Cytokines

Dr.Eman Albataineh,
Assistant Prof. Immunology
College of Medicine, Mu'tah university
Immunology, 2nd year students

Definition

- **Cytokines** are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems.
- They are produced by virtually all cells involved in innate and adaptive immunity,
- The cytokines, in turn, are then able to bind to specific cytokine receptors on other cells of the immune system and influence their activity.
- Cytokines are pleiotropic, redundant, and multifunctional.
- **Pleiotropic** means that a particular cytokine can act on a number of different types of cells rather than a single cell type.
- **Redundant** refers to the ability of a number of different cytokines to carry out the same function.
- **Multifunctional** means the same cytokine is able to regulate a number of different functions.
- **They can act locally or in a distance**

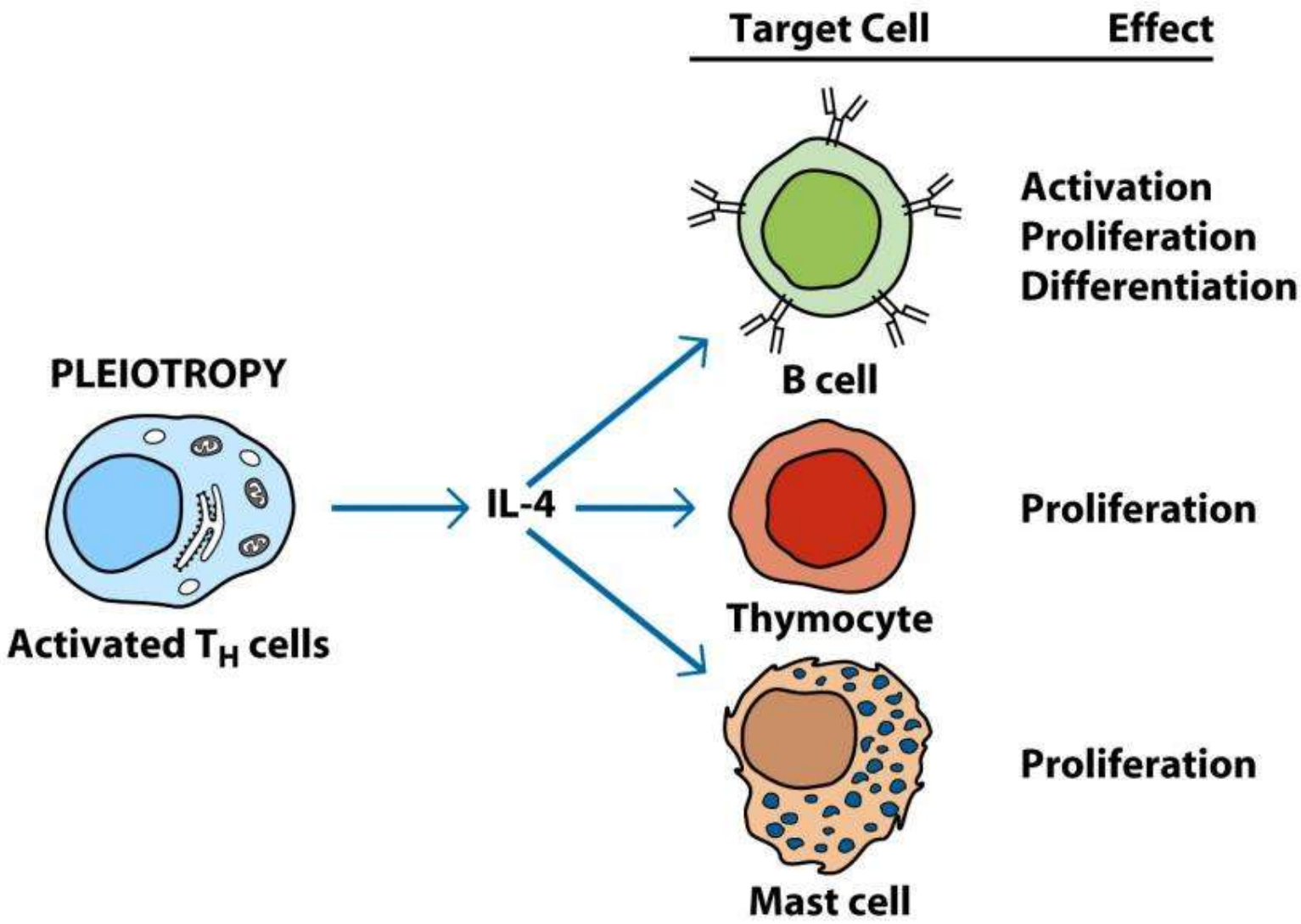

Figure 12-2a part 1
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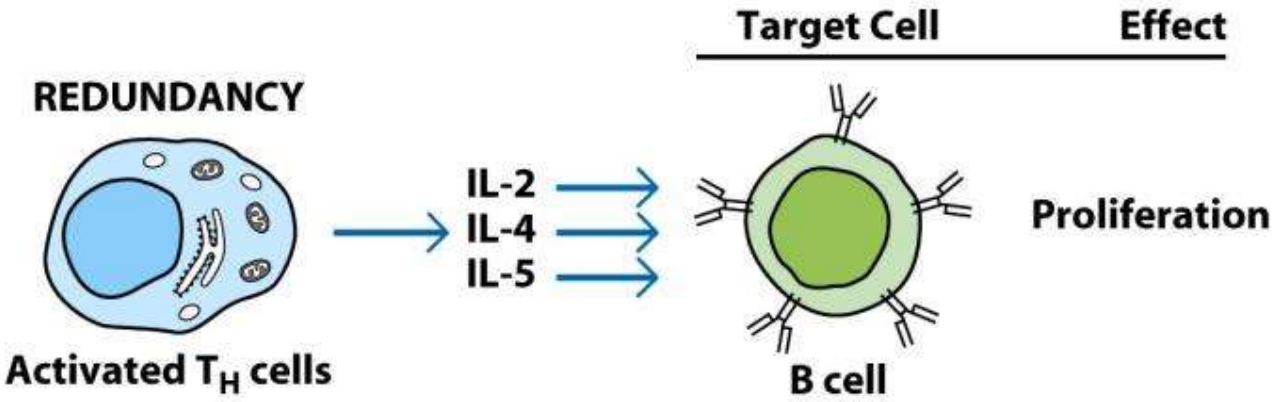
General Characteristics

Actions are redundant

- **(REDUNDANCY)**: different cytokines may have the same effect.



