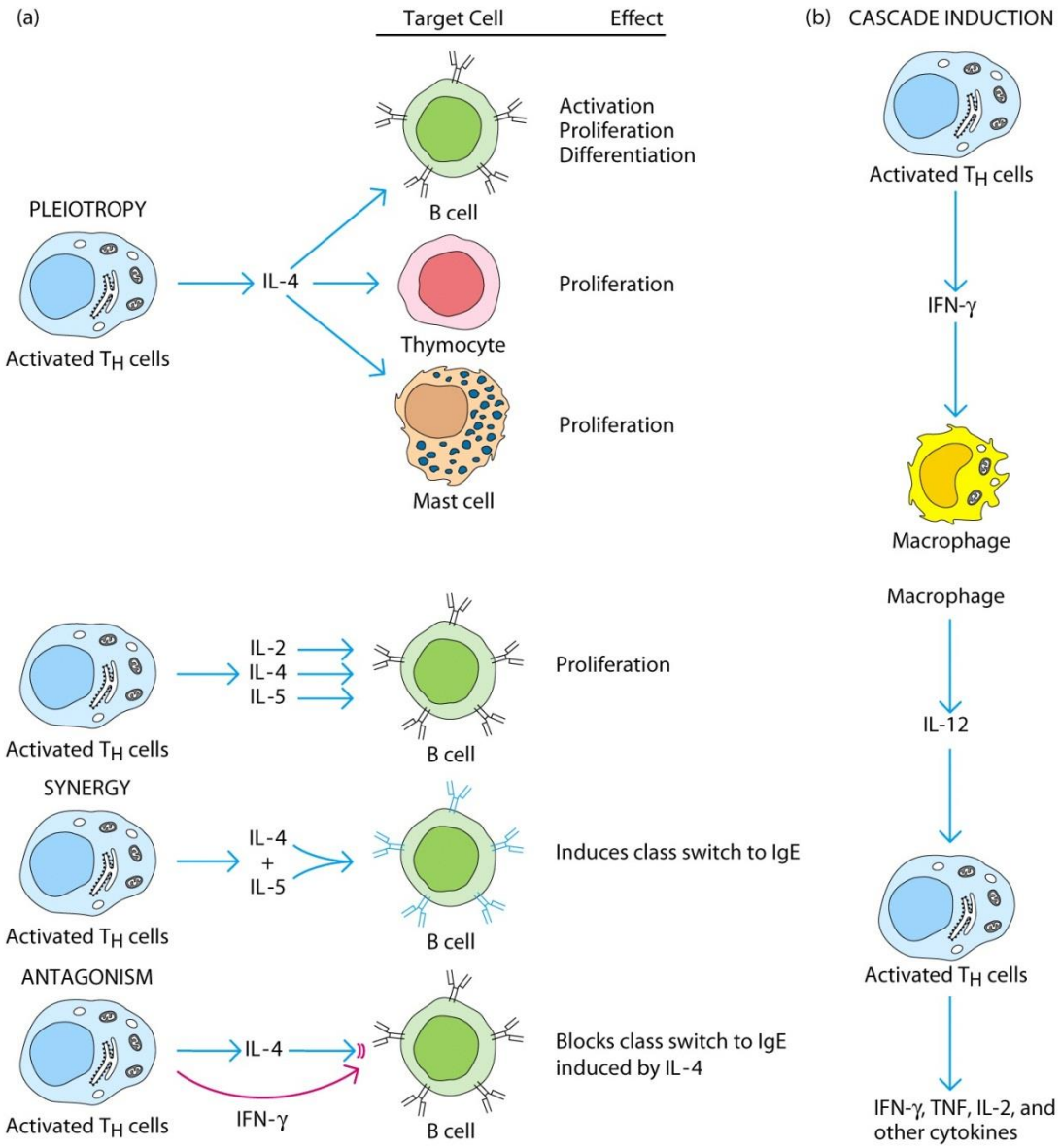

Figure 3: show the activity of different cytokines

Other names of cytokines:

1- lymphokines :The term cytokine encompasses those cytokines secreted by lymphocytes.

