Cytokines

Dr.Eman Albataineh,
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 target specific bind to specific cytokine receptors on other cells and do signal transduction with high affinity
- They are produced by virtually all cells involved in innate and adaptive immunity,
- 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.

Cytokine families

- the cytokine superfamily includes
  - interleukins,
  - chemokines,
  - colony-stimulating factors (CSF),
  - interferons,
  - Monokines and lymphokines.

Nomenclature...

- Interleukins – that act as mediators between leukocytes. The vast majority of these are produced by T-helper cells.
- Lymphokines – produced by lymphocytes.
- Monokines – produced exclusively by monocytes.
- Interferons – involved in antiviral responses.
- Colony Stimulating Factors – support the growth of cells blood cell .
- Chemokines – mediate chemoattraction (chemotaxis) between cells.

Functional features

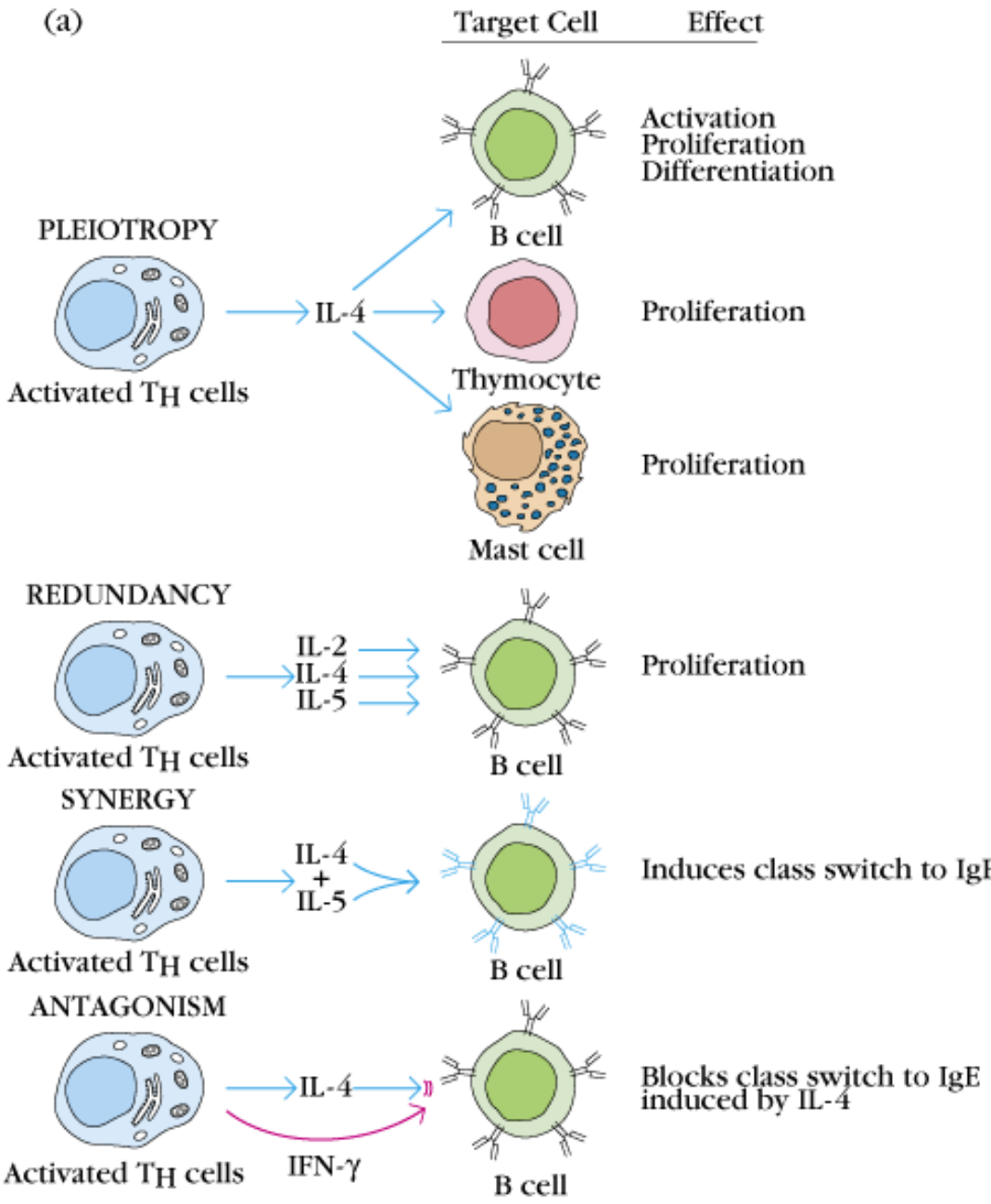
- Highly interactive