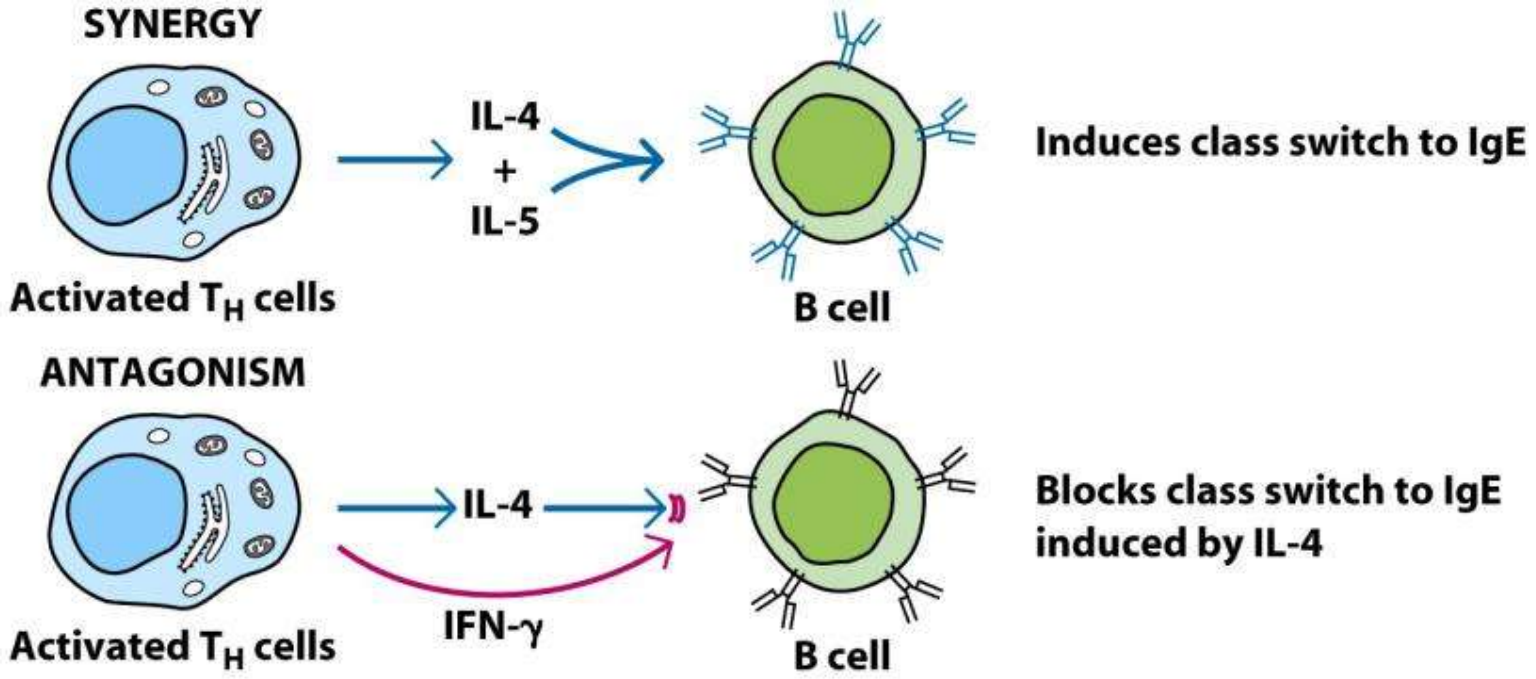


Figure 12-2a part 2
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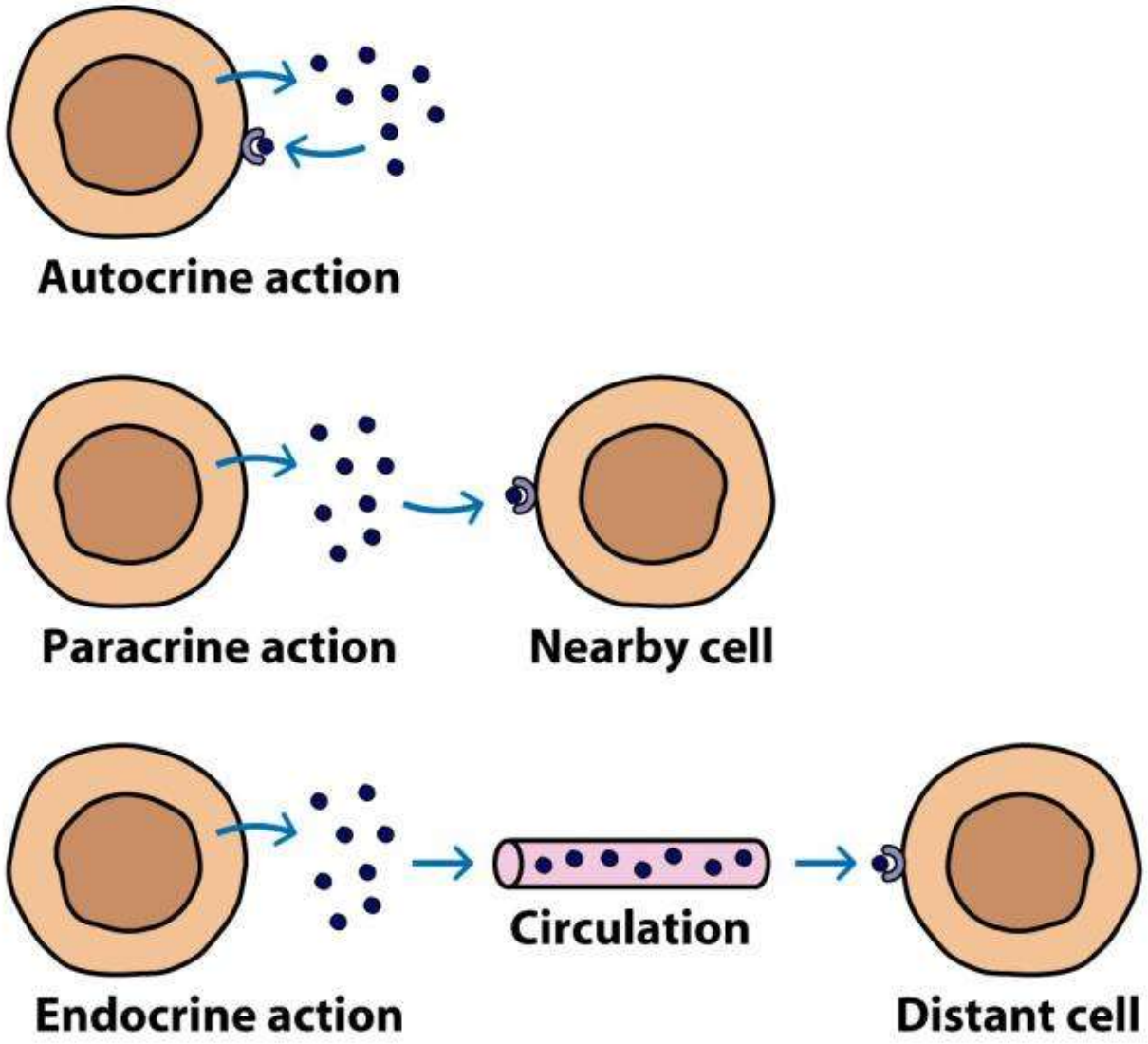

