

Cytokines

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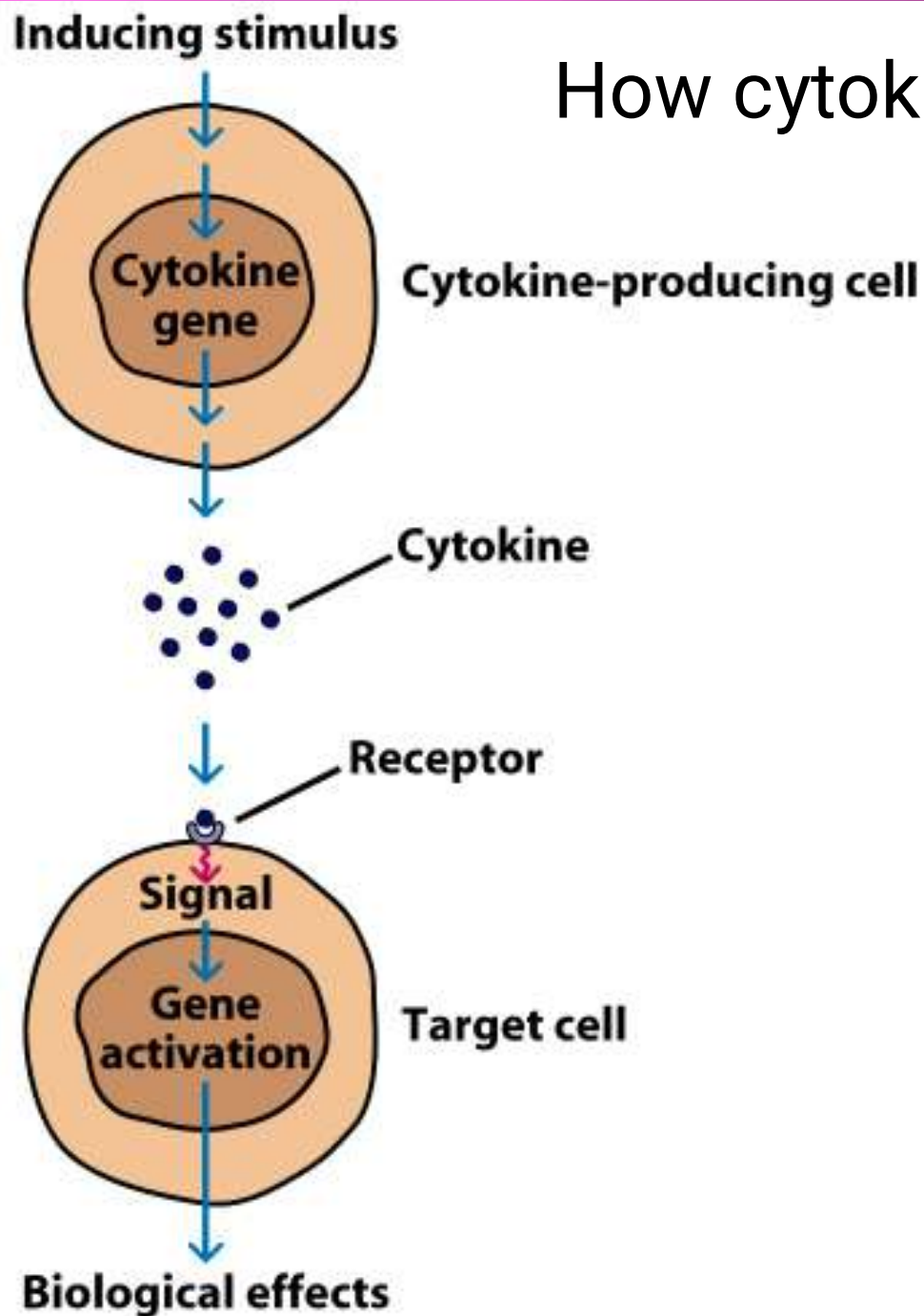
WHAT IS CYTOKINE?

