CYTOKINES

BY

PROF .DR . RAFAL KHALEEL FARHAN

Introduction

- The term " Cytokines" is derived from a combination of two Greek words – "cyto" meaning cell & "kinos" meaning movement.

• Cytokines are cell signaling molecules that aid cell to cell communication in immune responses & stimulate the movement of cells towards sites of infection.

• Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system.

• Cytokines are a category of signaling molecules that mediates and regulates immunity, inflammation & hematopoiesis.

• Cytokines are produced throughout the body by cells of diverse embryological origin.

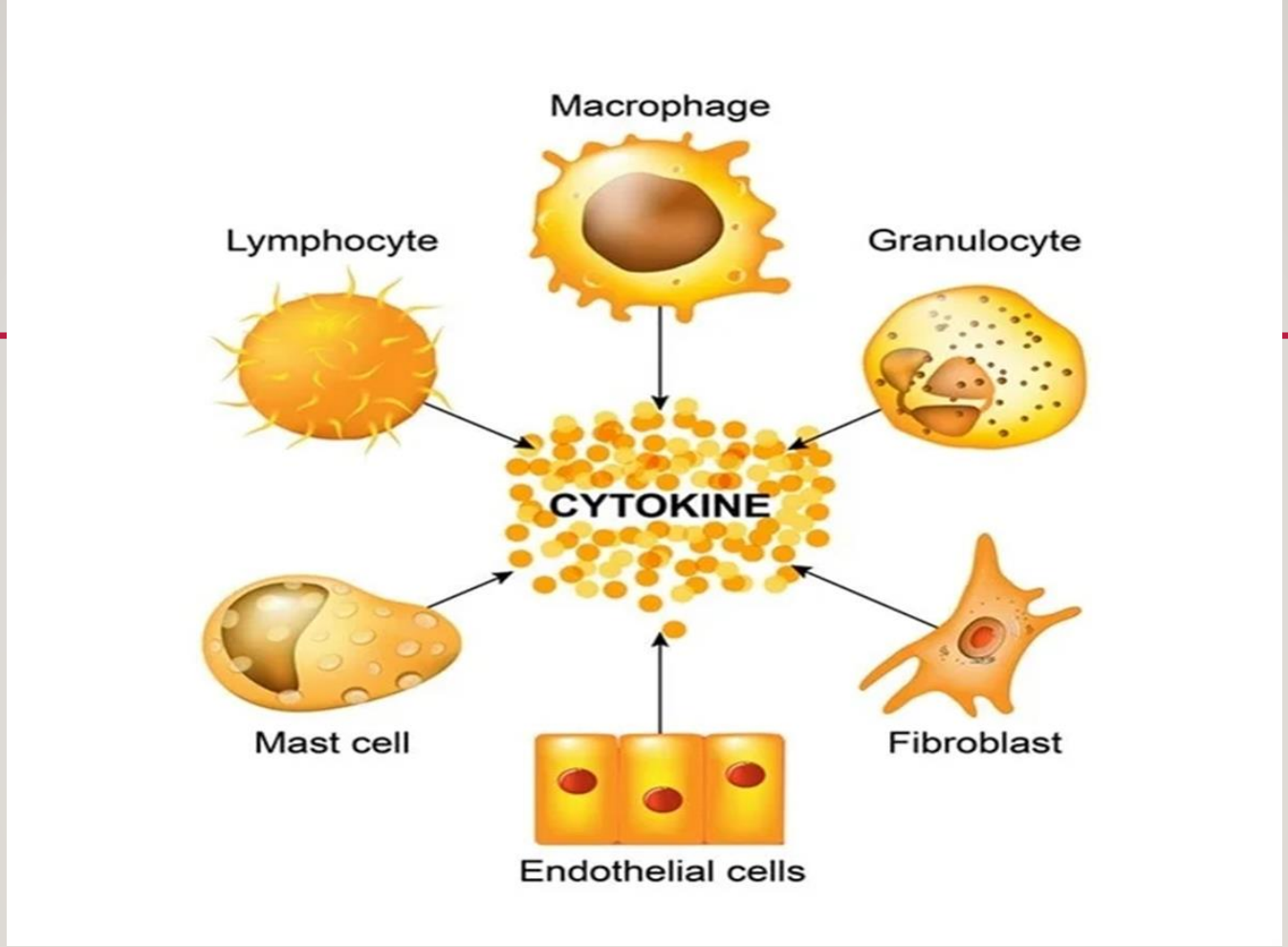


FIG SHOWING : CYTOKINES ARE PRODUCED BY CELLS OF DIVERSE EMBRYOLOGICAL ORIGIN.

-Many different and overlapping names have been given to the various cytokines:

- Cytokines produced by lymphocytes are often called lymphokines.

- Many cytokines are given the name interleukin (IL), followed by number (eg.IL-2). That act as mediators between leukocytes, the vast majority of these are produced by T- Helper cells.

- Chemokines mediate chemoattraction (chemotaxis) between cells. that are involved in the migration and activation of cells especially phagocytic cells.