Figure 12-1b
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Cytokines

- There are **three functional categories of cytokines**:

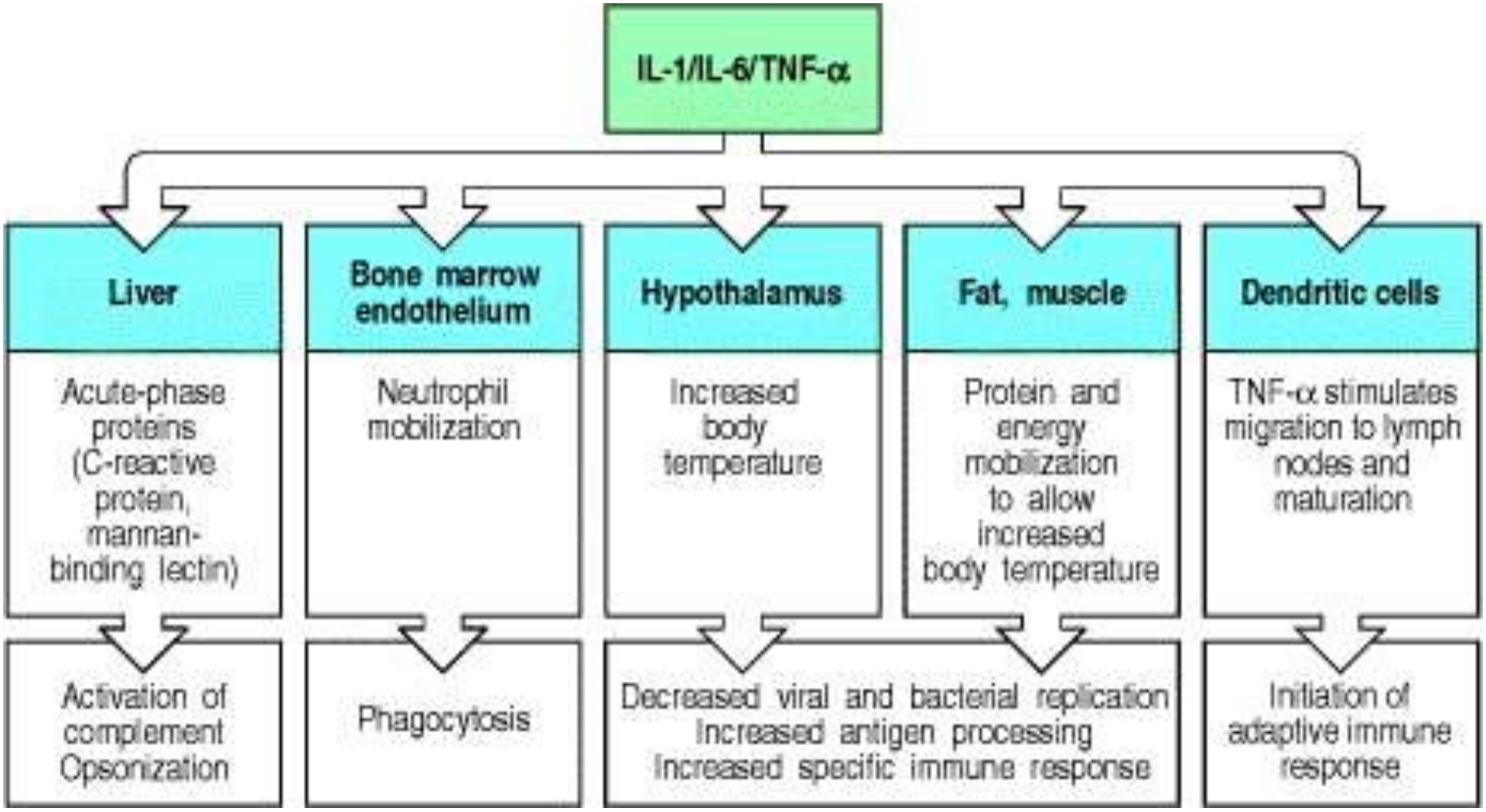
1. cytokines that produced by innate immune responses,
2. cytokines that produced by adaptive Immune responses, and
3. cytokines that stimulate hematopoiesis.