- Secreted polypeptide or low molecular weight regulatory protein or glycoproteins involved in cell-to-cell signaling.
- Assist in regulating development of immune effector cells
- act on many *cells involved in immune and inflammatory response*
- Some possess direct effector functions of their own
 - Cytotoxic, inflammatory, anti-inflammatory,
 - Immunostimulation (proliferation), chemotactic, hematopoiesis

Cytokines: main functions

- **Hematopoiesis** (ex. CSFs, colony stimulating factors).
- **Inflammatory reaction** (ex. IL1, TNF).
- **Chemotaxis** (ex. IL8, MIP1- macrophage inflammatory protein 1, BLC – B-lymphocyte chemoattractant).
- **Immunostimulation** (ex. IL12, IFN γ).
- **Suppression** (ex. IL10).
- **Angiogenesis** (ex. VEGFs - vascular endothelial growth factor).
- **Embryogenesis** (ex. TGF- β , LT - lymphotoxin).

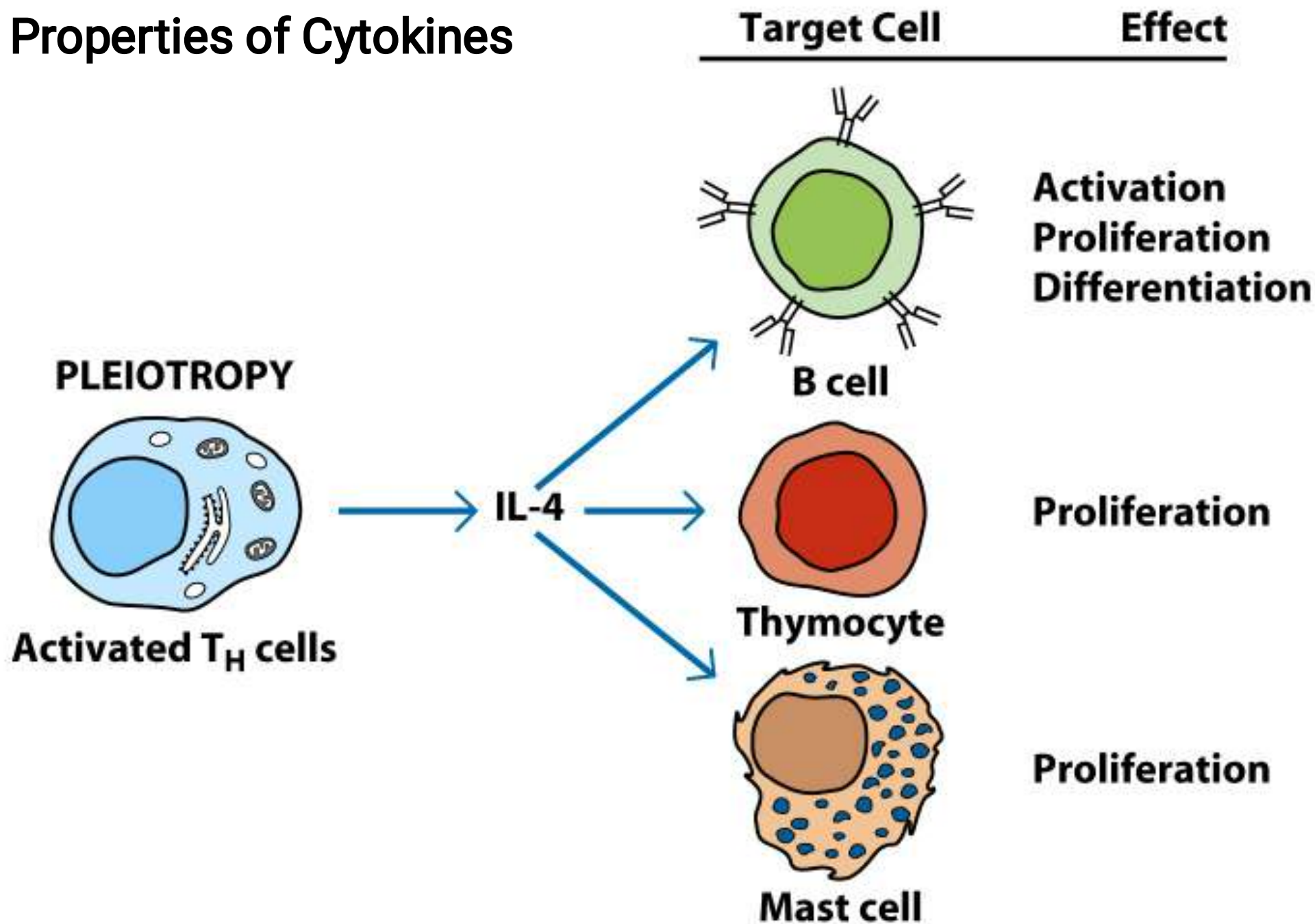
How cytokine mediate their biological effects



