

Immunology

Lecture 8 - Cytokines

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Cytokines (CKs)

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Quick Review

Functions of Cytokines:

1. Activation of B cells through T helper cells
2. Interleukin 2 plays a role in the proliferation of B cells
3. Chemotaxis
4. Class Switching – for example, Interleukin 4 stimulates class switching of the immunoglobulins on B cells to IgE and IgG₃.
5. Increase phagocytic activity
6. Stimulate differentiation of B and T cell
7. Aids in expression of certain receptors on cells
8. Participate in inflammation

Objectives

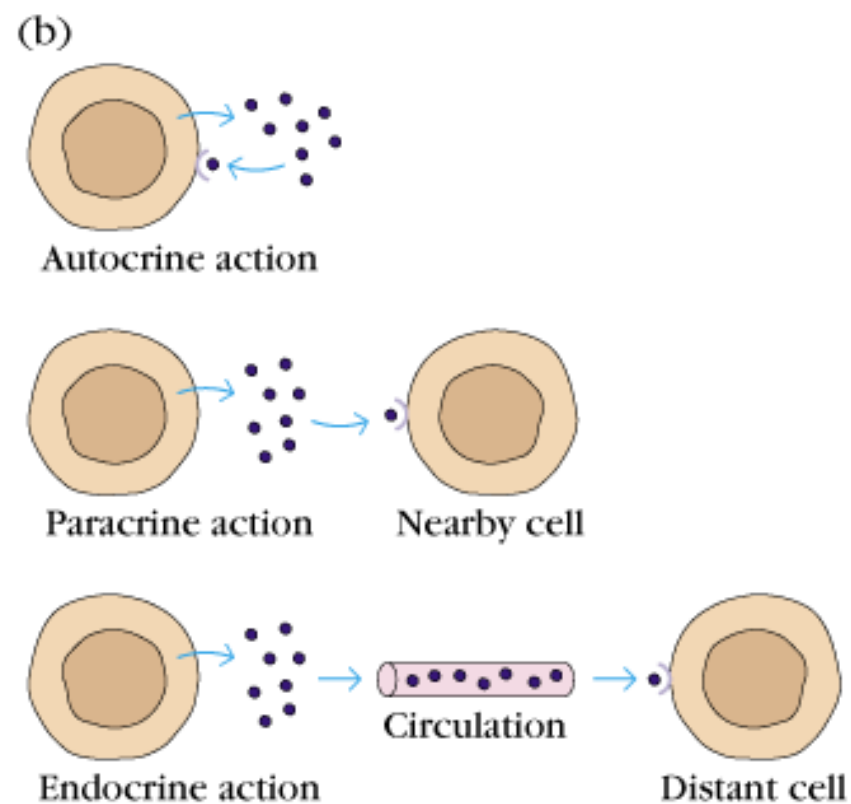
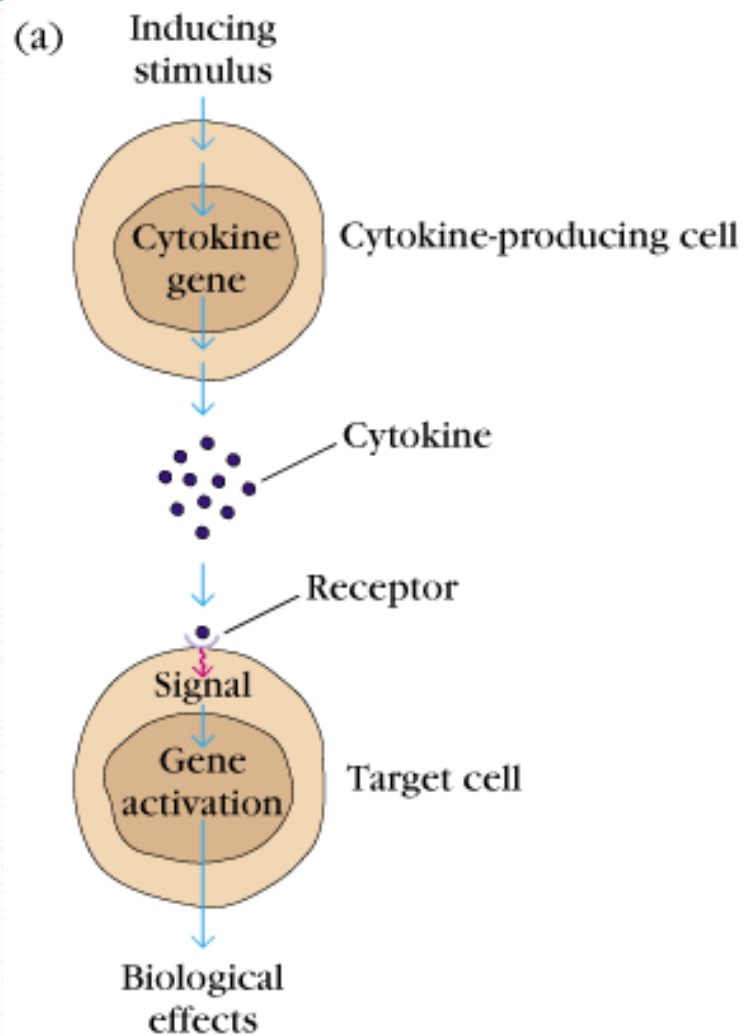
- ! Definition and general properties of cytokines
- ! Classification of cytokines
- ! Cytokine receptor
- ! Biological functions of cytokines
- ! Cytokine and disease

