Cytokines

- ✓ Intercellular communication in the immune system is accomplished in many cases through a heterogeneous family of soluble effector proteins known as **cytokines** that are produced by leukocytes and other cells.
- ✓ Cytokines regulate cellular functions in immune cells and activate various cell types.
- ✓ Cytokines are a diverse group of **non-antibody proteins** released by cells that act as intercellular mediators, especially in immune processes.
- ✓ **Low molecular weight** regulatory **soluble proteins or glycoproteins** secreted at nano- to- picomolar concentrations by white blood cells and various other cells in the body in response to a number of stimuli.
- ✓ They play major roles in the induction and regulation of the cellular interactions involving cells of the immune, inflammatory and hematopoietic systems.
- ✓ They are regulators of host responses to infection, immune responses, inflammation, and trauma. Some of them are proinflammatory, these are necessary to initiate an inflammatory response necessary to recruit granulocytes, and later on, lymphocytes, to fight disease. Other cytokines are

anti-inflammatory and serve to reduce inflammation and promote healing once the injury/infection/foreign body has been destroyed.

- ✓ They act via cell surface receptors to mediate and regulate the amplitude and duration of the immune-inflammatory responses, through activation of macrophages, controlling growth and differentiation of T and B cells.

❖ Naming of Cytokines

1. **Monokines** - produced by mononuclear phagocytes (monocytes).

2. **Lymphokines** - produced by activated T cells, primarily helper T cells . There are three main sub classes of T cells Th1 ,Th2 and T regulatory cells . Each has a specific function and produces a different set of cytokines.

3. **Interleukins** -cytokines made by one leukocyte and acting on other leukocytes.

4.**Chemokines**-cytokines with chemotactic activities.

❖ Cytokine Properties

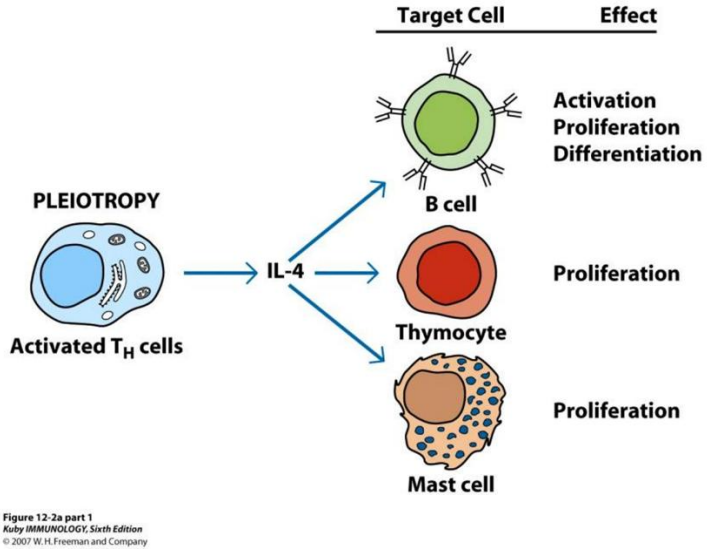
They permit them to regulate cellular activity in a coordinated, interactive way:

1. Produced by cells involved in both natural and specific immunity.

2. Mediate and regulate immune and inflammatory responses.

3. Secretion is brief and limited, not stored as pre-formed molecules.

4. Pleiotropic -different cell types to secrete the same cytokine or for a single cytokine to act on several different cell types.