pleiotropic

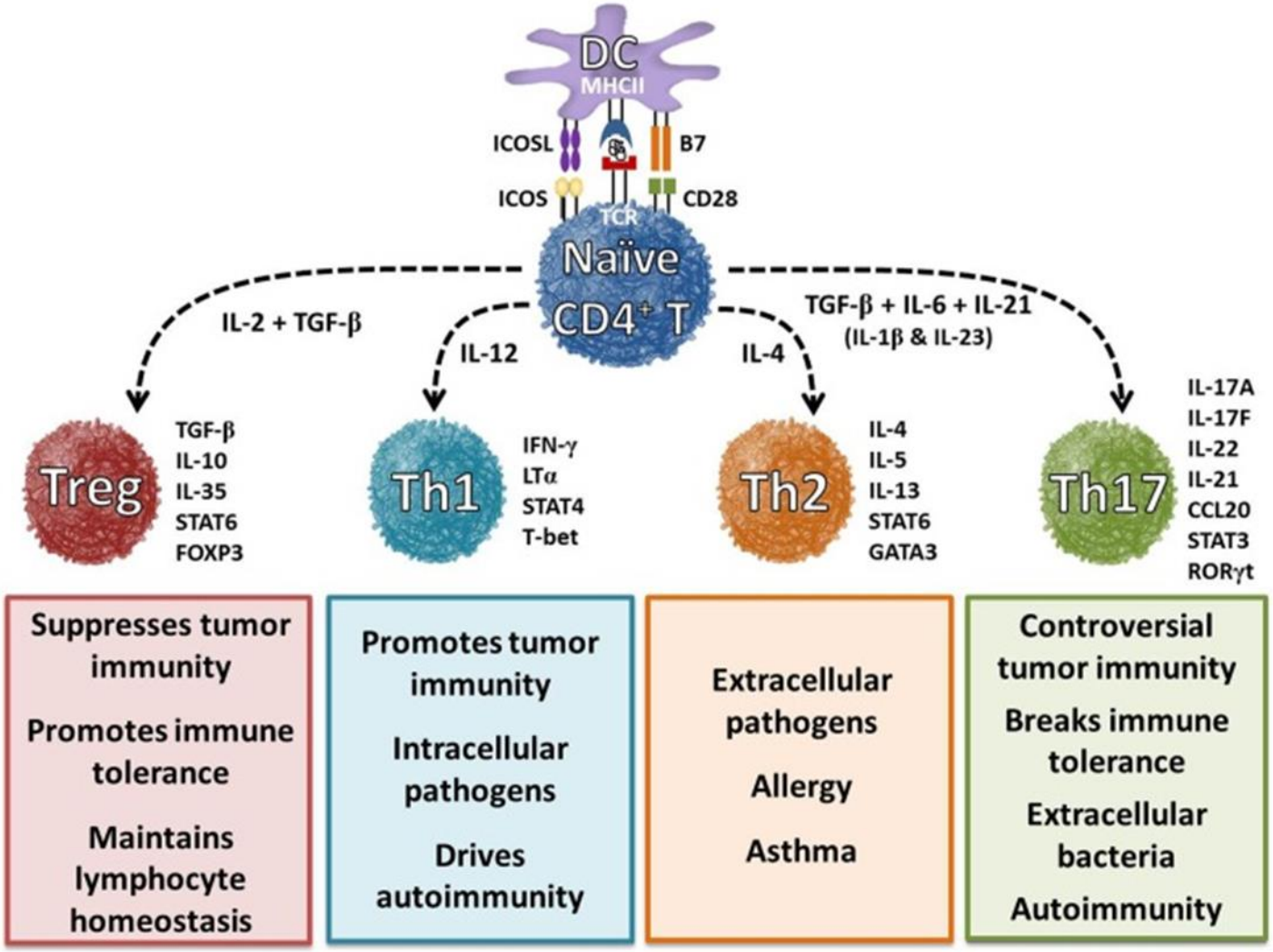
redundant

synergistic

antagonistic



Cascade effect



They can act locally or in a distance

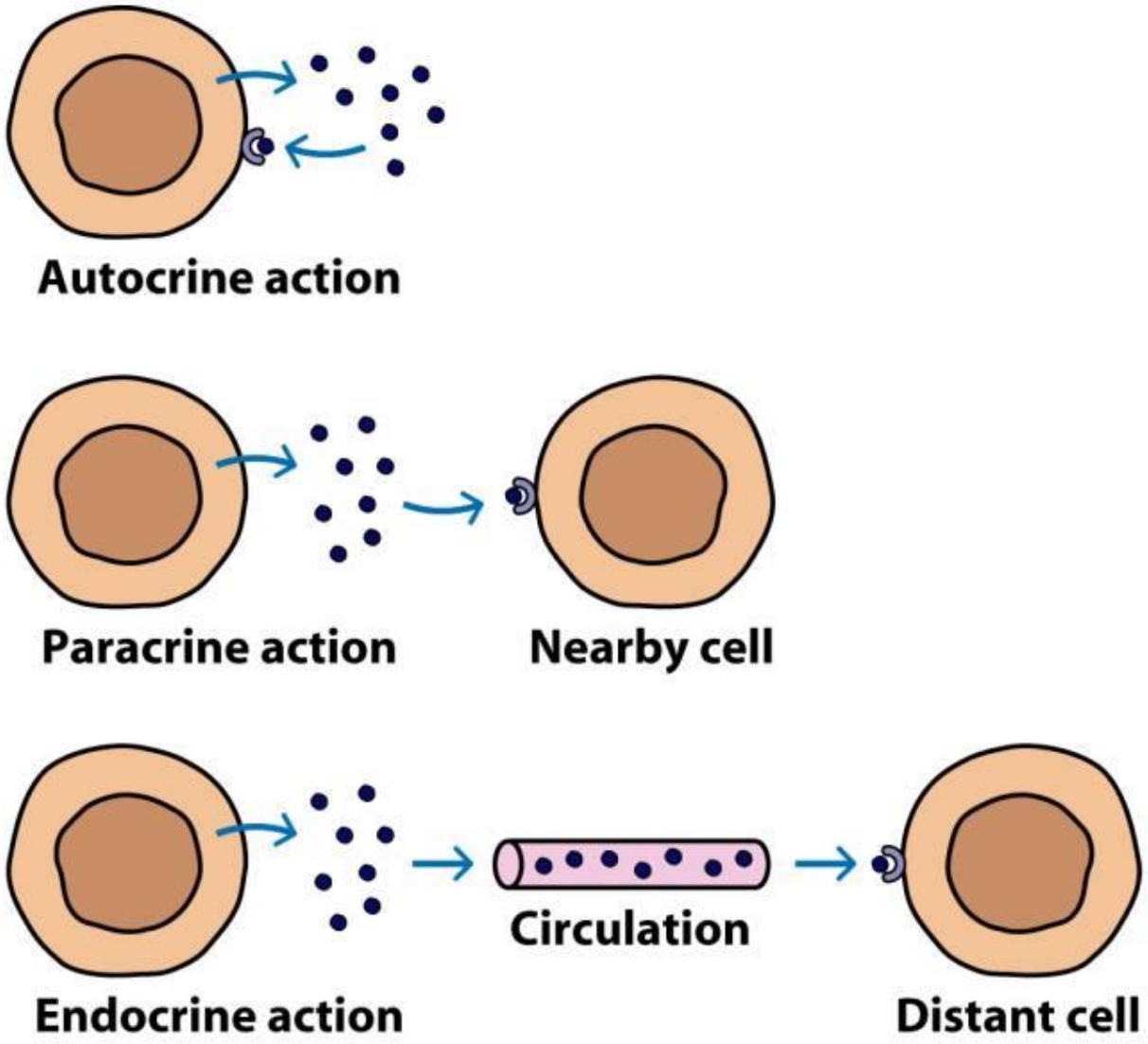


Figure 12-1b
Kuby IMMUNOLOGY, Sixth Edition

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.

Table 6.16 : Cytokines of innate immunity

Cytokine	Size	Principal cell sources	Principal cell targets and biological effects
Tumor necrosis factor (TNF)	17 kD; 51 kD homotrimer	Macrophages, T cells	Endothelial cells : activation (inflammation, coagulation) Neutrophils : activation Hypothalamus : fever Liver : synthesis of acute-phase proteins Muscle fat : catabolism (cachexia) Many cell types : apoptosis
Interleukin-1 (IL-1)	17 kD mature form, 33 kD precursors	Macrophages, endothelial cells, some epithelial cells	Endothelial cells : activation (inflammation, coagulation) Hypothalamus : fever Liver : synthesis of acute-phase proteins
Chemokines	8-12 kD	Macrophages, endothelial cells, T cells, fibroblasts, platelets	Leukocytes : chemotaxis, activation; migration into tissues
Interleukin-12 (IL-12)	Heterodimer of 35 kD + 40 kD subunits	Macrophages, dendritic cells	T cells : T_H1 differentiation NK cells and T cells : IFN-γ synthesis, increased cytolytic activity
Type I IFNs (IFN-α, IFN-β)	IFN-α : 15-21 kD IFN-β : 20-25 kD	IFN-α : macrophages IFN-β : fibroblasts	All cells : antiviral state, increased class I MHC expression NK cells : activation
Interleukin-10 (IL-10)	Homodimer of 34-40 kD, 18 kD subunits	Macrophages, T cells (mainly T_H2)	Macrophages, dendritic cells : inhibition of IL-12 production and expression of co-stimulators and class II MHC molecules
Interleukin-6 (IL-6)	19-26 kD	Macrophages, endothelial cells (mainly T_H2)	Liver : synthesis of acute-phase proteins B cells : proliferation of antibody-producing cells
Interleukin-15 (IL-15)	13 kD	Macrophages, others	NK cells : proliferation T cells : proliferation (memory CD^+ cells)
Interleukin-18 (IL-18)	17 kD	Macrophages	NK cells and T cells : IFN-γ synthesis