Definition

- ! A group of **low molecular weight** polypeptides or proteins which are secreted by activated immunocytes or some matrix cells and possess high activity and various functions.
- ! Cytokine or immunocytokine is a generic name used to describe a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to-picomolar concentrations
- ! Their major functions are to mediate and regulate immune response and inflammatory reactions.

General Properties

- ! Most cytokines are **low molecular weight** polypeptides or glycoprotein (8~80 KD), and most of them are **monomers**.
- ! Natural cytokines are secreted by activated cells such as activated immune cells, matrix cells and tumor cells
- ! One kind of cytokines can be produced by different cells. One kind of cells can secrete different cytokines
- ! Cytokines initiate their actions by binding to specific membrane receptors on target cells.
- ! Cytokines can act on the cells that produce them (autocrine), on other cells in the immediate vicinity (paracrine), or on cells at a distance (endocrine) after being carried in blood or tissue fluids.

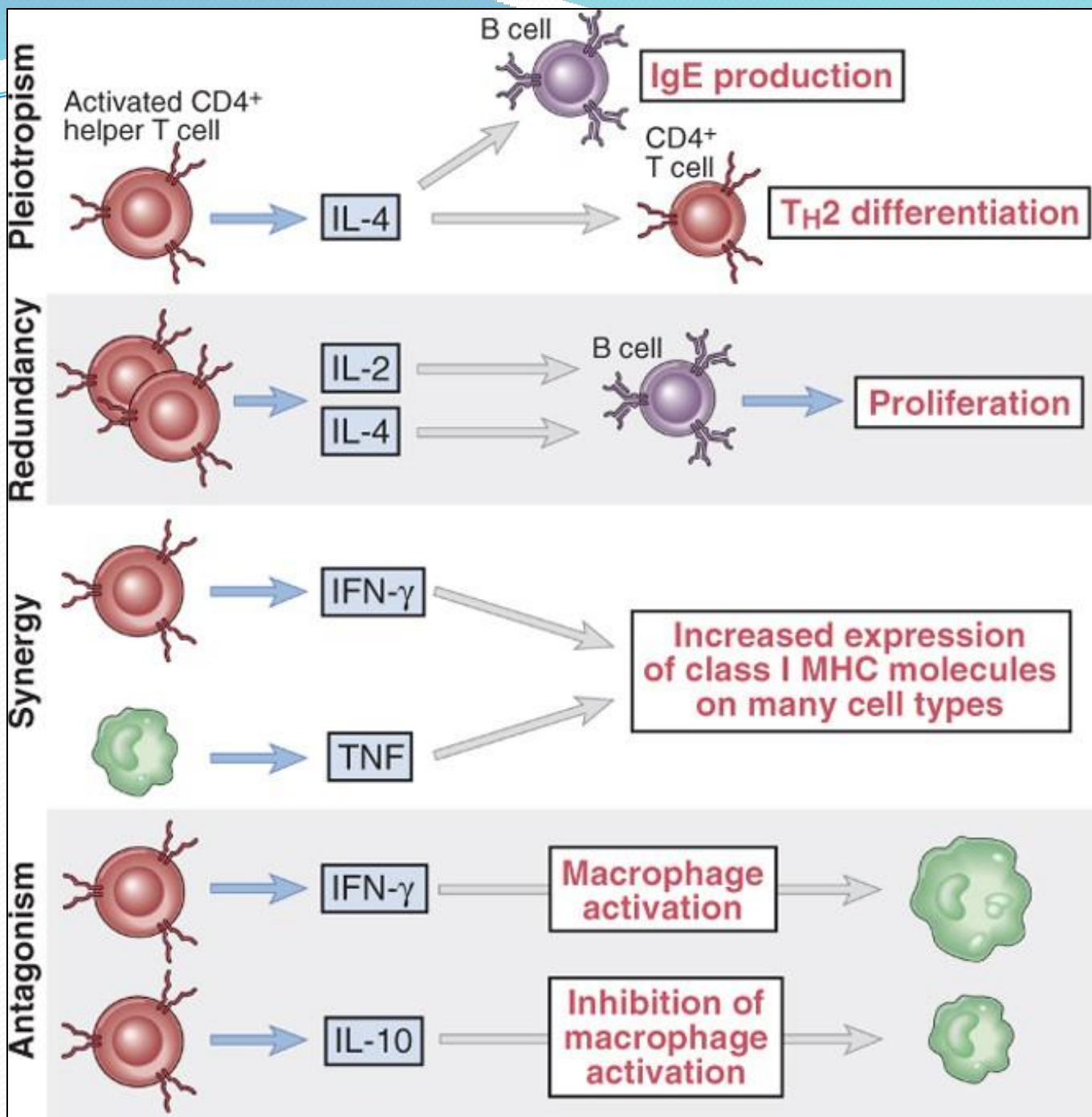


Cytokine Names

- ! Interleukins - produced exclusively by **leukocytes**
- ! Lymphokines - produced by **lymphocytes**
- ! Monokines - produced exclusively by **monocytes**
- ! Interferons - involved in **antiviral responses**
They are mostly produced by macrophages.
They are also produced by NK cells.
- ! Colony Stimulating Factors - **support the growth of cells in semisolid medias**
- ! Chemokines - promote **chemotaxis**

Effects of Cytokines

- ! **Pleiotropism** refers to the ability of one cytokine having multiple effects on diverse cell types.
- ! **Redundancy** refers to the property of multiple cytokines having the same or overlapping functional effects.
- ! **Synergy** refers to the property of two or more cytokines having greater than additive effects.