- Interferons are cytokines capable of inducing body cells to resist viral replication, but they have other important functions.

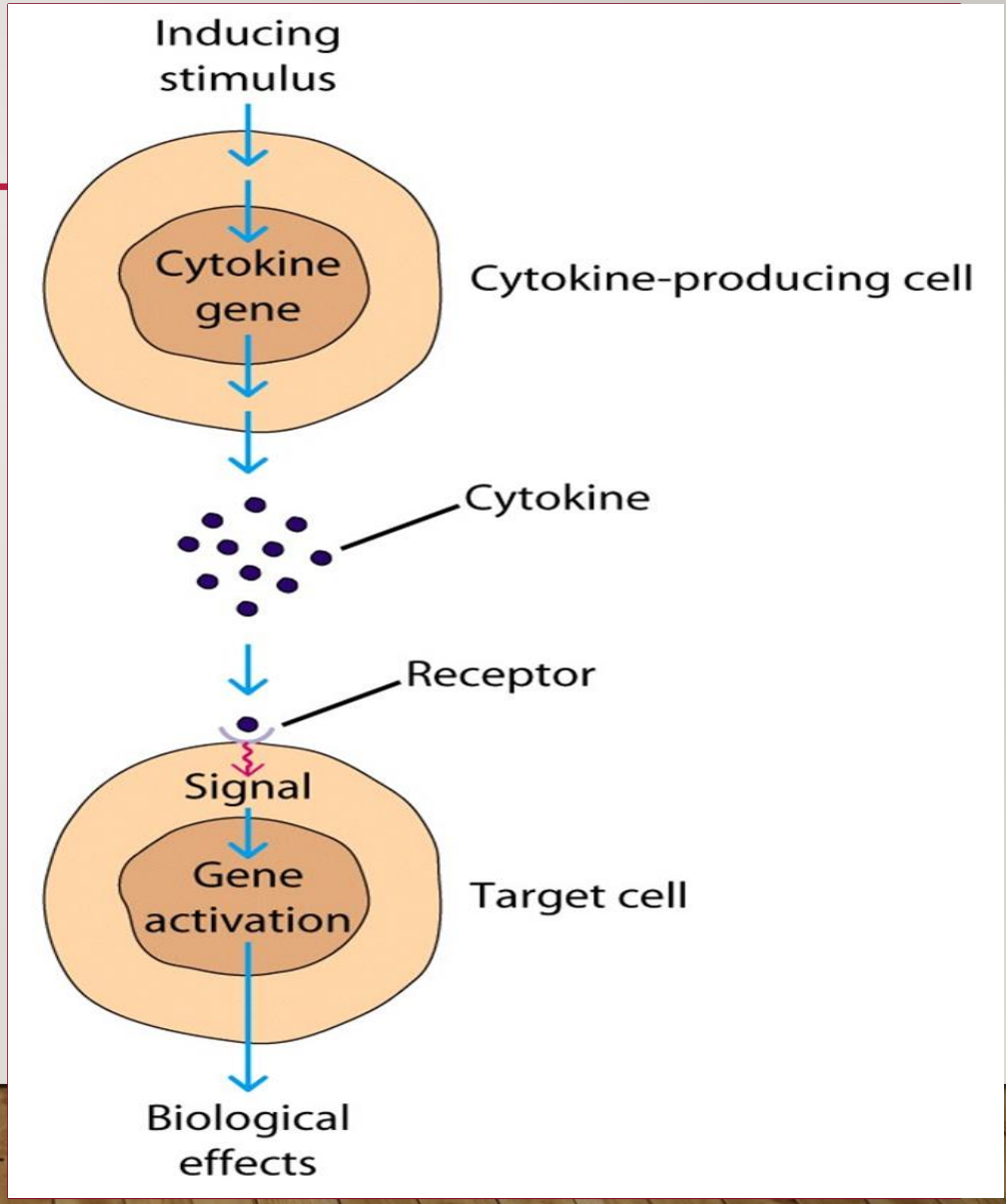
- Monokines: Produced exclusively by monocytes.
- Colony Stimulating Factor: Supports the growth of red blood cell.

Properties of Cytokines

• Cytokines bind to specific receptors on the membranes of target cells, triggering, signal-transduction pathways that ultimately alter gene expression in the target cells.