Features	Innate immunity	Adaptive immunity
Examples	*TNF-α*, IL-1, IL-12, IFN-γ *	IL-2, IL-4, IL-5, IFN-γ *
Major cell source	Macrophages, NK cells	T lymphocytes
Principal physiologic functions	Mediators of innate immunity and inflammation (local and systemic)	Adaptive immunity: regulation of lymphocyte growth and differentiation; activation of effector cells (macrophages, eosinophils, mast cells)
Stimuli	LPS (endotoxin), bacterial peptidoglycans, viral RNA, T cell–derived cytokines (IFN-γ)	Protein antigens
Amounts produced	May be high; detectable in serum	Generally low; usually undetectable in serum
Local or systemic effects	Both	Usually local only
Roles in disease	Systemic diseases (e.g., septic shock)	Local tissue injury (e.g., granulomatous inflammation)
Inhibitors of synthesis	Corticosteroids	Cyclosporine, FK-506

cytokines that produced by innate immune responses

- **cytokines that regulate innate immune responses are** produced primarily by mononuclear phagocytes, dendritic cells and NK (some of them called pro-inflammatory cytokines)

1. **Interleukin 1 (IL-1) and Tumor necrosis factor (TNF alpha) (PRO-INFLAMMATORY CYTOKINES); IL-1 function similarly to TNF in that it mediates acute inflammatory responses**. It also works synergistically with TNF to enhance inflammation.
    1. They stimulate the synthesis of adhesion factors on endothelial cells and leukocytes that help in cell migration
    2. They are both produced primarily by local activated monocytes, macrophages and by neutrophils.
    3. they produced in high quantity affecting on hypothalamus to increase prostaglandin syn. causing fever (endogenous pyrogens) (this is inhibited by aspirin)
    4. and stimulate the production of acute phase proteins from *liver*


IL-1/IL-6/TNF-α
Liver
Bone marrow endothelium
Hypothalamus
Fat, muscle
Dendritic cells
Acute-phase proteins (C-reactive protein, mannan-binding lectin)
Neutrophil mobilization
Increased body temperature
Protein and energy mobilization to allow increased body temperature
TNF-α stimulates migration to lymph nodes and maturation
Activation of complement Opsonization
Phagocytosis
Decreased viral and bacterial replication
Increased antigen processing
Increased specific immune response
Initiation of adaptive immune response

2. IL-12 is a primary mediator of immune responses to intracellular microbes (listeria, mycobacteria and viruses) produced by DC and macrophags

1. **It is an activator CD8 T cells differentiation,**
2. **TH1 cell differentiation when binding CD4 and APC include intacellular pathogen and CD40 and CD40L ligation**
3. **NK activation**
4. It also stimulates interferon-gamma production from these cells

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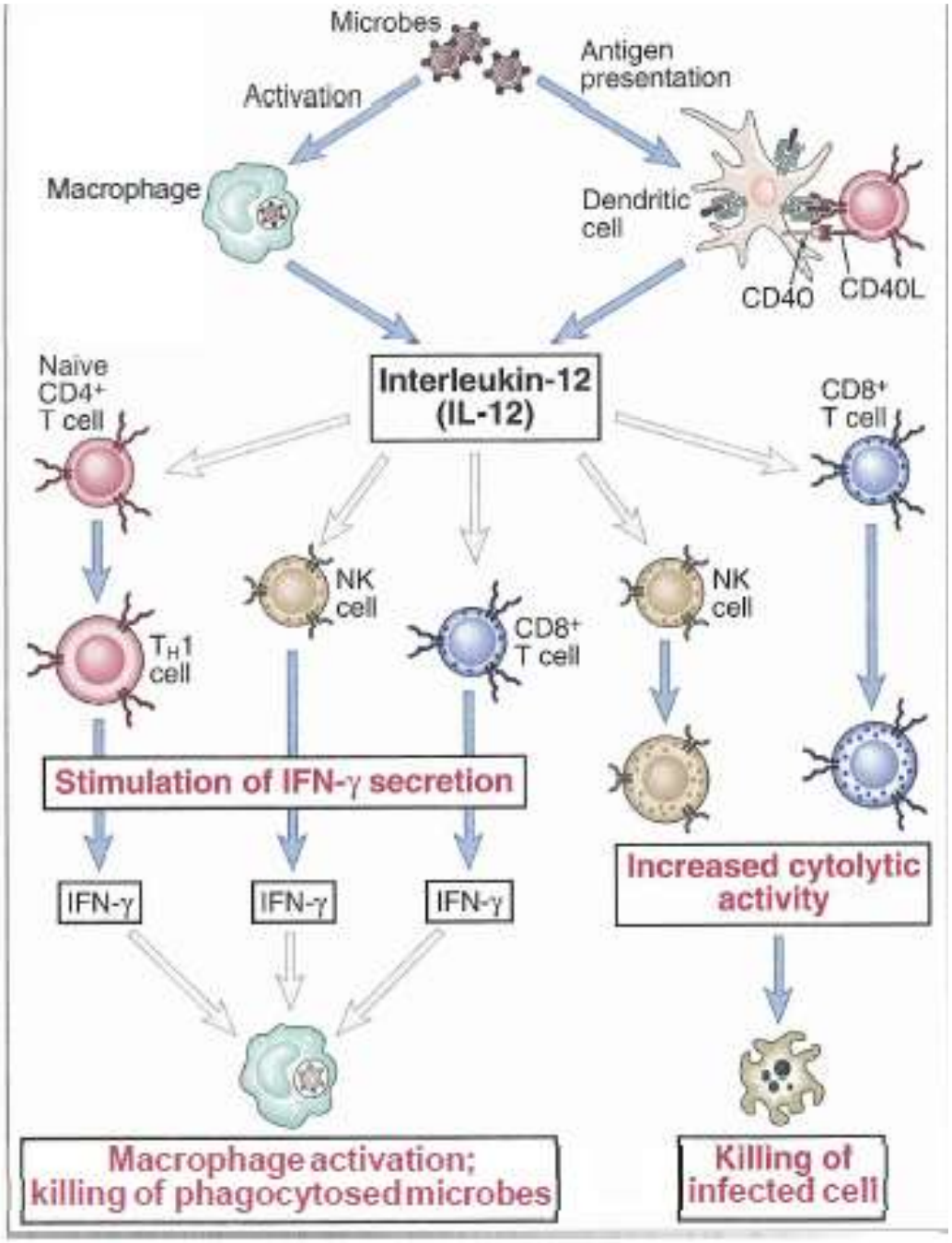