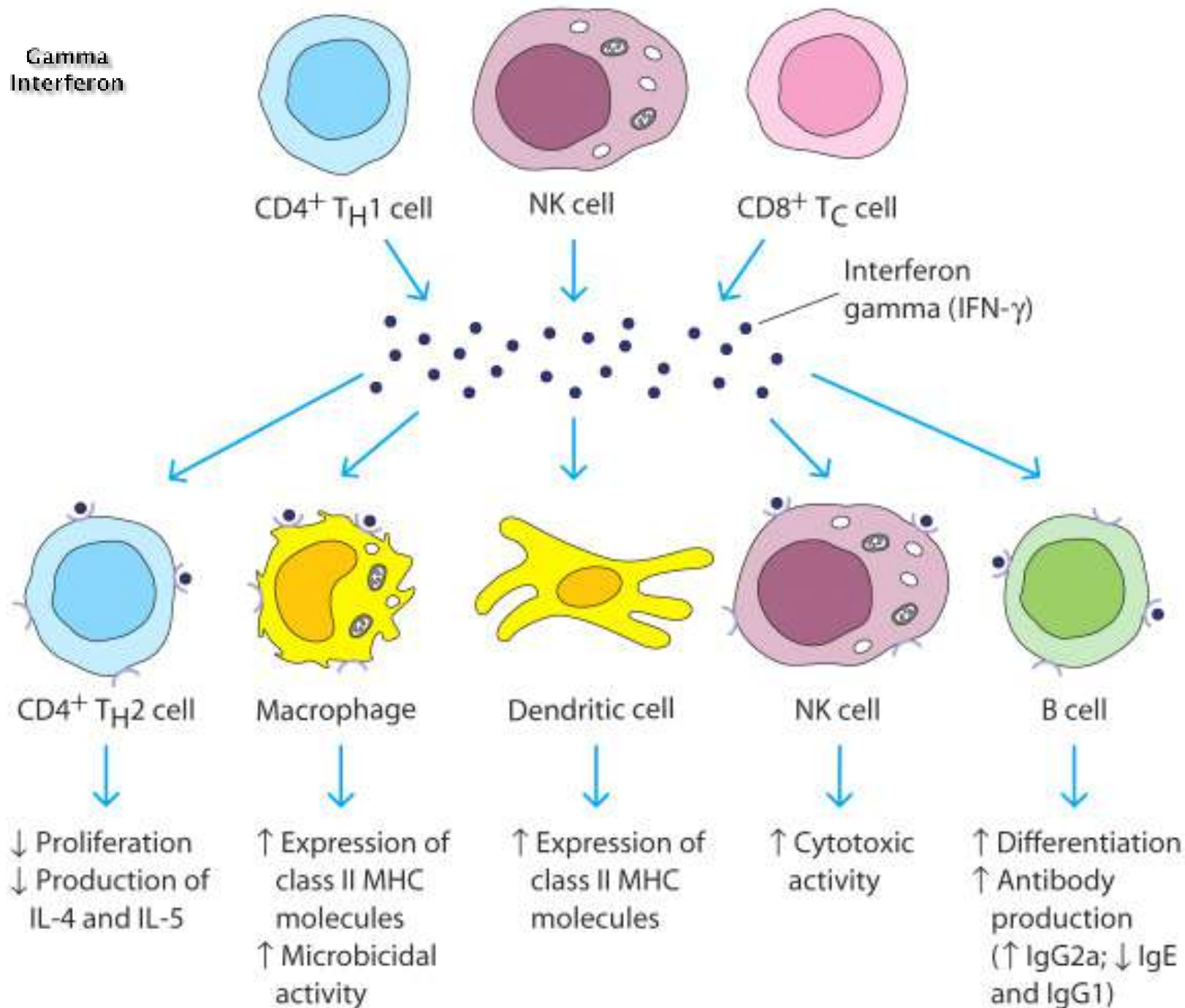
Acts through specific cellular receptors