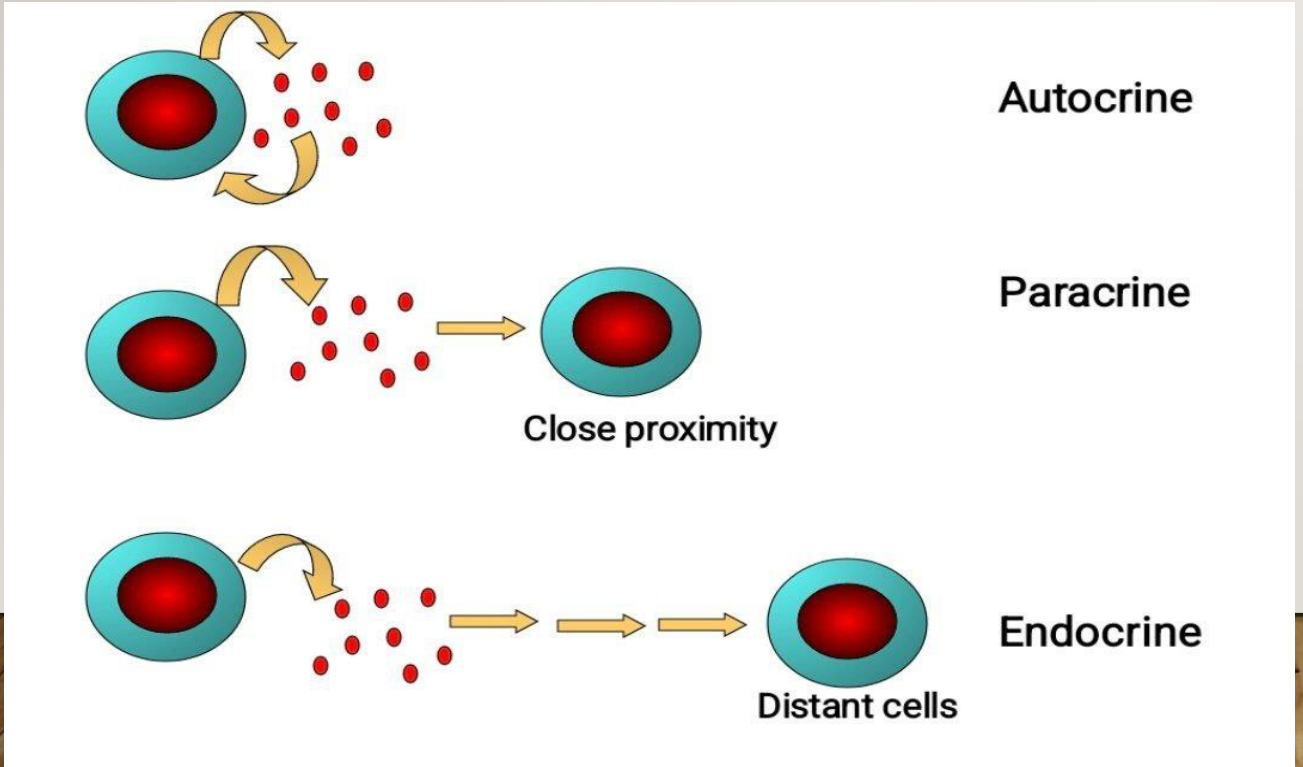
• The cytokines and their receptors exhibit very high affinity for each other, and can mediate biological effects.

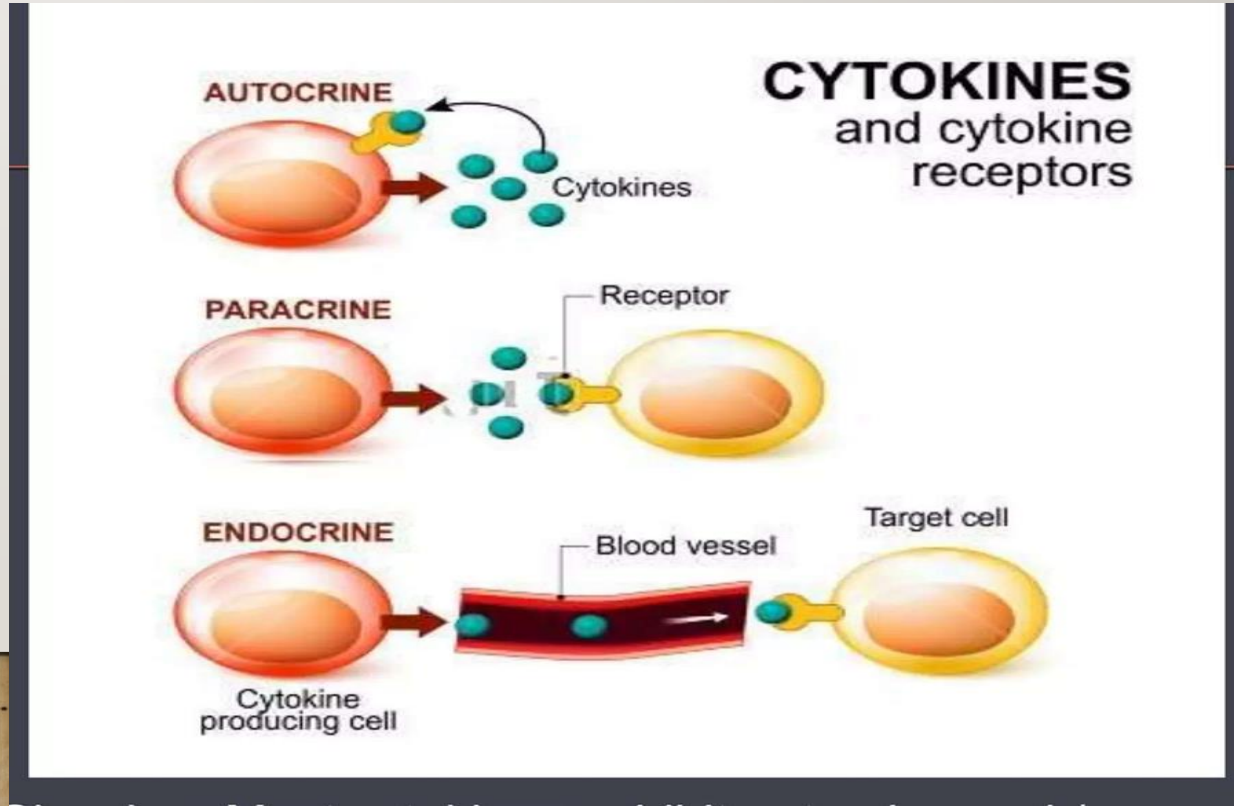
• Cytokines regulate the intensity and duration of the immune response by stimulating or inhibiting the activation, proliferation, and/ or differentiation of various cells and by regulating the secretion of antibodies or other cytokines.