Microbes
Activation
Antigen presentation
Macrophage
Dendritic cell
CD40
CD40L
Naive CD4+ T cell
Interleukin-12 (IL-12)
CD8+ T cell
NK cell
NK cell
CD8+ T cell
TH1 cell
Stimulation of IFN-γ secretion
IFN-γ
IFN-γ
IFN-γ
Increased cytolytic activity
Macrophage activation; killing of phagocytosed microbes
Killing of infected cell

3. Chemokines

- Although there are exceptions, recruitment of neutrophils is mainly mediated by CXC chemokines, monocyte recruitment is more dependent on CC chemokines, and lymphocyte recruitment is mediated by both CXC and CC chemokines.
- Chemokines are required for the migration of immune cells from sites of infection into draining lymph nodes CC-chemokine receptor 7 (CCR7).
- Neutrophils express receptors for (IL-8) CXCL8 produced by tissue resident macrophages , the major chemokine supporting neutrophil migration into tissues.
- classical monocytes, express CCR2. This receptor binds chemokines for monocyte recruitment being CCL2

4. Type 1 interferon

- **Type I Interferons,** include 13 subtypes of interferon-alpha, interferon-beta and others. (There is only one **type II interferon**, interferon-gamma, which is involved in the innate and adaptive immune response.)

- The **most powerful stimulus for type I interferons is the first immune reaction against viral infection**
- produced by any virus-infected cell; act paracrine; **induce uninfected cells to produce enzymes capable of degrading viral mRNA**.(becomes virus resistant)ِ .Also as autocrine; **blocks viral protein synthesis** and replication in side the cell.
  - it also help in CD4 differentiation to TH1cells by increase expression of IL-12
  - and help in activation of CD8 cell in killing virus infected cells
  - Activate NK to act against the virus

1-Interferon-alpha (leukocyte) is produced by monocytes/macrophages;

2- interferon-beta (fibroblast) by virus-infected cells, and fibroblasts

5. IL-6 and IL-10

- **IL-6 functions to**
  - IL-6 is produced by macrophages, monocytes.(PRO-INFLAMMATORY CYTOKINE) **stimulate the liver to produce acute phase proteins**
  - **From TH2 to stimulates the differentiation and growth of B-lymphocytes .**
  - and to differentiate TH to TH17 if TGF beta present
- **IL-10 (regulatory cytokine) is**
  - **an inhibitor of activated macrophages and dendritic cells and as such, inhibit production of IL-12 and co-stimulator molecules like MHC2 (inhibit TH1, CD8)**
  - **regulates innate immunity and cell-mediated immunity**
  - IL-10 is produced mainly by Treg, and Th2 cells.

Cytokines that produced by Adaptive Immune Responses (Humoral Immunity and Cell-Mediated Immunity)

- Cytokines that regulate adaptive immunity are produced primarily by T-lymphocytes Examples include:

1. Interleukin-2 (IL-2) IL-2 (growth factor)
    1. is produced by DC and T cells, it is a growth factor for Th1, Th2 and CD8 -lymphocytes upon activation (3^{rd} signal) ,
2. Interleukin-4 (IL-4) IL-4 is
    1. a B cell growth major stimulus for production of IgE in B cells
    2. It also antagonizes the effects of interferon-gamma and thus inhibits cell-mediated immunity.
    3. IL-4 is produced mainly by Th2 cells and mast cells.
3. Interleukin-5 (IL-5) IL-5 is
    1. a growth and activating factor for eosinophils as a defense against helminths.
    2. It also stimulates the proliferation and differentiation of antigen-activated B-lymphocytes
    3. IL-5 is produced mainly by Th2 cells.
4. IL-13 by Th2 cells act on B cells

4. **Interferon-gamma (IFN-gamma).** Type II interferon is produced by activated TH1 , NK and CD8 to promote the activity of the cell-mediated immune system.against intracellular pathogen

-IFN-gamma is the principal cytokine for activating macrophages. It also promote cell-mediated immunity

- IFN-gamma inhibits the proliferation of Th2 cells;
- stimulates the production of IgG subclasses that activate the complement pathway and promote opsonization.

5. **Transforming growth factor-beta (TGF-beta)**

- regulatory cytokine functions to inhibit the proliferation and effector function of T-lymphocytes; inhibit the proliferation of B-lymphocytes; and inhibits macrophage function .

-TGF-beta is produced by T-reg.

- The generation of some regulatory T cells requires the cytokine TGF-β. And IL-2

-TGF beta with IL-6 lead to differentiation of TH17

6. .**Lymphotoxin (LT).** LT plays a role in the **recruitment and activation of neutrophils** and in lymphoid organogenesis. Being chemically similar to TNF, LT is also pro-**inflammatory responses** .LT is made by T-lymphocytes.