- ❑ Cytokines bind to specific receptors
- ❑ Trigger signal transduction pathways that alter gene expression in target cells
- ❑ Exhibit pleiotropy, redundancy, synergy, antagonism, cascade induction

Properties of Cytokines



Gamma Interferon



Pleiotropic activity of Interferon Gamma.

Immunology, 5th Edition, Figure 15-15, p. 355

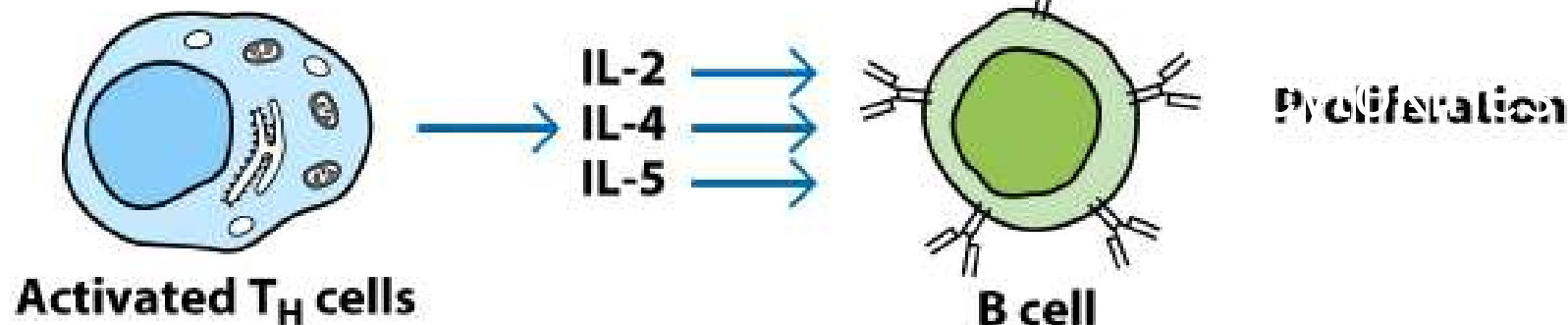
Multiple effects induced by single cytokine