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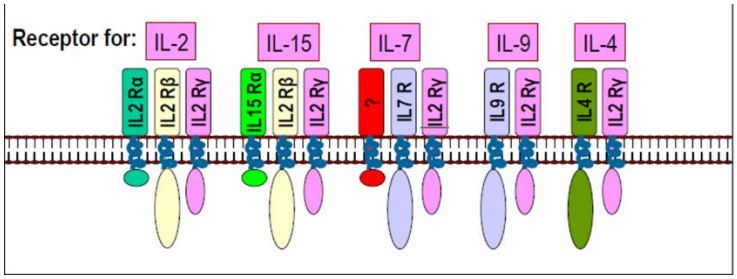
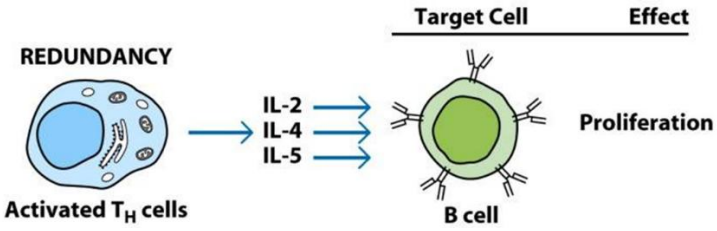
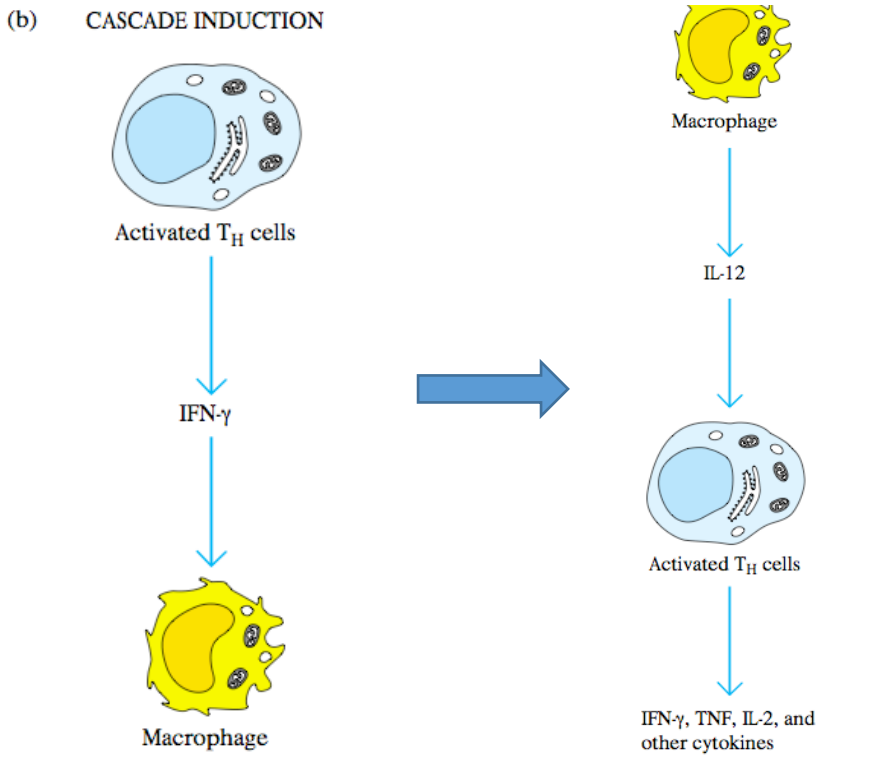
5. Redundancy -similar functions can be stimulated by different cytokines. Redundancy makes it difficult to ascribe a particular activity to a single cytokine. Receptors for cytokines are heterodimers (sometimes heterotrimers) that can be grouped into families in which one subunit is common to all members of a given family.





6. Often influence the synthesis of other cytokines :They can **produce cascades**, or enhance or suppress production of other cytokines .They exert positive or negative regulatory mechanisms for immune inflammatory responses.

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**.



7. Often influence the action of other cytokines:

- Antagonistic - effects of one cytokine inhibit or offset the effects of another cytokine.

-Synergistic -two or more cytokines acting together (greater than additive). This occurs when the combined effect of two cytokines on cellular activity is greater than the additive effects of the individual cytokines.