- Cytokines induce their effects in three ways :

- Autocrine effect: i.e, they act on the same cell that produces the cytokine e.g, IL-2.
- Paracrine effect: that effect other cells in the vicinity e.g, IL-7 in the bone marrow act on B cells progenitors.
- Endocrine effect: they affect many cells systemically e.g, IL-1 and TNF-α which produce acute-phase response during inflammation.





- Pleiotrophy: It is common for different cell types to secrete the same cytokine or for a single cytokine to act on several different cell types.

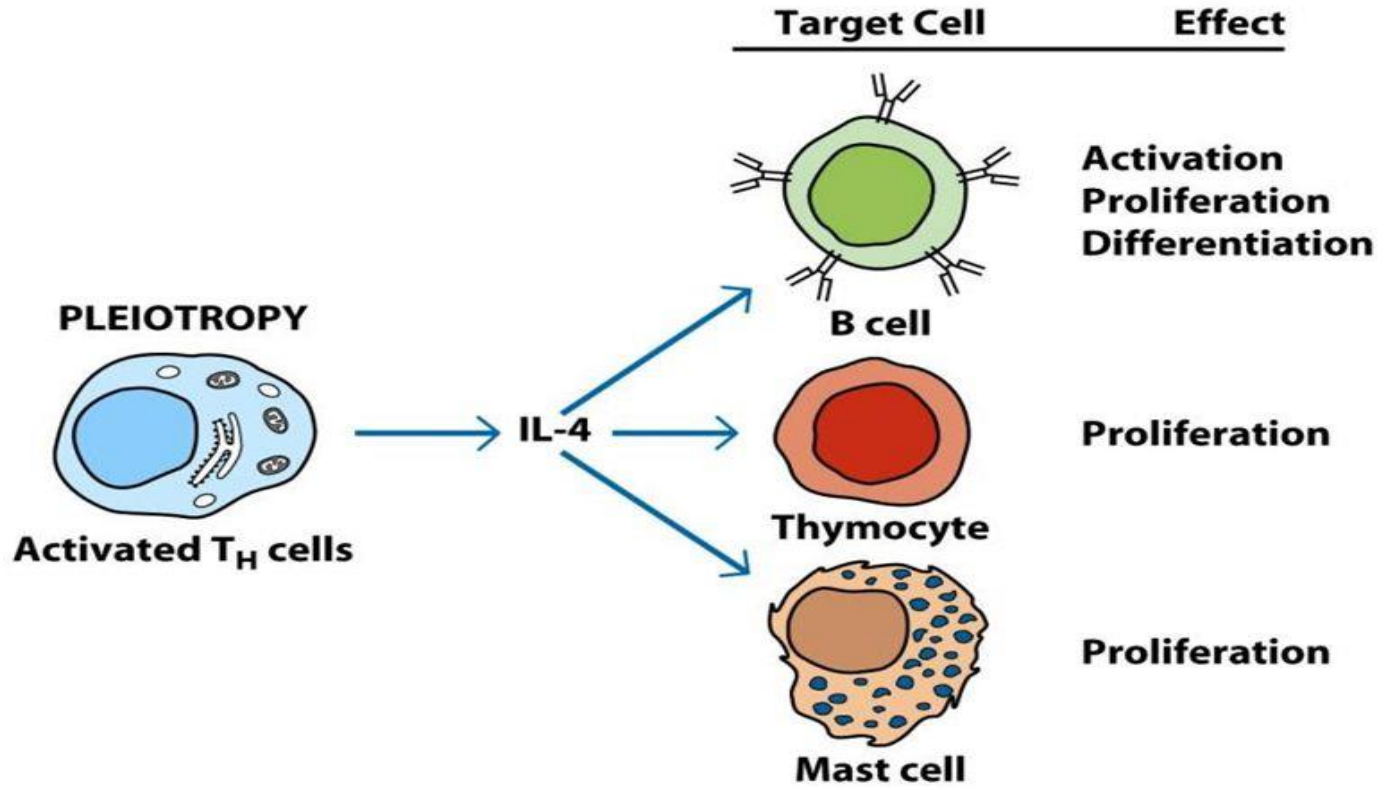


Figure 12-2a part 1
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- Cytokines are redundant in their activity, meaning similar functions can be stimulated by different cytokines.