2- monokines : the cytokines that secreted by monocytes and macrophages. Although these other two terms continue to be used, they are misleading because secretion of many lymphokines and monokines is not limited to lymphocytes and monocytes as these terms imply, but extends to a broad

spectrum of cells and types. For this reason, the more inclusive term cytokine is preferred.

3- interleukins, a name indicating that they are secreted by some leukocytes and act upon other leukocytes**.**

4- chemokines, a group of low-molecular weight cytokines that affect chemotaxis and other aspects of leukocyte behavior. These molecules play an important role in the inflammatory response**.**

Biological Functions of cytokines:

Although a variety of cells can secrete cytokines, the two principal producers are the **Th** cell and the **macrophage**. Cytokines released from these two cell types activate an entire network of interacting cells**.**

Among the numerous physiologic responses that require cytokine involvement are:

1- development of cellular and humoral immune responses.
2- induction of the inflammatory response.
3- regulation of hematopoiesis.
4- control of cellular proliferation and differentiation, and the healing of wounds.
5- they affect whatever cells they encounter that bear appropriate receptors and are in a physiological state that allows them to respond.

Cytokines are involved in a broad array of biological activities including

innate immunity, adaptive immunity, inflammation, and hematopoiesis**.**

Cytokine Receptors :

As noted already, to exert their biological effects, cytokines must first bind to specific receptors expressed on the membrane of responsive target cells. Because these receptors are expressed by many types of cells, the cytokines can affect a diverse array of cells. Biochemical characterization of cytokine receptors initially progressed at a very slow pace because their levels on the membrane of responsive cells is quite low. As with the cytokines themselves, cloning of the genes encoding cytokine receptors has led to rapid advances in the identification and characterization of these receptors.

Cytokine Receptors Fall Within Five Families Receptors for the various cytokines are quite diverse structurally, but almost all belong to one of five families of receptor proteins (Figure 4):

- a- Immunoglobulin superfamily receptors .
- b- Class I cytokine receptor family (also known as the hematopoietin receptor family).
- c- Class II cytokine receptor family (also known as the interferon receptor family).
- d- TNF receptor family
- Chemokine receptor family.

Many of the cytokine-binding receptors that function in the immune and hematopoietic systems belong to the class I cytokine receptor family**.**