Properties of Cytokines

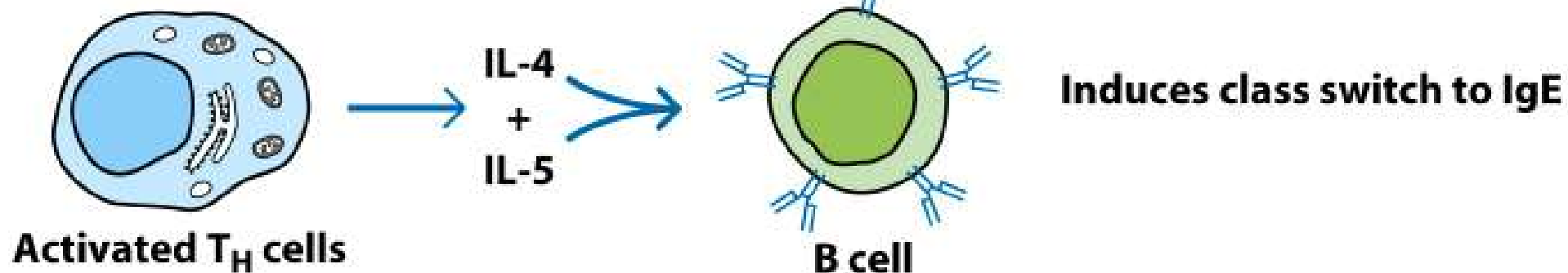
Target Cell

Effect

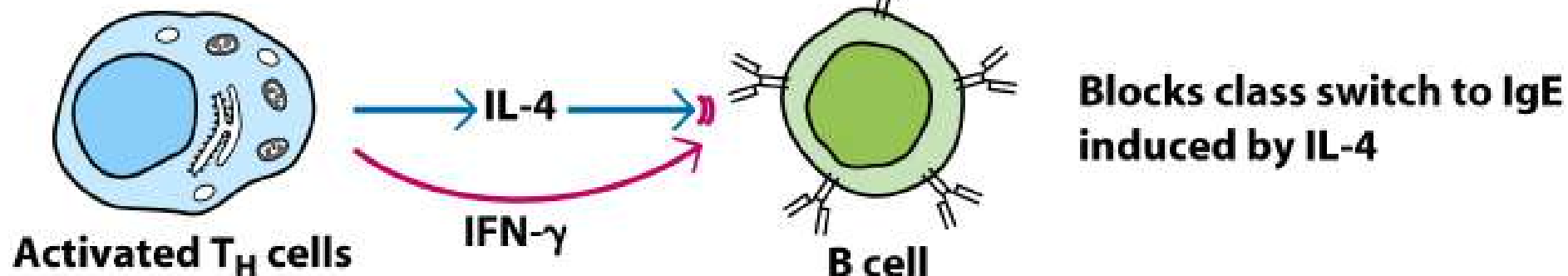
REDUNDANCY



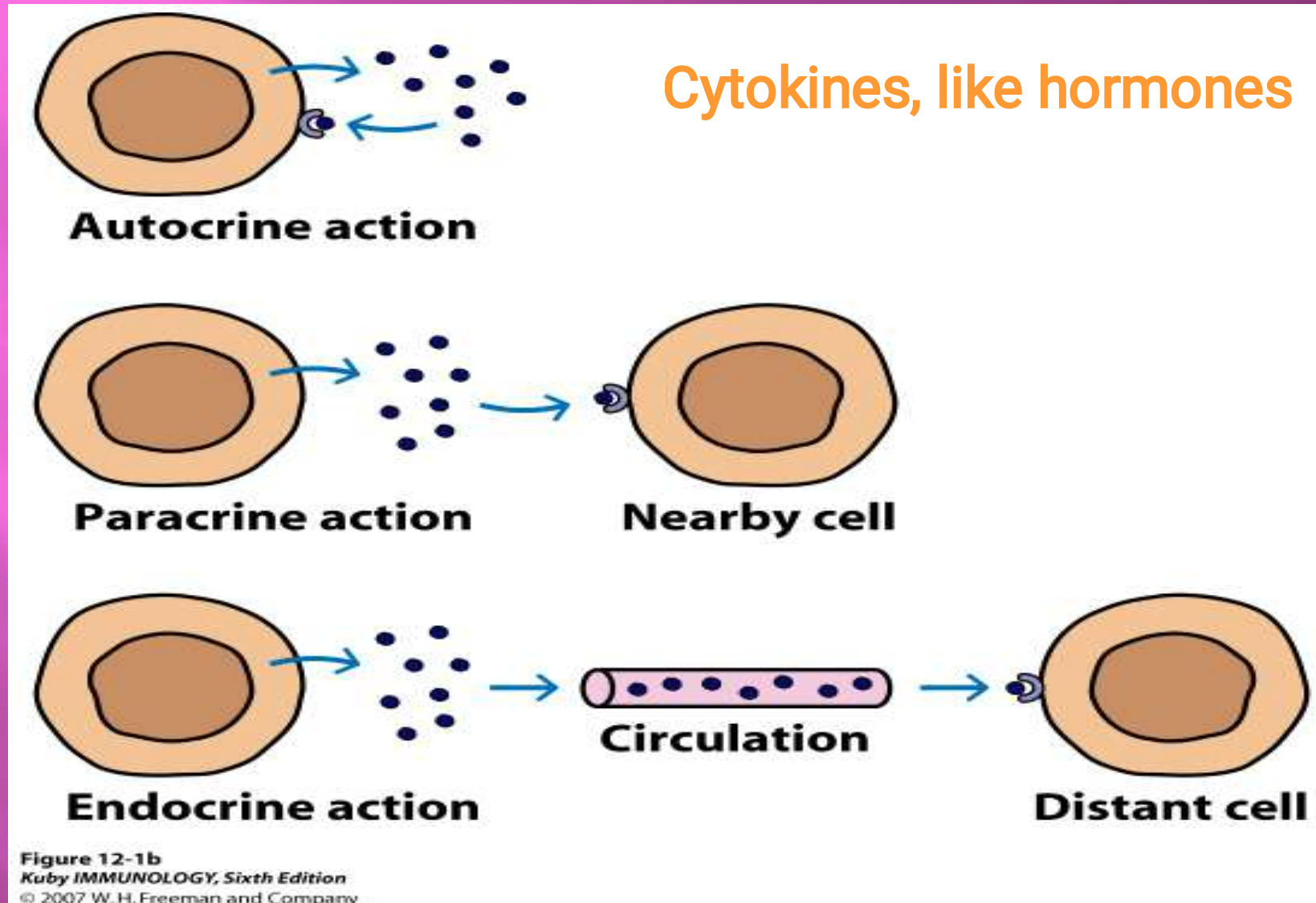
SYNERGY



ANTAGONISM



Acts in paracrine or autocrine fashion *through specific cellular receptors*



- Can be produced by cells of any tissue and act on many *cells involved in immune and inflammatory response*.

Cytokine nomenclature

- ❑ **Lymphokines** - produced by activated T lymphocytes direct the immune system response by signaling between its cells
- ❑ **Interleukins** - presumed targets are principally leukocytes
- ❑ **Chemokines** - specific class of cytokines. Mediates chemoattraction (**chemotaxis**) between cells, stimulate leukocyte movement and regulate the migration of leukocytes from the blood to tissues.
- ❑ **Monokines** - derived primarily from mononuclear cells such as **macrophages**