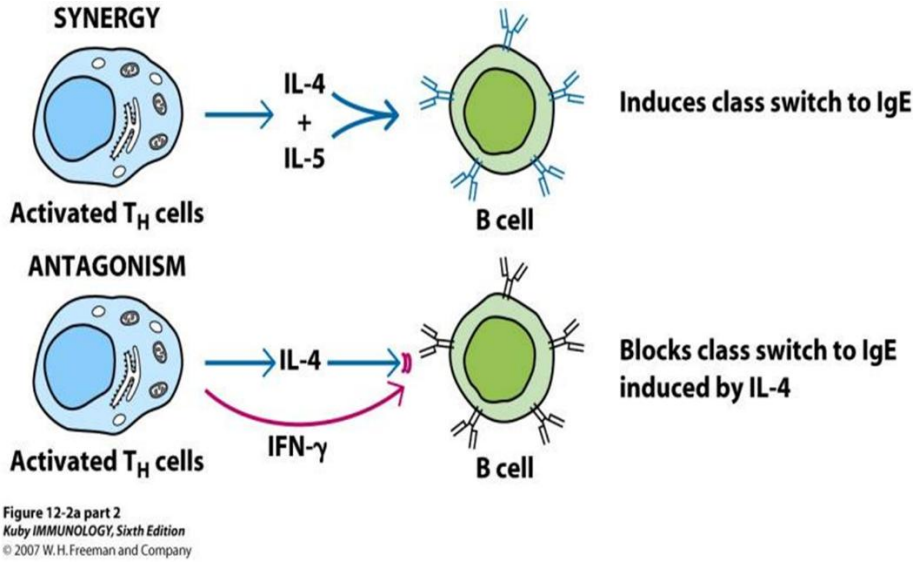


Figure 12-2a part 2
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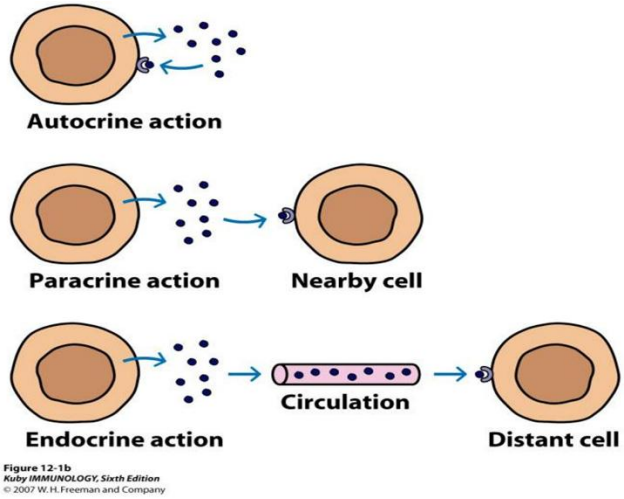
8. Bind to specific receptors on target cells with high affinity.

9. Cellular responses to cytokines are generally slow (hours), require new mRNA and protein synthesis.

❖ **<u>Cytokine action can be</u>**

- **AUTOCRINE ACTION**: cytokine may bind to receptors on the membrane of the same cell that secreted it.
- **PARACRINE ACTION**: cytokine may bind to receptors on a target cell in close proximity to the producer cell.
- **ENDOCRINE ACTION**: cytokine may bind to target cells in distant parts of the body.



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❖ Functional Categories of Cytokines

Cytokines classified according to their biologic actions into three groups:

1**) Mediators and regulators of innate immunity**

- Produced by activated microphages and NK cells in response to microbial infection.

- They act mainly on endothelial cells and leukocytes to stimulate the early inflammatory response to microbes.

2**) Mediators and regulators of acquired immunity**

- Produced mainly by T lymphocytes in response to specific recognition of foreign antigens.

- They include IL-2, IL-4, IL-5, IL-13, IFN, Transforming growth factor-β (TGF-β) and lymphotoxin (TNF- β).

3**) Stimulators of hematopoiesis**

- Produced by bon marrow, stormal cells, leukocytes

- Stimulate growth and differentiation of leukocytes

- Stem cell factor, IL-3, IL-7, GM-CSF[Granulocyte-macrophage colony-stimulating factor].