cytokines that produced by innate immune responses

.

- **Interleukin 1 (IL-1) and Tumor necrosis factor (TNF alpha) (PRO-INFLAMMATORY CYTOKINES); IL-1 function similarly to TNF produced by local macrophages and innate cells**
- **It mediates acute inflammatory responses at beginning of infection and help in stimulation the whole immune response**. It also works synergistically with TNF

IL-1 Cytokines – Key Mediators of Inflammation

Overview:

- IL-1 cytokines include **IL-1α** and **IL-1β**, primarily produced by activated macrophages, monocytes, and dendritic cells.
- **Functions**:
  - Promote inflammation by inducing the release of additional cytokines and chemokines.
  - Stimulate the liver to produce **acute-phase proteins** (e.g., C-reactive protein).
  - Induce **fever** by acting on the hypothalamus to increase prostaglandin syn. causing fever (endogenous pyrogens) (this is inhibited by aspirin)
- **Clinical Relevance:**
  - Overproduction of IL-1 is linked to **autoimmune diseases** such as **rheumatoid arthritis**. [IL-1 promotes the production of **inflammatory mediators** like IL-6, TNF-α, and prostaglandins, creating a **vicious cycle** of inflammation. This leads to persistent joint inflammation, a hallmark of rheumatoid arthritis].
  - IL-1 inhibitors are used as treatments in inflammatory diseases.
- IL-1α: Primarily **acts locally** at the site of inflammation [as an **alarm to** nearby immune cells].
- IL-1β: **Acts systemically,** contributing to fever and acute inflammation [Induces **acute-phase responses,** such as the production of C-reactive protein (CRP) by the liver].

TNF Cytokines – Regulators of Inflammation and Apoptosis

Overview:

- Members of the **TNF family** induce inflammation, immune responses, and cell death.
- Exist as **soluble** or **membrane-bound** forms.
- Key roles in tissue homeostasis, immune cell activation, and apoptosis.

Key Members:

•**TNF-α**:
- Produced by macrophages, T-cells, and fibroblasts.
- Promotes inflammation, fever, and endothelial activation.
- Contributes to autoimmune diseases (e.g., rheumatoid arthritis).

•**TNF-β** (Lymphotoxin):
- Produced by activated T-cells and B-cells.
- Plays a role in lymphoid organ development and inflammation.

•**Fas Ligand (FasL)**:
- Induces apoptosis in target cells.
- Important in maintaining immune homeostasis and preventing autoimmunity.

TNF Cytokines – Regulators of Inflammation and Apoptosis

Mechanism of Action:

- TNF-α binds to **TNFR1** and **TNFR2,** activating:
  - **NF-κB pathway**: Promotes inflammation and survival.
  - **Caspase pathway**: Induces apoptosis.
  - The final effect depends on balance between these two pathways
- FasL binds to **Fas receptors** → Activates caspases → Apoptosis.