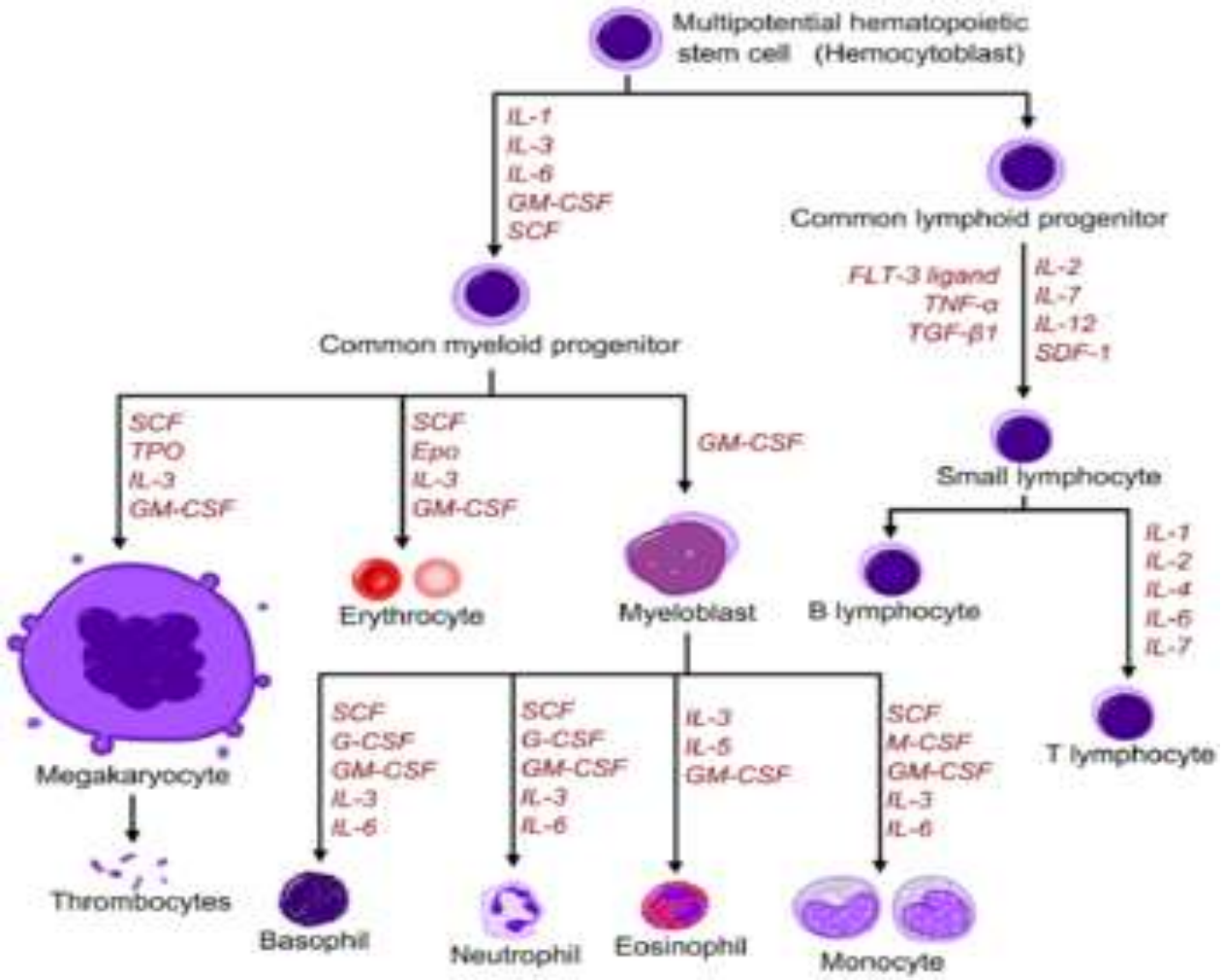
- The TH17 subset is primarily produce IL-17 that involved in
- recruiting neutrophils and macrophages to site of infection,
- inducing inflammation

Cytokines that Stimulate Hematopoiesis

- Produced by bone marrow stromal cells, these cytokines stimulate the growth and differentiation of immature leukocytes .Examples include:

1. Colony-stimulating factors (CSF) Promote the production of colonies of the different leukocytes in the bone marrow and enhance their activity .Examples include granulocyte macrophage colony stimulating factor (GM-CSF) granulocytes (neutrophils, eosinophils, and basophils) and monocytes. , granulocyte colony stimulating factor (G-CSF), and macrophage colony stimulating factor (M-CSF)
2. Stem cell factor. Stem cell factor makes stem cells in the bone marrow more responsive to the various CSFs

3. Interleukin-3 and IL-7, supports the growth of multi-lineage bone marrow stem cells .


Multipotential hematopoietic stem cell (Hemocytoblast)
IL-1
IL-3
IL-6
GM-CSF
SCF
Common lymphoid progenitor
FLT-3 ligand
TNF-α
TGF-β1
IL-2
IL-7
IL-12
SDF-1
Common myeloid progenitor
Small lymphocyte
SCF
TPO
IL-3
GM-CSF
SCF
Epo
IL-3
GM-CSF
GM-CSF
IL-1
IL-2
IL-4
IL-6
IL-7
Erythrocyte
Myeloblast
B lymphocyte
T lymphocyte
Megakaryocyte
SCF
G-CSF
GM-CSF
IL-3
IL-6
SCF
G-CSF
GM-CSF
IL-3
IL-6
IL-3
IL-5
GM-CSF
SCF
M-CSF
GM-CSF
IL-3
IL-6
Thrombocytes
Basophil
Neutrophil
Eosinophil
Monocyte