- Cytokines can also act synergistically (two or more cytokines acting together) or antagonistically (cytokines causing opposing activities).

- Cytokines are often produced in a cascade, as one cytokine stimulates its target cells to make additional cytokines.

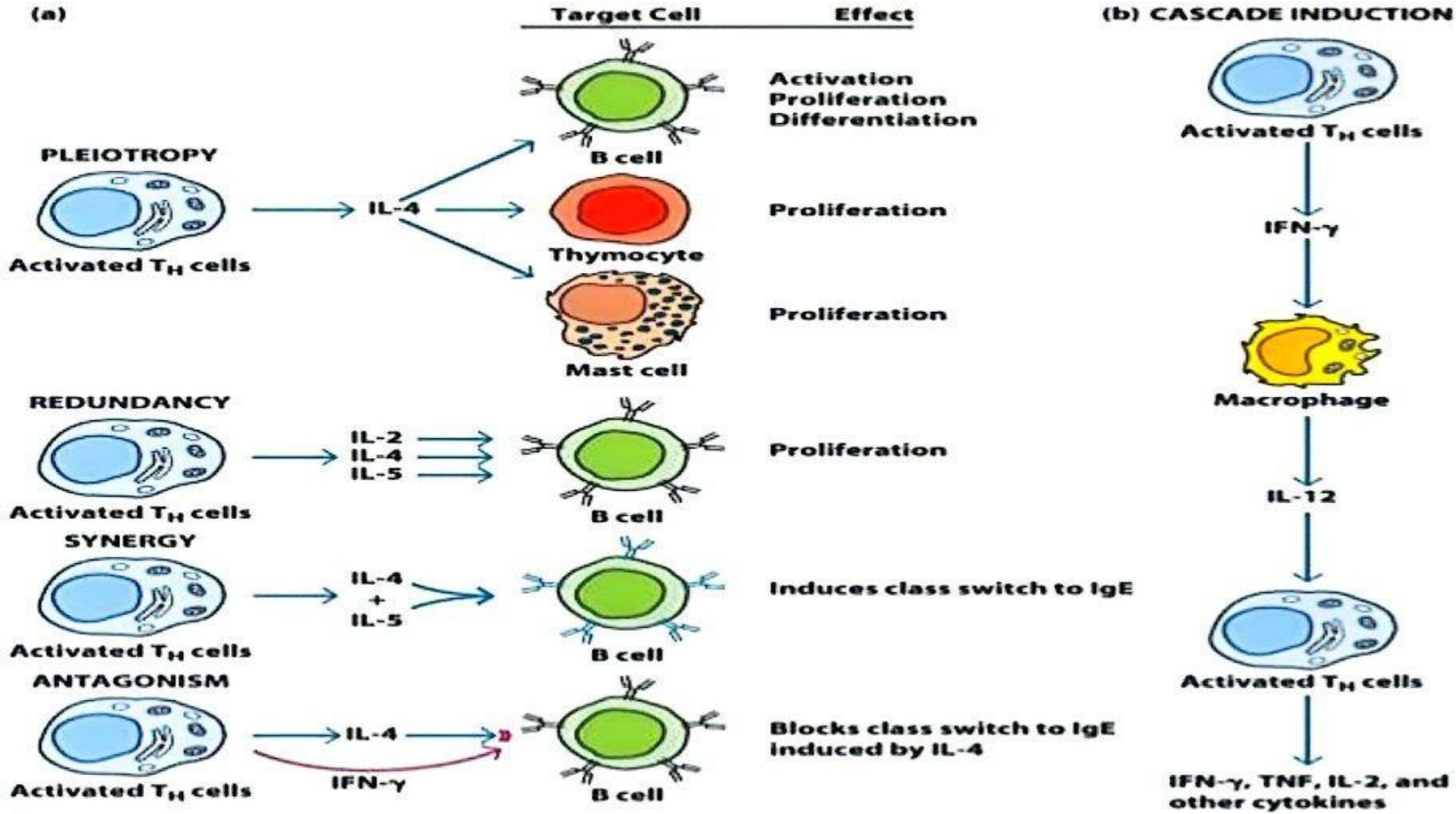

Figure 12-2
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Some of the major Biological functions of cytokines are following

1. Stimulate development of cellular and humeral immune response
2. Induction of inflammatory response
3. Regulation of hematopoiesis
4. Control of cellular proliferation and differentiation
5. Healing of wounds

Classification and Functions

- Cytokines can be categorized into groups based on their common functions. Examples of functional categories are immunoregulatory, proinflammatory, anti-inflammatory, and growth and differentiation.
- Because of its major role in antigen presentation, an important immunoregulatory cytokine is IFN-γ.
- Proinflammatory cytokines are commonly seen in infectious diseases, and they include IL-1, IL-6, TNF- α, and the IFNs.
- The anti-inflammatory cytokines include TGF-β, IL-10, IL-11, and IFN-β. These may be required to dampen or downregulate an overactive inflammatory response.