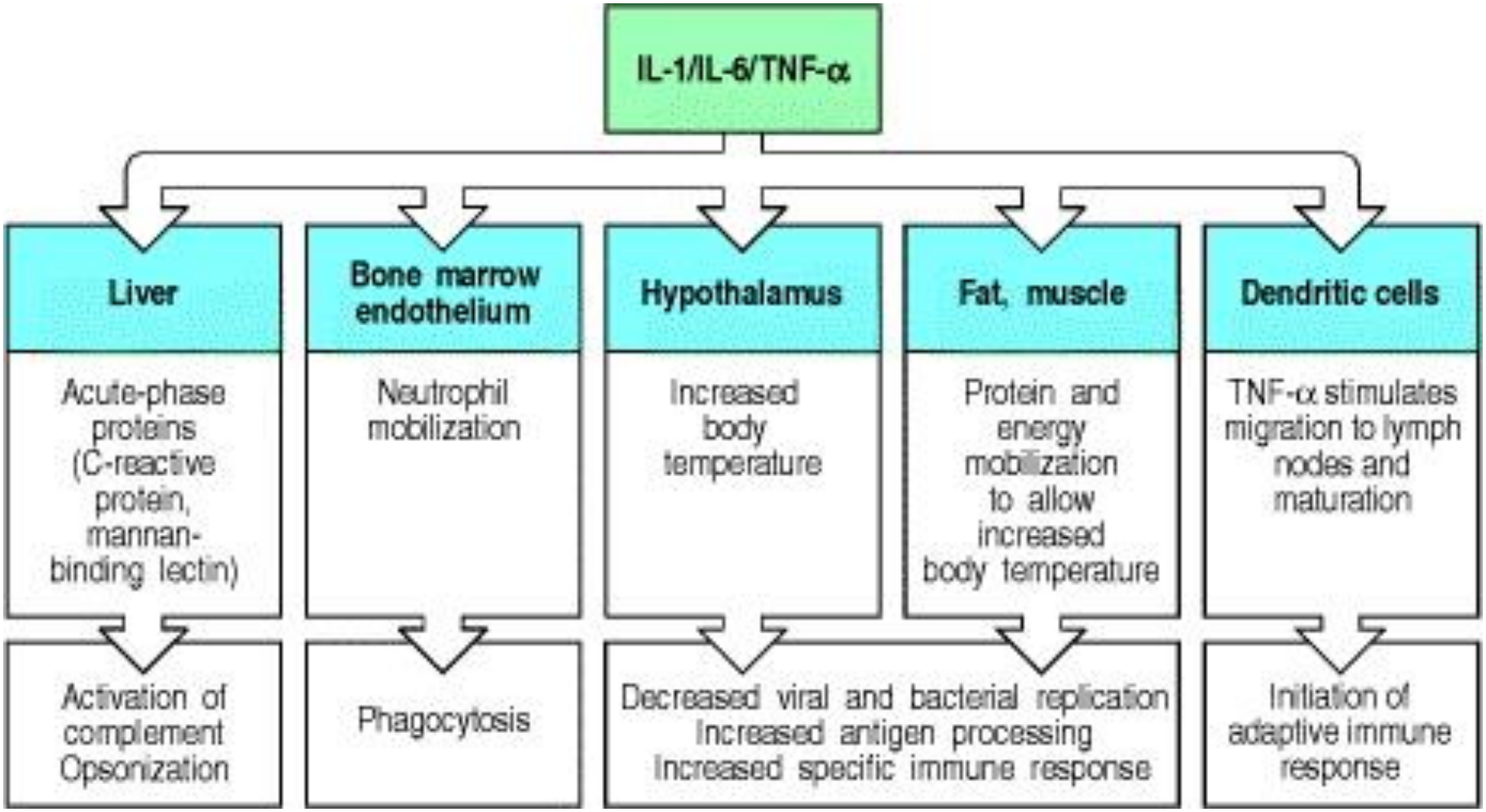
Clinical Relevance:

- **Overproduction of TNF-α**:
  - Linked to autoimmune diseases like **rheumatoid arthritis, Crohn's disease,** and **psoriasis**.

- **Therapeutic Targeting**:
  - Anti-TNF drugs reduce inflammation in autoimmune conditions.
  - FasL-targeted therapies in cancer and immune disorders [FasL-targeted therapies enhance anti-tumor immunity].

- **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 .**
  - **From B cells to activate TH2 cells**
  - Help in differentiation of TH17 if TGF beta present