Cytokines and Ab differentiation

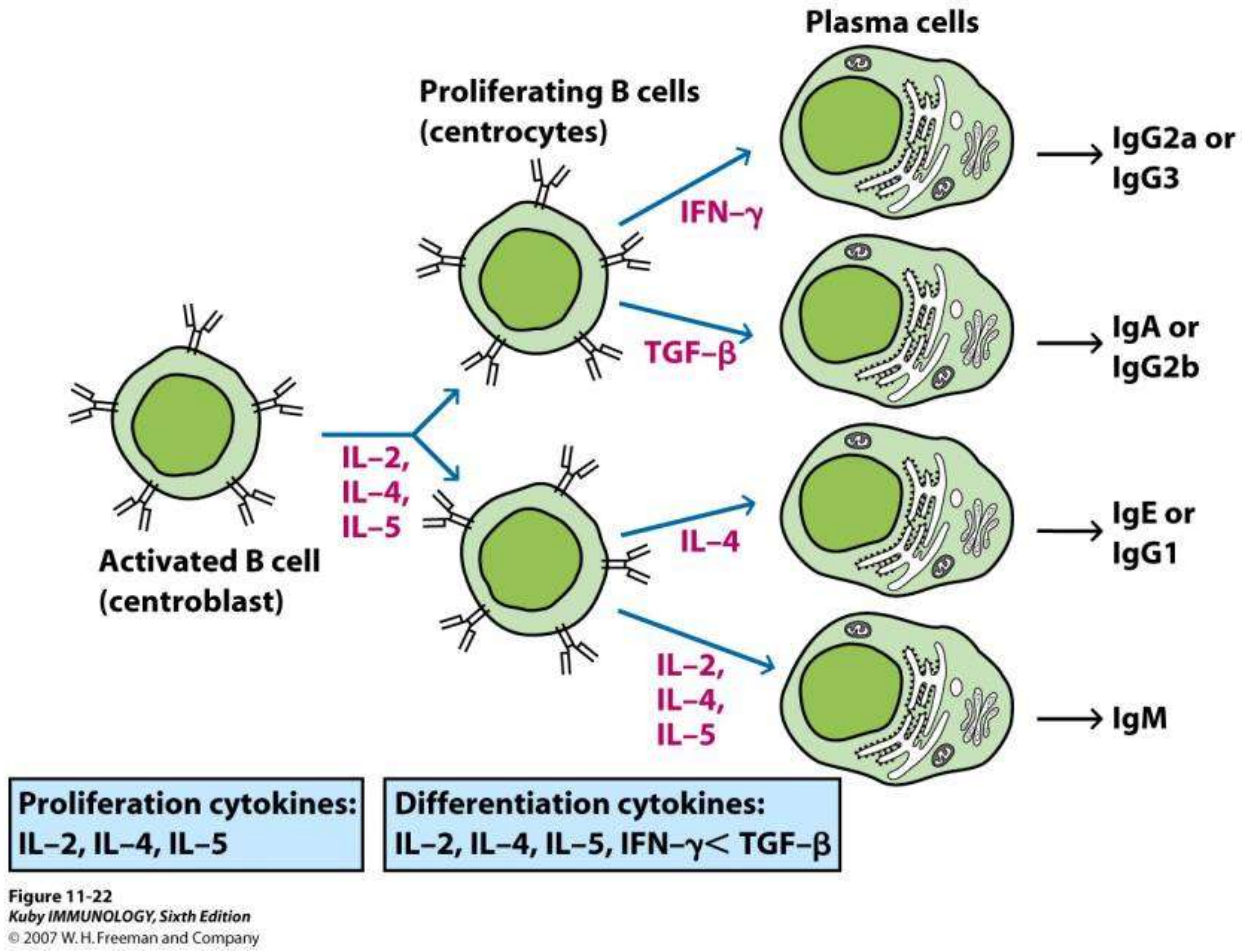


Figure 11-22
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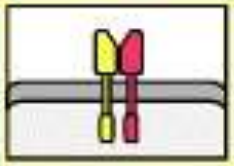
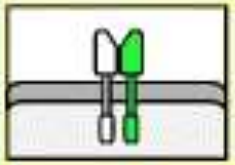
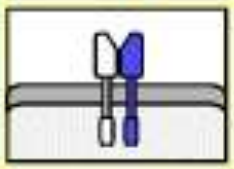
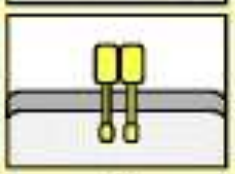
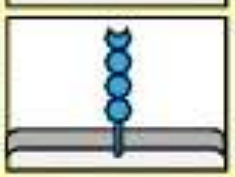
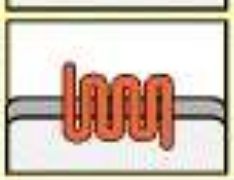
Cytokines receptors

Class I cytokine receptor (Hematopoietin-receptor family)		Receptors for erythropoietin, growth hormone, and IL-13
		Receptors for IL-3, IL-5, and GM-CSF share a common chain, CD131 or β_c (common beta chain)
		Receptors for IL-2, IL-4, IL-7, IL-9 and IL-15 share a common chain CD132 or γ_c (common gamma chain). IL-2 receptor also has a third chain, a high-affinity subunit IL-2Rα (CD25)
Class II cytokine receptor		Interferon-α, -β, and -γ receptor, IL-10 receptor
TNF-receptor family		Tumor necrosis factor (TNF) receptors I and II CD40, Fas (Apo 1), CD30, CD27, nerve growth factor receptor
Chemokine-receptor family		CCR1–5, CXCR1–4

Cytokine Receptors

- 5 Major Families
  - Immunoglobulin Superfamily
  - Hematopoietin Receptor Family (Class I)
  - Interferon Receptor Family (Class II)
  - TNF Receptor Family
  - Chemokine Receptor Family
- Class I and II (Majority Of Receptors)

- the TH1 cytokines, which secrete interferon (**IFN**)-γ, and the TH2 cells, which secrete **IL**-4, **IL**-5, **IL**-10.
- autoimmune disease is associated with the activation of TH1cytokines, which activate macrophages and drive an inflammatory **immune response** .In animal models of experimentally induced autoimmune disease, the relative activation of the TH1 is more than TH2 subsets of **T lymphocytes** .TH2 response that confers protection against disease can be manipulated by cytokines immunotherapy
- The preferential activation of TH 1or TH2 cells can be achieved by direct manipulation of the cytokine environment or by administering **antigen** by particular routes, for example by feeding

- **Immune modulation** aims to alter the balance between different subsets of responding **T cells** such that helpful responses are promoted and damaging responses are suppressed. As a therapy for autoimmunity (INCREASE TH2 RESPONSE) or in allergy (increase in TH1) it has the advantage that one might not need to know the precise nature of the autoantigen or allergen. However, the drawback of this approach is the unpredictability of the results.

Cytokine as a therapy

- Suppression of TH and Tc in auto-immune diseases by
  - Blocking antibodies against IL-2R
  - Or IL-2 analogue that prevent IL-2 binding
- using IL2 to activate lymphocytes to attack a cancer in a patient