Some Kinds of Cytokine and their effects :

Cytokine	Cell Source	Cell Target	Primary Effects
IL-1	Monocytes Macrophages Fibroblasts Epithelial cells Endothelial cells Astrocytes	T cells; B cells Endothelial cells Hypothalamus Liver	Costimulatory molecule Activation (inflammation) Fever Acute phase reactants
IL-2	T cells; NK cells	T cells B cells Monocytes	Growth Growth Activation
IL-3	T cells	Bone marrow progenitors	Growth and differentiation
IL-4	T cells	Naive T cells T cells B cells	Differentiation into a Th 2 cell Growth Activation and growth; Isotype switching to IgE

IL-5	T cells	B cells Eosinophils	Growth and activation
IL-6	T cells; Macrophages; Fibroblasts	T cells; B cells Mature B cells Liver	Costimulatory molecule Growth (in humans) Acute phase reactants
IL-8 family	Macrophages; Epithelial cells; Platelets	Neutrophils	Activation and chemotaxis
IL-10	T cells (Th2)	Macrophages T cells	Inhibits APC activity Inhibits cytokine production
IL-12	Macrophages; NK cells	Naive T cells	Differentiation into a Th 1 cell

IFN-gamma	T cells; NK cells	Monocytes Endothelial cells Many tissue cells; especially macrophages	Activation Activation Increased class I and II MHC
TGF-beta	T cells; Macrophages	T cells Macrophages	Inhibits activation and growth Inhibits activation
GM-CSF	T cells; Macrophages; Endothelial cells, Fibroblasts	Bone marrow progenitors	Growth and differentiation
TNF-alpha	Macrophages; T cells	Similar to IL-1	Similar to IL-1

IL = interleukin GM-CSF = granulocyte-macrophage colony stimulating factor
IFN = interferon TNF = tumor necrosis factor
TGF = transforming growth factor

❖ Cytokine Receptors

Divided into several families based on their structure and activities

- **Hematopoietin family**

- receptors are dimers or trimmers
- conserved cysteines in their extracellular domains and a conserved Trp-Ser-X-Trp-Ser sequence.
- Examples are receptors for IL-2 through IL-7 and Granulocyte-macrophage colony-stimulating factor (GM-CSF).

- **Interferon family**

- receptors have the conserved cysteine residues but not the Trp-Ser-X-Trp-Ser sequence,
- e.g. the receptors for IFNα, IFNβ, and IFN ɣ.

- **Tumor Necrosis Factor family**

-receptors have four extracellular domains; they include receptors for soluble TNFαand TNFβ as well as membrane-bound CD40 (important for B cell and macrophage activation) 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.

- 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.
- A cytokine can only act on a cell that expresses a receptor for it.
- The activity of particular cytokines is directed to specific cells by regulation of the cell's profile of cytokine receptors.

❖ CYTOKINES VS HORMONES VS GROWTH FACTORS

SIMILARITY: All three are secreted soluble factors that elicit their biological effects at Picomolar concentrations by binding to receptors on target cells

• **DIFFERENCES 1**

• GROWTH FACTORS: produced constitutively

• CYTOKINES & HORMONES:

secreted in response to discrete stimuli, and secretion is short lived, generally ranging from a few hours to a few days

• **DIFFERENCE 2**

• HORMONES: generally act long range in an endocrine fashion; produced by specialized glands and tend to have a unique action on one or a few types of target cell

• CYTOKINES: act over a short distance in an autocrine or paracrine fashion; often produced by, and bind to, a variety of cells.

❖ **Therapeutic Uses of Cytokines**

1) Interferon in treatment of viral diseases, cancer.

2) Several cytokines are used to enhance T-cell activation in immune deficiency diseases, e.g. IL-2, IFN-ɣ,TNF-α.

3) IL-2 and lymphokine activating killer cells (LAK) in treatment of cancer.

4) GM-CSF induces increase in white cell count, it is used:

a- To restore leukocytic count after cytotoxic chemotherapy induced neutropenia

b- After bone marrow transplantation

C- To correct AIDS-associated leukopenia

5) Anti-cytokines antibodies in management of autoimmune diseases and transplant rejection:

- Anti-TNF in treatment rheumatoid arthritis
- Anti-IL2R to reduce graft rejection
- Anti-TNF antibodies in treating septic shock.
- Anti-IL-2R in treating adult T-cell leukemia.
- Anti-IL-4 is under trial for treatment of allergies.