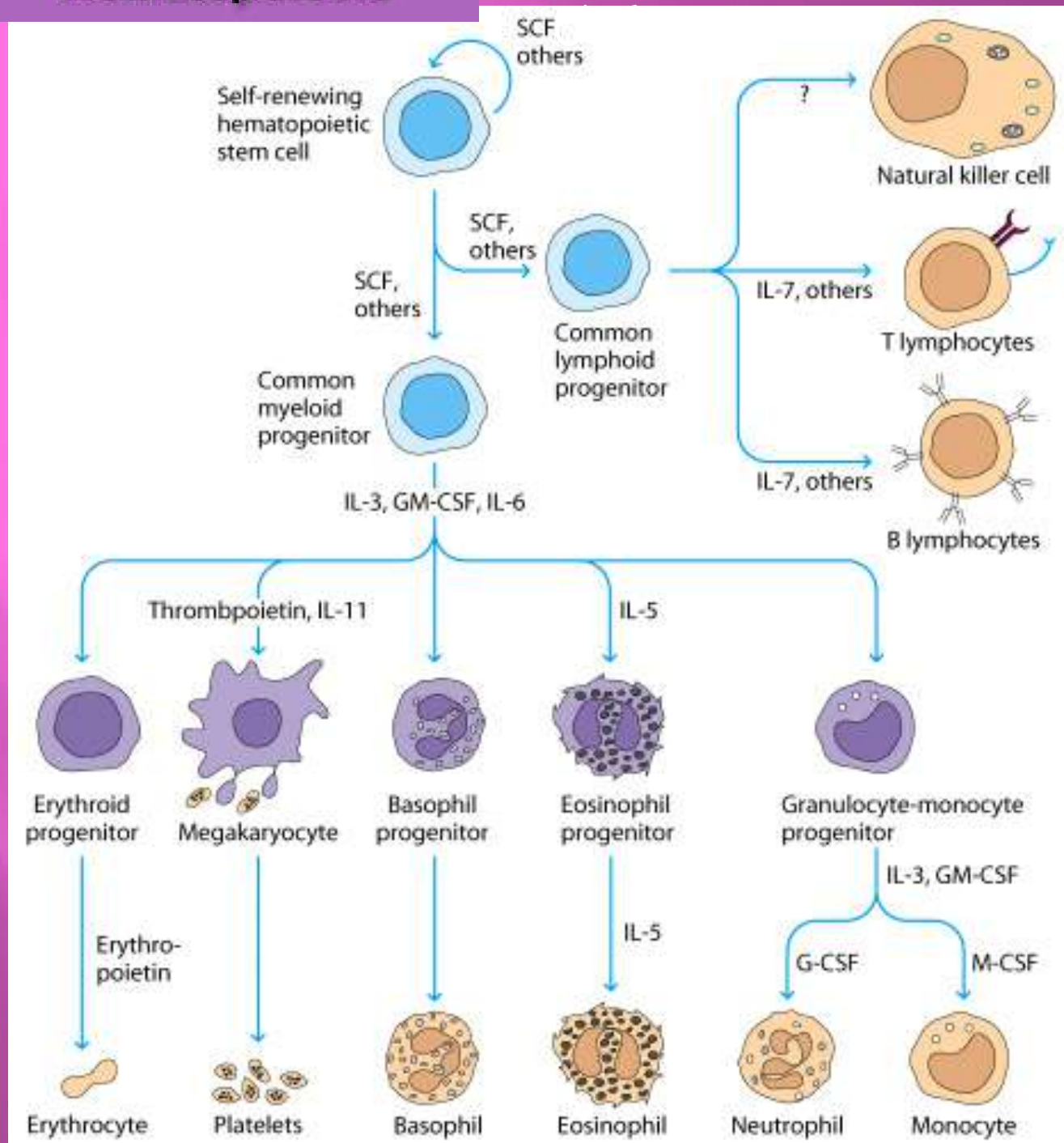
Functions of Cytokines

Cytokines in Hematopoiesis

Cytokines in Innate and Adaptive
immunity

Hematopoiesis

Stem Cell Factor from Bone Marrow Stromal



Lymphocytes

Hematopoietic Cytokines and Hematopoiesis:

Immunology, 5th Edition, Figure 12-16, p. 297

-----Myelocytes-----

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/ <i>c-kit</i> ligand Stem Cell Production	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 Myelocyte Production	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 Lymphocyte Production	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, <i>Encyclopedia of Life Sciences: Haematopoietic growth factors</i> , Nature Publishing Group.		

Table 12-5

Kuby IMMUNOLOGY, Sixth Edition

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TABLE 12-1 Functional groups of selected cytokines*

Cytokine†	Secreted by†	Targets and effects
SOME CYTOKINES OF INNATE IMMUNITY		
Interleukin 1 (IL-1)	Monocytes, macrophages, endothelial cells, epithelial cells	Vasculature (inflammation); hypothalamus (fever); liver (induction of acute phase proteins)
Tumor necrosis factor- α (TNF- α)	Macrophages	Vasculature (inflammation); liver (induction of acute phase proteins); loss of muscle, body fat (cachexia); induction of death in many cell types; neutrophil activation
Interleukin 12 (IL-12)	Macrophages, dendritic cells	NK cells; influences adaptive immunity (promotes T_H1 subset)
Interleukin 6 (IL-6)	Macrophages, endothelial cells	Liver (induces acute phase proteins); influences adaptive immunity (proliferation and antibody secretion of B cell lineage)
Interferon α (IFN- α) (this is a family of molecules)	Macrophages	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK cells
Interferon β (IFN- β)	Fibroblasts	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK cells
SOME CYTOKINES OF ADAPTIVE IMMUNITY		
Interleukin 2 (IL-2)	T cells	T-cell proliferation; can promote AICD. NK cell activation and proliferation; B-cell proliferation
Interleukin 4 (IL-4)	T_H2 cells, mast cells	Promotes T_H2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T_H2 cells	Eosinophil activation and generation
Transforming growth factor β (TGF- β)	T cells, macrophages, other cell types	Inhibits T-cell proliferation and effector functions; inhibits B-cell proliferation; promotes isotype switch to IgA; inhibits macrophages
Interferon γ (IFN- γ)	T_H1 cells, CD8 ⁺ cells, NK cells	Activates macrophages; increases expression MHC class I and class II molecules; increases antigen presentation
*Many cytokines play roles in more than one functional category. †Only the major cell types providing cytokines for the indicated activity are listed; other cell types may also have the capacity to synthesize the given cytokine. †Also note that activated cells generally secrete greater amounts of cytokine than unactivated cells.		