- Cytokines that have a key role in growth and differentiation include the colony stimulation factors (CSFs) and stem cell factor.

- We have also seen that T cells use cytokines for differentiation into T-cell subsets. Whereas Th1 cells are generated in the presence of IFN-γ, Th2 cells are differentiated in the presence of IL-4.

- Th17 cells are produced in the presence of TGF-β and IL-6, but Treg cells are formed in the presence of TGF-β alone. Each of these T-cell subsets now secretes its own set of cytokines that have distinct regulatory properties.

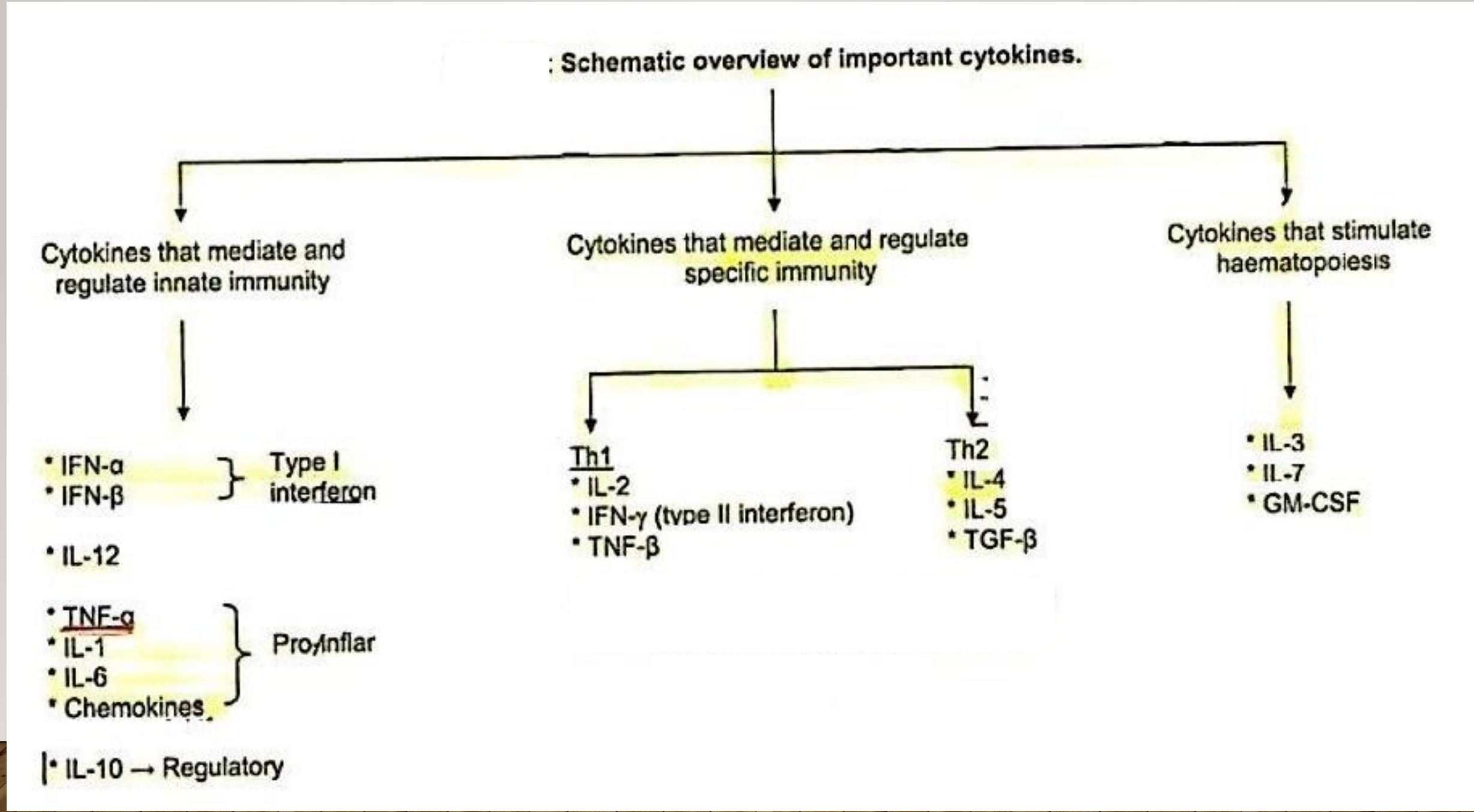
: Schematic overview of important cytokines.
Cytokines that mediate and regulate innate immunity
Cytokines that mediate and regulate specific immunity
Cytokines that stimulate haematopoiesis
• IFN-α
• IFN-β
Type I interferon
• IL-12
• TNF-α
• IL-1
• IL-6
• Chemokines
Proinflar
• IL-10 → Regulatory
Th1
• IL-2
• IFN-γ (type II interferon)
• TNF-β
Th2
• IL-4
• IL-5
• TGF-β
• IL-3
• IL-7
• GM-CSF