- ! **Antagonism** refers to the ability of one cytokine inhibiting the action of another. *Regulatory T cells produce many of these suppressor cytokines.*



Cytokine General Actions

- ! Development of cellular and humoral immune responses
- ! Induction of inflammation
- ! Regulation of hematopoiesis (*by colony stimulating factors*)
- ! Control of cellular proliferation and differentiation
- ! Induction of wound healing
- ! Chemotaxis

Classification of cytokines

- ! Interleukin, IL
- ! Interferon , IFN
- ! Tumor necrosis factor, TNF
- ! Colony stimulating factor, CSF
- ! Chemokine
- ! Transforming growth factor

1. Interleukin (IL)

- ! Cytokines **secreted by leukocytes** that have the ability to act as signal molecules between different population of leukocytes
- ! IL-1~IL-29
 - ! Th1: IL-2
 - ! Th2: IL-4, IL-5
 - ! Th3/Treg: IL-10 (*function: inhibition or suppression*)
 - ! Th17: IL-17

2. Interferon (IFN)

! A group of glycoproteins that produced by human or animal cells following the infection of virus and exposure to various inducing agents

	Types	Produced cells	Main functions
IFN- α	Type I	leukocyte	anti-virus , immune regulation
IFN- β	Type I	fibroblast	anti-tumor
IFN- γ	Type II	Th1, NK	weaker anti-virus effect, stronger immune regulation effect , anti-tumor

3. Tumor Necrosis Factor (TNF)

- ! TNFs were originally thought of as selective antitumour agents, but are now known to have a multiplicity of actions.

TNF- α is produced mainly by LPS (*found in gram negative bacteria*) activated monocytes and macrophages.

- ! TNF- β is produced mainly by activated Th0 and Th1.

4. Colony-Stimulating Factors (CSF)

- ! Cytokines that stimulate proliferation or differentiation of pluripotent hematopoietic stem cell and different progenitors.
 - ! Multi-CSF (IL-3)
 - ! Granulocyte macrophage-CSF (GM-CSF)
 - ! Monocyte-CSF (M-CSF)
 - ! Granulocyte-CSF (G-CSF)
 - ! Stem cell factor (SCF)
 - ! Erythropoietin (EPO)

5. Chemokine

! Chemokines are cytokines which recruits monocytes, granulocytes and lymphocytes in blood to the sites of inflammation.