Table 12-1

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Cytokine Receptors

- ⌘ Cytokine receptors fall into families
 - ⌘ Immunoglobulin superfamily receptors
 - ⌘ Class I cytokine receptor family (hematopoietin)
 - ⌘ Class II cytokine receptor family (interferon)
 - ⌘ TNF receptor family
 - ⌘ Chemokine receptor family

Human Disease due to Over-production of Cytokines

Bacterial Septic Shock:

- **Bacterial Cell-wall Endotoxins**
-
- **Macrophage Overproduction of IL-1 and TNF-alpha**
- **Example organisms potentially producing endotoxins:**
- **Neisseria meningitidis, E coli, Pseudomonas aeruginosa, Enterobacter aerogenes, Klebsiella pneumoniae**

Bacterial Toxic Shock

- Polyclonal activation of T-cells by Super-Antigens
-
- Over-production of IL-1, TNF, other cytokines
- Example organisms producing super-antigens:
- Staphylococcus aureus, Streptococcus pyrogenes

See pages 291 and 292, Kuby, Edition
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Other Sources of Cytokines used in Host Response to Pathogens:

e.g. Mediators in Type I Immediate Hypersensitivity

TABLE 15-3**Principal mediators involved in type I hypersensitivity**

Mediator	Effects
PRIMARY	
Histamine, heparin	Increased vascular permeability; smooth muscle contraction
Serotonin (rodents)	Increased vascular permeability; smooth muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases (tryptase, chymase)	Bronchial mucus secretion; degradation of blood vessel basement membrane; generation of complement split products
SECONDARY	
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth muscle contraction
Cytokines	
IL-1 and TNF- α	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells
IL-4 and IL-13	Increased IgE production
IL-3, IL-5, IL-6, IL-10, TGF- β , and GM-CSF	Various effects (see Table 12-1)

Table 15-3

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Cytokines in Therapy of Diseases

Cytokines have potent activities at low concentrations in controlling responses of host cells to normal and pathological events & thus we use them in therapy

Cytokine Therapies in the Clinic

Cytokine-based therapies in clinical use

Agent	Nature of agent	Clinical application
Enbrel	Chimeric TNF-receptor/IgG constant region	Rheumatoid arthritis
Remicade or Humira	Monoclonal antibody against TNF- α receptor	Rheumatoid arthritis Crohn's disease
Roferon	Interferon α -2a*	Hepatitis B Hairy-cell leukemia Kaposi's sarcoma
Intron A	Interferon α -2b	Hepatitis C [†] Melanoma
Betaseron	Interferon β -1b	Multiple sclerosis
Avonex	Interferon β -1a	Multiple sclerosis
Actimmune	Interferon γ -1 β	Chronic granulomatous disease (CGD) Osteopetrosis
Neupogen	G-CSF (hematopoietic cytokine)	Stimulates production of neutrophils Reduction of infection in cancer patients treated with chemotherapy, AIDS patients
Leukine	GM-CSF (hematopoietic cytokine)	Stimulates production of myeloid cells after bone marrow transplantation
Neumega or Neulasta	Interleukin-11 (IL-11), a hematopoietic cytokine	Stimulates production of platelets
Epogen	Erythropoietin (hematopoietic cytokine)	Stimulates red-blood-cell production

*Interferon α -2a is also licensed for veterinary use to combat feline leukemia.

[†]Normally used in combination with an antiviral drug (ribavirin) for hepatitis C treatment.