Autoreactive T cell destruction

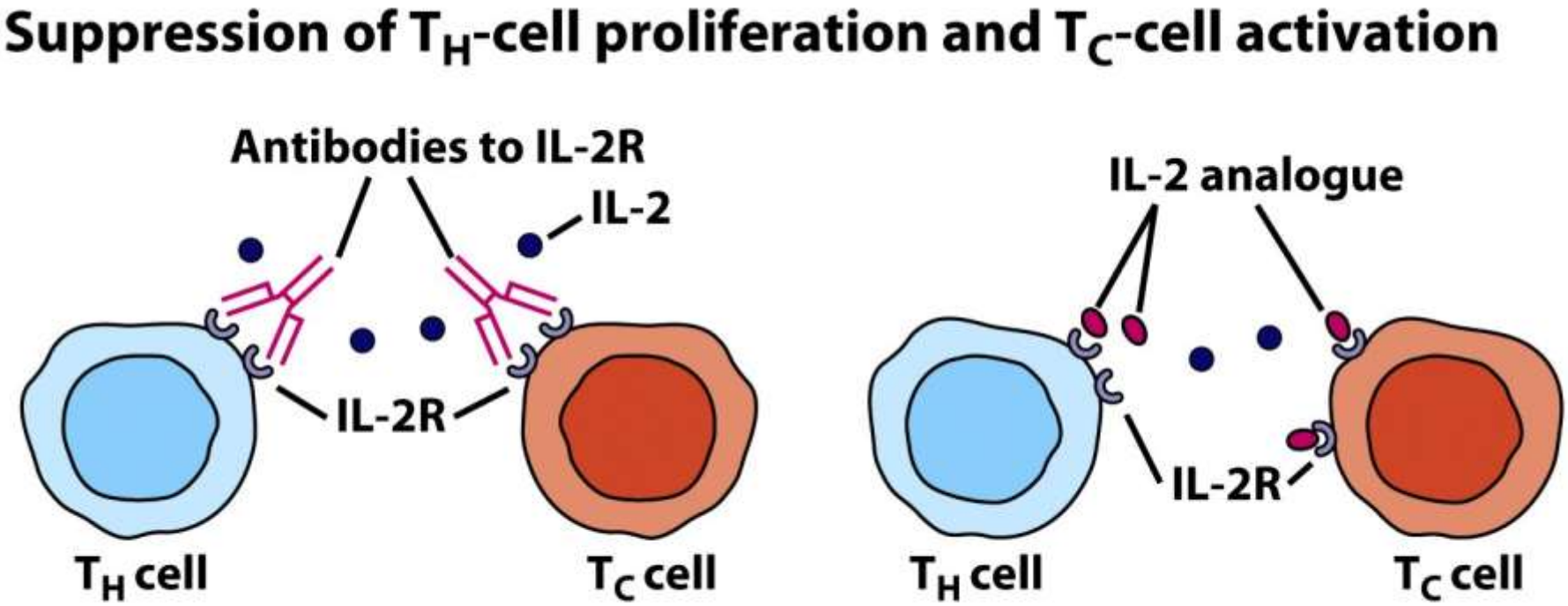


Figure 12-15a
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Autoreactive T cell destruction

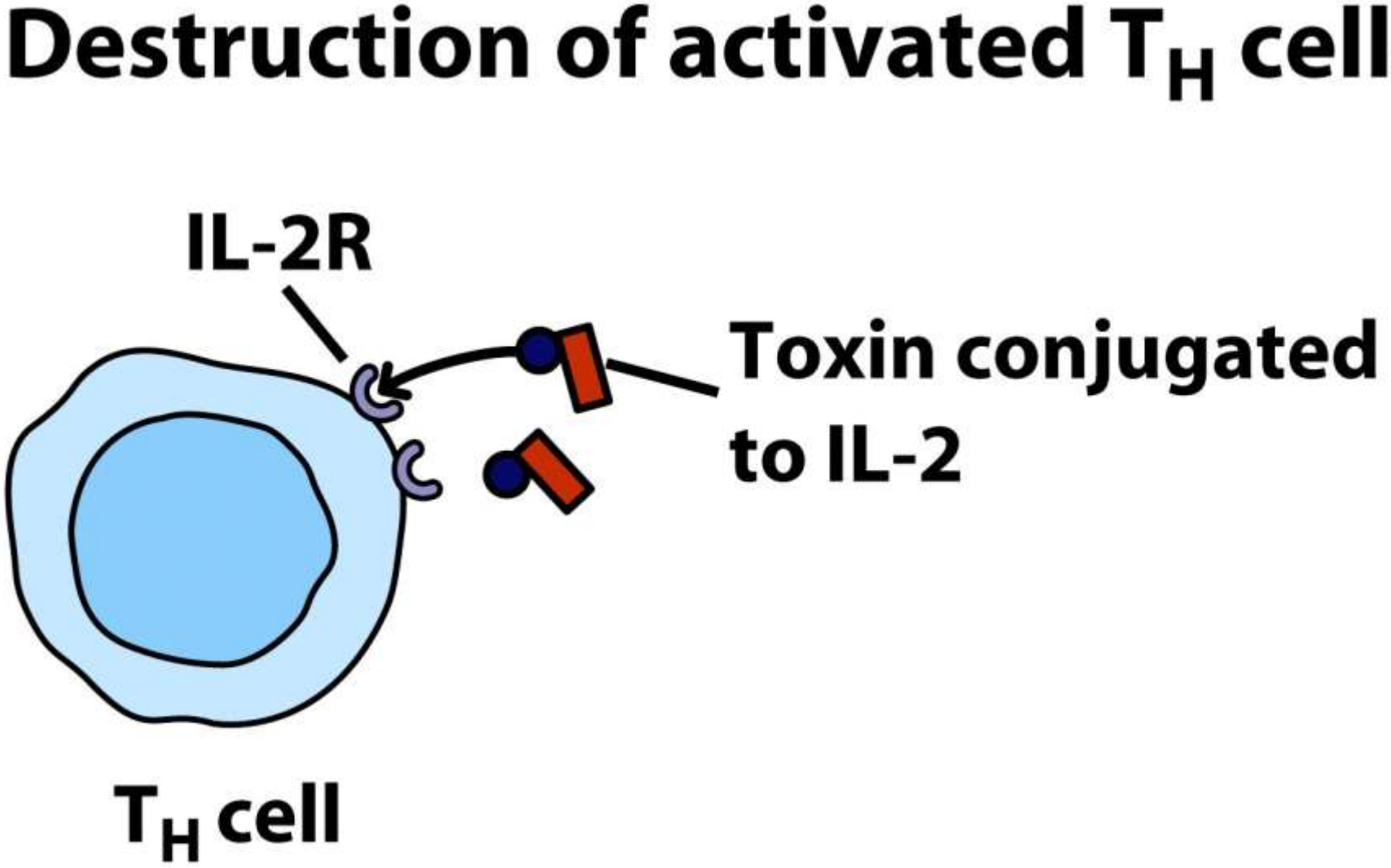

Figure 12-15b
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