- CXC chemokines (α subgroup)
- CC chemokines (β subgroup)
- C chemokines (γ subgroup)
- CX₃C chemokines (δ subgroup)

X = amino acid

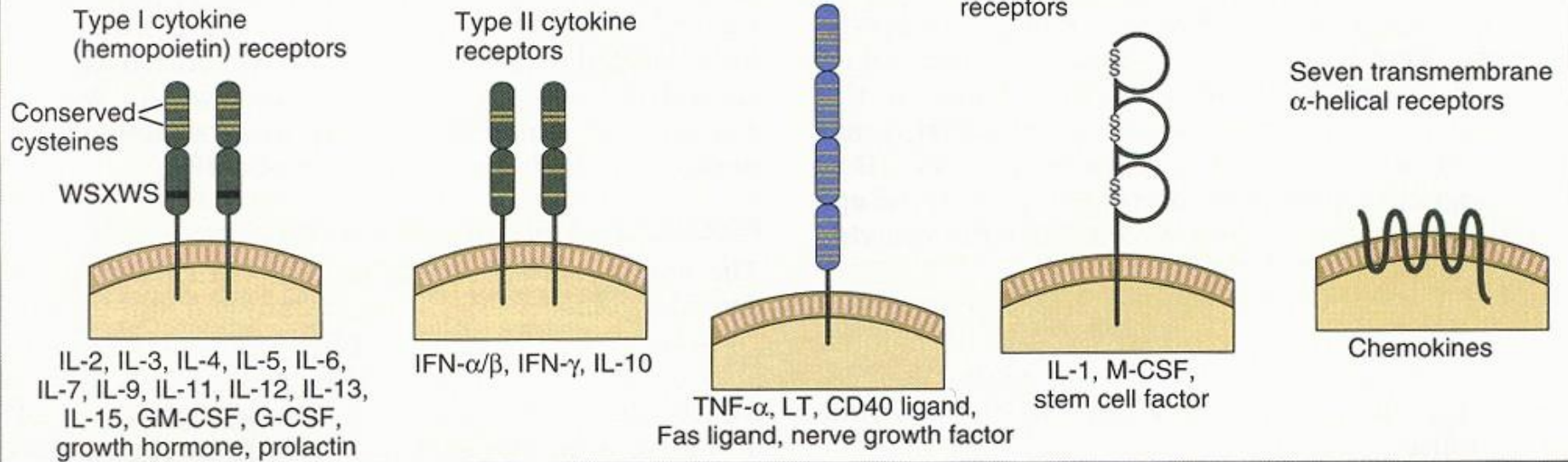
6. Transforming Growth Factor

- ! Growth-factor are cytokines which stimulate the growth of their target cells.
- Transforming growth factor- β (TGF- β)
- Epithelia growth factor (EGF)
- Vascular endothelia cell growth factor (VEGF)
- Fibroblastic growth factor (FGF)

CK receptor

- ! Membrane-binding cytokine receptors:
- ! The receptor consists of **extra-cellular region**, **trans-membrane region** and **cytoplasmic region**.
- ! CK receptors can be grouped into five families according to structure and function:
 - ! Ig receptor superfamily
 - ! Type ICK receptor superfamily
 - ! Type II CK receptor superfamily
 - ! Type III CK receptor superfamily
 - ! G-protein linked receptor superfamily

A Cytokine receptor families



The function of an interleukin might not be specific, but it binds specifically to its receptor.

Functional Categories

- ! Mediate/regulate innate immunity
 - ! TNF, IL-1, IL-12, IFN type1, IL-10
- ! Mediate/regulate adaptive immunity
 - ! IL-2, IL-4, IFN- γ , TGF- β
- ! Stimulates hematopoiesis
 - ! IL-3, IL-7

Functions

- **IL1:** Play role in inflammation
- **IL2:** Growth factor for B and T cells (clonal expansion)
- **IL3:** Haematopoietic growth factor which stimulates colony formation of blood cells
- **IL4:** Stimulates development of Th2 cells from naïve Th cell. Stimulates Ig class switch from IgG1 to IgE (allergy)
- **IL5:** Produced by Th2 cells and aids in the growth and differentiation of eosinophils
- **IL6:** acute phase response
- **IL10:** **Suppresses** inflammatory responses and Inhibits production of IFN- γ , IL-2, IL-3, TNF α , GM-CSF

Cytokines and Clinical Applications

- ! Cytokines and cytokines inhibitors can be used in many clinical applications and treatments.
 - ! Advantages: Known ligands, receptors and mechanisms of action
 - ! Problems with cytokine therapies: Effective dose levels, short half-life, can cause unpredictable side effects
- ! **Colony stimulating factors (CSFs):** hematological disorders associated with cancer therapy
- ! **Erythropoietin (EPO):** anemia associated with kidney disease
- ! **Interferon α :** antiviral therapy (chronic Hepatitis B and C)
- ! **IFN- β :** multiple sclerosis
- ! **IFN- γ :** chronic granulomatous disease (CGD)
- ! **IL-2:** kidney cancer, melanoma