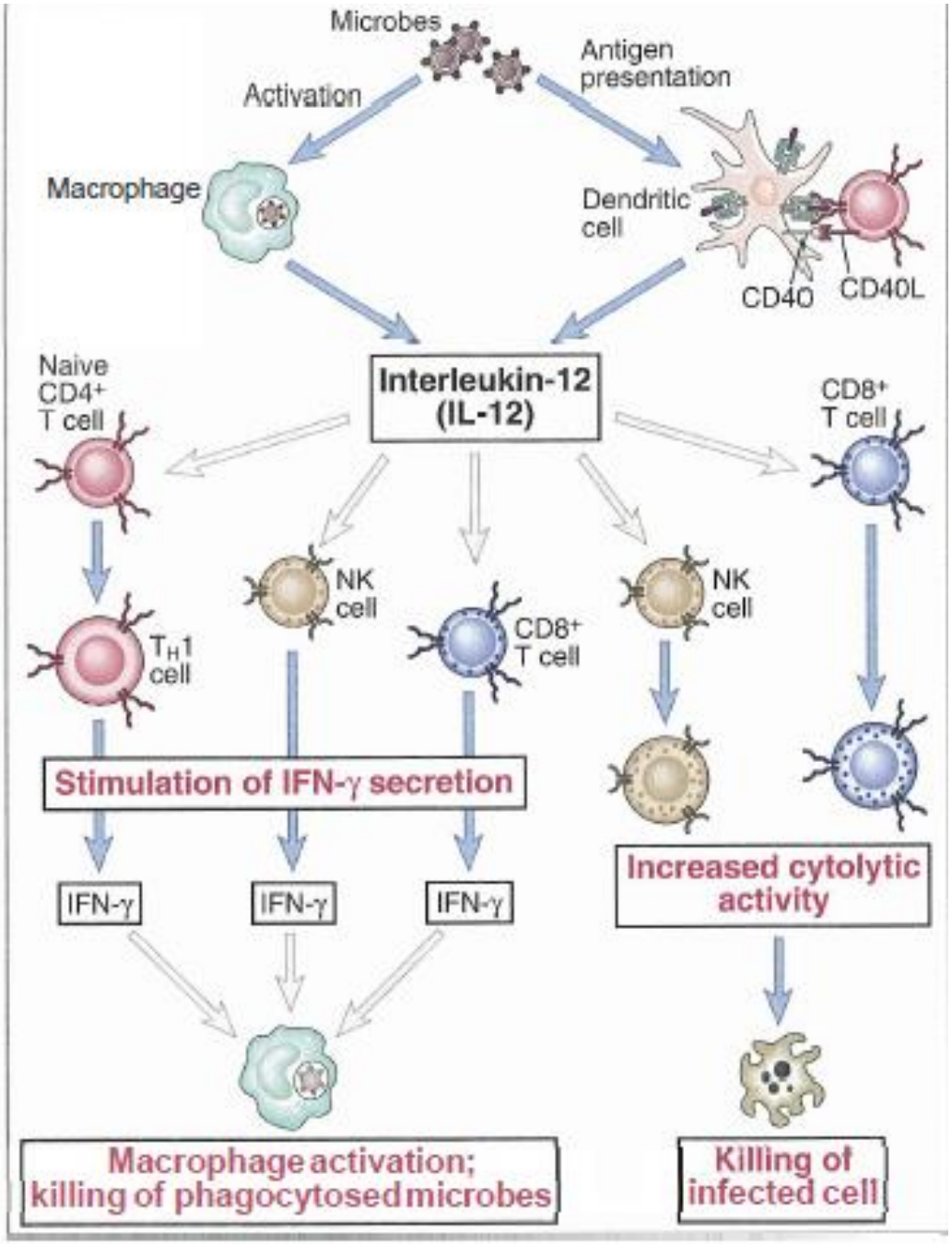
Proinflammatory cytokines



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**
3. **It also stimulates interferon-gamma production from CD8 and TH1 cells**
4. **Increase cytolytic activity of these cells**

.


Microbes
Antigen presentation
Activation
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

Chemokines

- Although there are exceptions, recruitment of neutrophils is mainly mediated by CXC chemokines, monocyte and eosinophil recruitment is more dependent on CCL chemokines, lymphocyte and mast cells 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 receptor binds CCL2 chemokines
- They also trigger intracellular signaling pathways.
- Clinical Relevance: the increase in
  - Chronic Inflammation:
  - Overexpression leads to diseases like rheumatoid arthritis and asthma.
- Therapeutic Targets:
  - Blocking chemokine receptors limits disease progression.

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 adaptive immune response.)
- The **most powerful stimulus for type I interferons is viral infection**
- **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.
  - and help in activation of CD8 cell in killing virus infected cells
  - Activate NK to act against the virus
  - Stimulates production of IFN-gamma by activated T cells

1-Interferon-alpha (leukocyte) is produced by monocytes/macrophages;
2- interferon-beta (fibroblast) by virus-infected cells, and fibroblasts