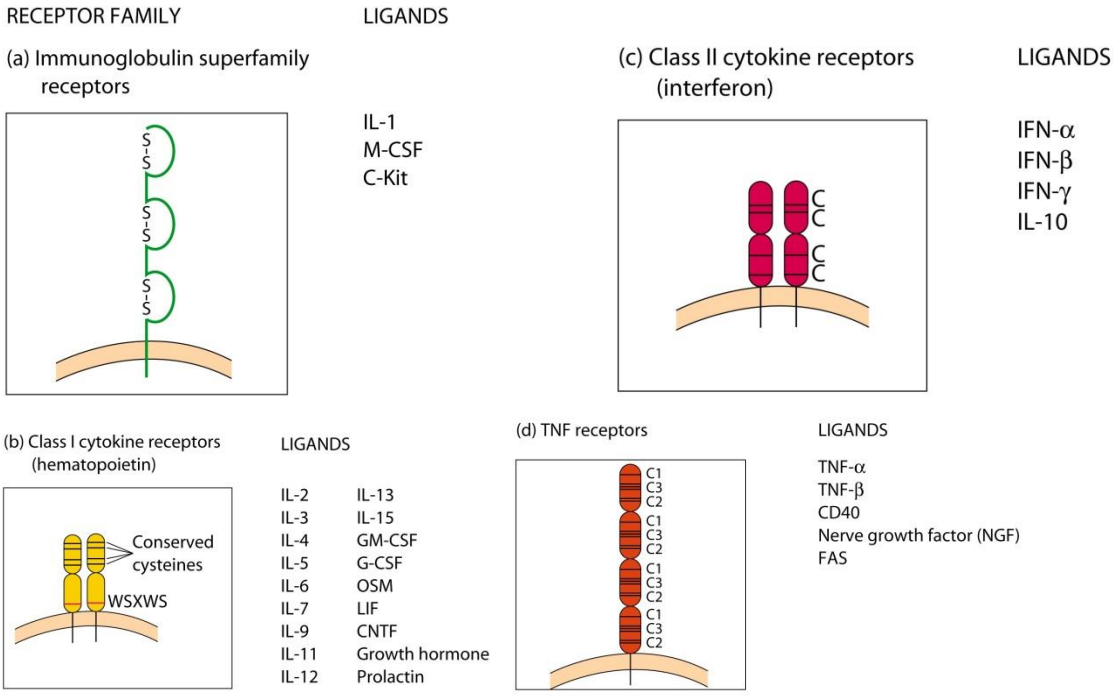

Figure 4. show the types of cytokines receptors

Cytokine Antagonists:

A number of proteins that inhibit the biological activity of cytokines have been reported. These proteins act in one of two ways: either they bind directly to a cytokine receptor but fail to activate the cell, or they bind directly to a cytokine, inhibiting its activity. The best-characterized inhibitor is the IL-1 receptor antagonist (IL-1Ra), which binds to the IL-1 receptor but has no activity. Binding of IL-1Ra to the IL-1 receptor blocks binding of both IL-1 and IL-1, thus accounting for its antagonistic

properties. Production of IL-1Ra has been thought by some to play a role in regulating the intensity of the inflammatory response. It has been cloned and is currently being investigated as a potential treatment for chronic inflammatory diseases. Cytokine inhibitors are found in the bloodstream and extracellular fluid.

Some viruses also produce cytokine-binding proteins or cytokine mimics.

The evolution of such anti-cytokine strategies by microbial pathogens is good biological evidence of the importance of cytokines in organizing and promoting effective anti-microbial immune responses. The poxviruses, for example, have been shown to encode a soluble TNF-binding protein and a soluble IL-1–binding protein**.**

The Development of TH1 and TH2 Subsets Is Determined by the Cytokine Environment :

The cytokine environment in which antigen-primed TH cells differentiate determines the subset that develops. In particular, IL-4 is essential for the development of a Th2 response, and IFN-γ, IL-12, and IL-18 all are important in the physiology of the development of Th1 cells.

Cytokine-Related Diseases:

Defects in the complex regulatory networks governing the expression of cytokines and cytokine receptors have been implicated in a number of diseases.

Bacterial Septic Shock Is Common and Potentially Lethal. The role of cytokine overproduction in pathogenesis can be illustrated by bacterial septic shock. This condition may develop a few hours after infection by certain gram-negative bacteria, including E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter aerogenes, and Neisseria meningitidis. The symptoms of bacterial septic shock, which is often fatal, include a drop in blood pressure, fever, diarrhea, and widespread blood clotting in various organs.

Bacterial septic shock apparently develops because bacterial cell-wall endotoxins stimulate macrophages to overproduce IL-1 and TNF- to levels that cause septic shock. A variety of microorganisms produce toxins that act as superantigens. the superantigens bind simultaneously to a class II MHC molecule and to the V domain of the T-cell receptor, activating all T cells bearing a particular V domain. Because of their unique binding ability, superantigens can activate large numbers of T cells irrespective of their antigenic specificity. these elevated concentrations of cytokines can induce systemic reactions that include fever, widespread blood clotting, and shock

Therapeutic Uses of Cytokines and Their Receptors:

The availability of purified cloned cytokines and soluble cytokine receptors offers the prospect of specific clinical therapies to modulate the immune response. A few cytokines—notably, interferons and colony stimulating factors, such as GM-CSF, have proven to be therapeutically useful.