TABLE 8-2 SELECTED CYTOKINES: PRODUCTION AND ACTIVITIES

Cytokine Family	Primary Cell Type*	Activity
Interferons		
Alpha	Leukocytes	Antiviral, immunoregulatory, (enhance MHC class I, NK cell activity), anti-proliferative
Beta	Fibroblasts, epithelial cells	Antiviral, immunoregulatory, (enhance MHC class I, NK cell activity), anti-proliferative
Gamma	T cell, NK cells	Antiviral, immunoregulatory, (enhance MHC class I and II and macrophage activation) anti-proliferative
TNF		
Alpha	Macrophage, lymphocytes	Activate macrophages and cytotoxic cells, induce cachexia, acute phase proteins, induces cytokines such as IL-1 and IL-6.
Beta	T cells	Activate macrophages, induces cytokines (IL-1, IL-6)
Interleukins		
IL-1	Most cells, macrophages, dendritic cells	Induces inflammation, fever and sepsis, activate TNF-α
IL-2	T cells	Induces proliferation and maturation of T cells
IL-6	Most cells	B cell stimulation, mediator of acute phase reactions
IL-10	T cells, monocytes/macrophages	Inhibits IFN-γ and IL-12 production
IL-11	Bone marrow stromal cells, mesenchymal cells	Synergistic effects on hematopoiesis and thrombopoiesis, cytoprotective effects on epithelial cells, induces immunosuppression
IL-12	Dendritic cells, macrophages, B cells	Induces production of IFN-γ, TNF-α, and IL-2 by resting and activated T and NK cells
IL-15	T cells, atrocytes, microglia, fibroblasts, epithelial cells	Biological activities similar to IL-2, induces proliferation of peripheral blood, mononuclear cells, maturation of NK cells (IL-1, IFN-γ, TNF-α)
IL-17 (6 members) (IL-17 A-F)	Th17 cells	Stimulates epithelial, endothelial, and fibroblastic cells to produce IL-6, IL-8, G-CSF, and ICAM-1
IL-23	Macrophages, dendritic cells	Similar to IL-12 (induces IFN-γ) helps to differentiate CD4 T cells to TH17
Growth Factors		
M-CSF	Monocytes	Proliferation of macrophage precursors
G-CSF	Macrophages	Proliferation, differentiation, and activation of neutrophils
GM-CSF	T cells, macrophages	Proliferation of granulocytes and macrophages precursors
Stem cell factor	Bm stromal cells, fibroblasts, fetal liver cells	Proliferation and differentiation of early myeloid and lymphoid cells (synergizes with other cytokines)
TGF-β	Most cells	Anti-inflammatory, drives differentiation of CD4 T cells to T regs; in presence of IL-6 drives CD4 T cells to Th17
VEGF-A	Most cells	Stimulates vasculogenesis and angiogenesis
Chemokines		
IL-8 (CXCL8)	Most cells	Neutrophil activation and chemotoxis
Rantes (CCL5)	Most cells	Chemotactic for T cells monocytes, eosinophils and basophils
CXCL9, CXCL10, CXCL11	Most cells	Chemotactic for Th1 cells (CXCR3 positive T cells) and induced by the IFNs
Adhesion Molecules		
ICAM-1	Endothelial cells	Adhesion and migration
VCAM-1	Leukocytes	Adhesion and migration
E-selectin	Endothelial cells	Adhesion and migration

*This list is not inclusive; primary cells have been identified

Cytokines in Haematopoiesis

- 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.

- A myeloid progenitor in the presence erythropoietin would proceed down a pathway that leads to the production of erythrocytes.

- 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.

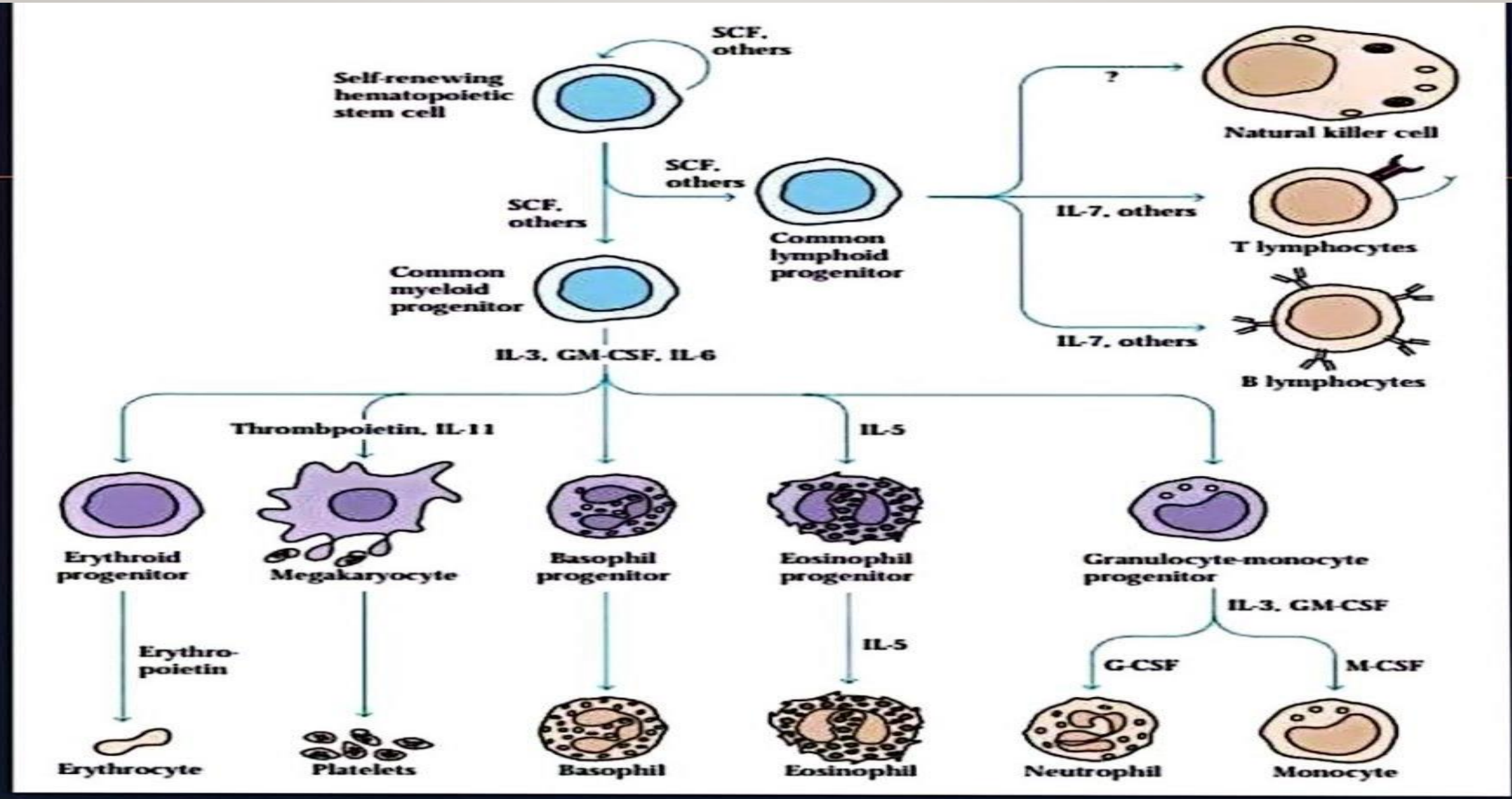

Fig Showing: Hematopoietic cytokines and hematopoiesis.

TABLE 12-5 Hematopoietic cytokines

Hematopoietic growth factor	Sites of production	Main functions
Erythropoietin	Kidney, liver	Erythrocyte production
G-CSF	Endothelial cells, fibroblasts, macrophages	Neutrophil production
Thrombopoietin	Liver, kidney	Platelet production
M-CSF	Fibroblasts, endothelial cells, macrophages	Macrophage and osteoclast production
SCF/*c-kit* ligand	Bone marrow stromal cells, constitutively	Stem cell, progenitor cells survival/division; mast cell differentiation
Flt-3 ligand	Fibroblasts, endothelial cells	Early progenitor cell expansion; pre–B cells
GM-CSF	T cells (T_H1 and T_H2), macrophages, mast cells	Macrophage, granulocyte production; dendritic cell maturation and activation
IL-3	T cells (T_H1 and T_H2), macrophages	Stem cells and myeloid progenitor cell growth; mast cells
IL-5	Activated helper, T cells—T_H2 response only	Eosinophil production; murine B-cell growth
IL-6	Activated T cells, monocytes, fibroblasts, endothelial cells	Progenitor-cell stimulation; platelet production; immunoglobulin production in B cells
IL-7	Bone marrow and lymphoid stromal cells	T-cell survival
IL-11	Bone marrow stromal cells and IL-1-stimulated fibroblasts	Growth factor for megakaryocytes

G-CSF, granulocyte colony–stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; M-CSF, macrophage colony–stimulating factor; SCF, stem cell factor. Adapted from D. Thomas and A. Lopez, 2001, *Encyclopedia of Life Sciences:* Haematopoietic growth factors, Nature Publishing Group.

Cytokines and Disease

Bacterial Septic Shock

Cell wall endotoxin stimulate macrophages to overproduce IL-1 and TNF alpha, Treatment is with antibodies against TNF alpha and use of recombinant IL-1 receptor antagonists.

Lymphoid and Myeloid Cancers

- High levels of IL-6 are produced
- by Cardiac myxoma cells, myeloma, plasmacytoma cells, cervical and bladder cancer cells

- IL-6 works in an autocrine manner to stimulate cell proliferation

T cell leukemia is associated with HTLV-1 retrovirus

- HTLV-1 protein called “Tax” induces factors that bind to the promotor regions of genes encoding IL2 and IL2 receptors and activating them.

Reference

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2-Subhash Chandra Parija. (2012).Textbook of Microbiology and Immunology. 2nd Edition.

Thank you