Cytokines in Hematopoiesis:

As in figure 3, Many cytokines have been shown to play essential roles in hematopoiesis. During hematopoiesis, cytokines act as developmental signals that direct commitment of progenitor cells into and through particular lineages.suitable concentrations of a group of cytokines including IL-3, GM-CSF, IL-1, and IL-6 will cause it to enter differentiation pathways that lead to the generation of monocytes, neutrophils, and other leukocytes of the myeloid group. The participation of leukocytes in immune responses often results in their death and removal

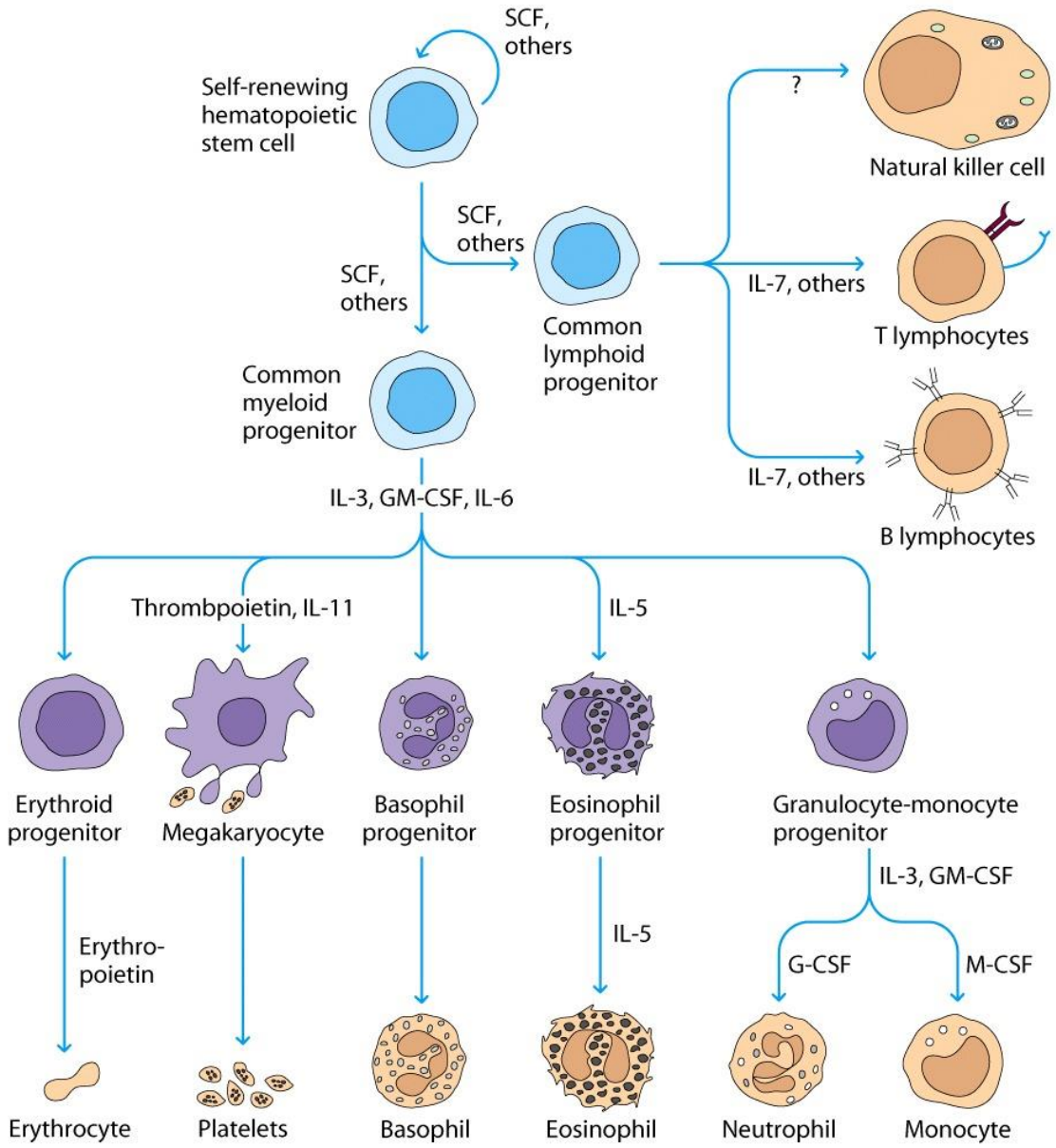

Figure 5. show the role of cytokines in hematopoiesis