Table 6.17 : Cytokines of adaptive immunity

Cytokine	Size	Principal cell sources	Principal cell targets and biological effects
Interleukin-2 (IL-2)	14-17 kD	T cells	T cells : proliferation, increased cytokine synthesis; potentiates Fas-mediated apoptosis NK cells : proliferation, activation B cells : proliferation, antibody synthesis (*in vitro*)
Interleukin-4 (IL-4)	18 kD	$CD4^+$ T cells (T_H2), mast cells	B cells : isotype switching to IgE T cells : T_H2 differentiation, proliferation Macrophages : inhibition of IFN-γ mediated activation Mast cells : proliferation (*in vitro*)
Interleukin-5 (IL-5)	45-50 kD; homodimer of 20 kD subunits	$CD4^+$ T cells (T_H2)	Eosinophils : activation increased production B cells : proliferation, IgA production
Interferon-γ (IFN-γ)	50 kD (glycosylated); homodimer of 21 to 24 kD subunits	T cells (T_H1,$CD8^+$ T cells), NK cells	Macrophages : activation (increased microbial functions) B cells : isotype switching to opsonizing and complement-fixing IgG subclasses T cells : T_H1 differentiation Various cells : increased expression of class I and class II MHC molecules, increased antigen processing and presentation to T cells
Transforming growth factor-β (TGF-β)	25 kD homodimer of 12.5 kD subunits	T cells, macrophages, other cell types	T cells : inhibition of proliferation and effector functions B cells : inhibition of proliferation; IgA production Macrophages : inhibition
Lymphotoxin (LT)	21-24 kD secreted as homotrimer or associated with $LT\beta_2$ on the cell membrane	T cells	Recruitment and activation of neutrophils lymphoid organogenesis
Interleukin-13 (IL-13)	15 kD	$CD4^+$ T cells (T_H2)	B cells : isotype switching to IgE Epithelial cells : increased mucus production Macrophages : inhibition

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 and B cells, it is a growth factor for Th1, Th2, TH17, B , Treg and CD8 -lymphocytes upon activation (3rd signal),
    2. B7 ligates T cell CD28, activating the T cell to produce IL-2 and its receptor (IL-2R). The cytokine acts in an autocrine fashion. The cell divides and differentiates into an effector T cell
2. Interleukin-4 (IL-4) IL-4 is
    1. 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 B cells and DC.
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

5. **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 by activating CD8 and NK

- Help in priming of Th1 cells

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

6. **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 from CD4 cells requires the cytokine TGF-β. And IL-2

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

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

8. IL-10

- **IL-10 (regulatory cytokine) is**
  - **An inhibitor of activated macrophages and dendritic cells**
  - **Inhibit production of IL-12 and co-stimulator molecules like MHC2 (inhibit TH1, TH2 and CD8)**
  - **Regulates innate immunity and cell-mediated and humoral immunity**
  - IL-10 is produced mainly by Treg, and Th2 cells.

IL-17 Cytokines – Drivers of Inflammation

Overview:

- **IL-17 family** cytokines are involved in:
  - **Inflammation**.
  - **Host defense** against extracellular pathogens.
  - **Autoimmune disease pathogenesis**.
- Produced mainly by **Th17 cells**, a subset of CD4+ T cells.

Key Members:

- **IL-17A**: The prototype cytokine, drives inflammation and **neutrophil recruitment**.
- **IL-17C, IL-17D, IL-17E (IL-25), IL-17F**: Involved in tissue-specific immunity and inflammation.

IL-17 Cytokines – Drivers of Inflammation

Functions:

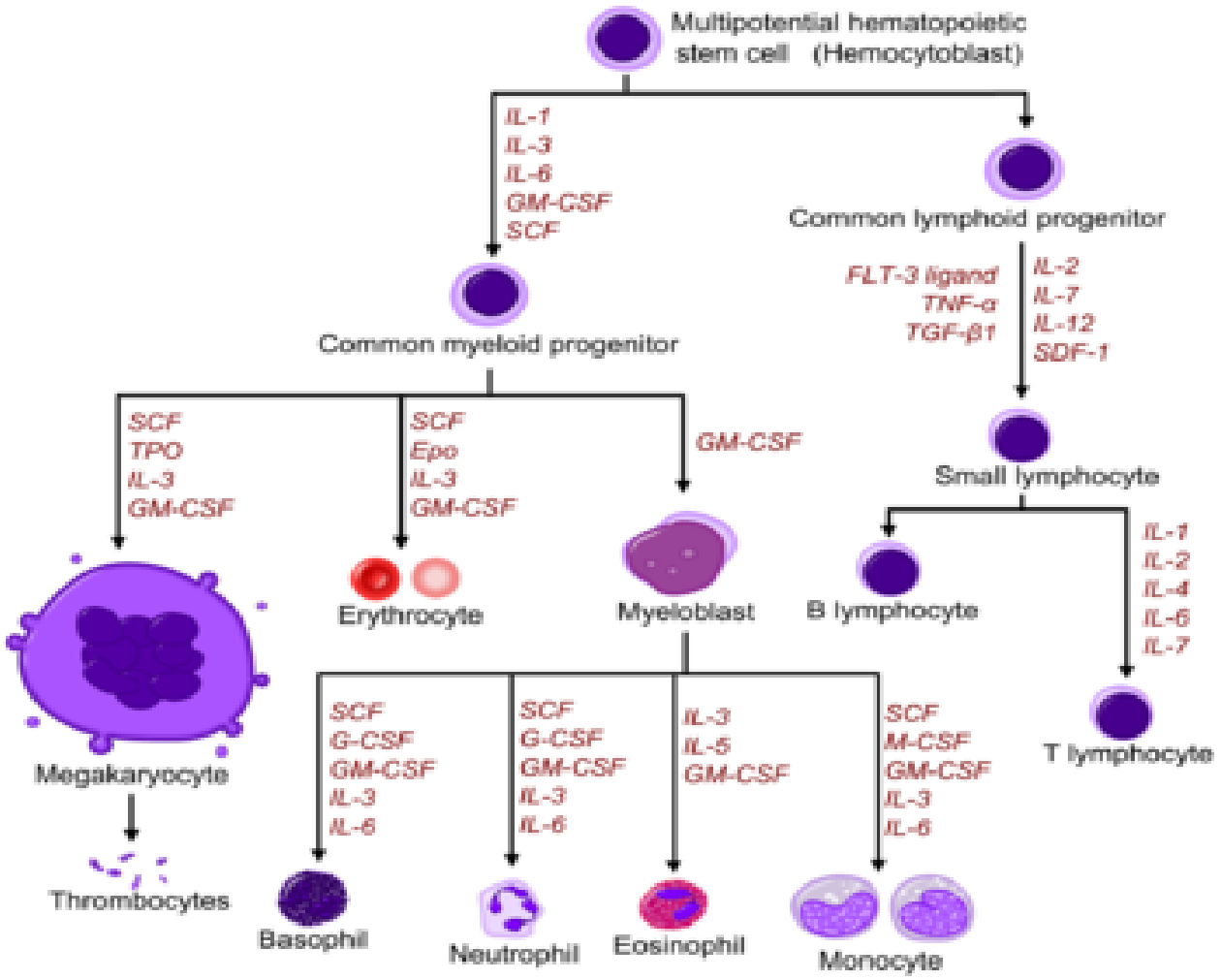
- **Promotes Inflammation**:
  - Stimulates production of pro-inflammatory cytokines (e.g., IL-6, TNF-α).
  - Induces chemokines **for neutrophil recruitment.**
- **Host Defense**:
  - Essential for defense against fungal (e.g., *Candida*) and bacterial infections (e.g., *Staphylococcus*).
- **Autoimmune Diseases**:
  - Overexpression linked to conditions like **psoriasis,** and **rheumatoid arthritis**.

Clinical Relevance:

- **IL-17 in Autoimmunity**:
  - Dysregulated IL-17 levels drive chronic inflammation in diseases like psoriasis.
- **Therapeutic Targeting**:
  - Anti-IL-17 monoclonal antibodies are used in treating psoriasis.

Cytokines that Stimulate Hematopoiesis

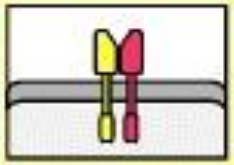
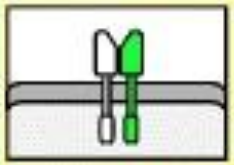
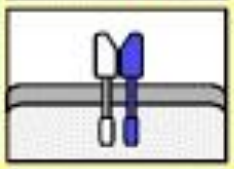
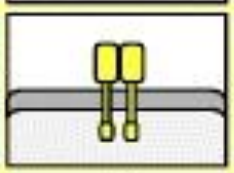
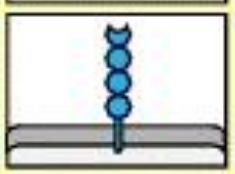
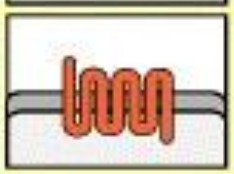
1. Colony-stimulating factors (CSF) Promote the production of colonies of the different leukocytes in the bone marrow and enhance their activity .Examples include granulocyte macrophage colony stimulating factor (GM-CSF) granulocytes (neutrophils, eosinophils, and basophils) and monocytes. , granulocyte colony stimulating factor (G-CSF), and macrophage colony stimulating factor (M-CSF)
2. Erythropoietin for RBC production
3. 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 .
4. Clinically; used to stimulate production of blood cells after bone marrow transplantation and in immune deficiency diseases


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

Hypercytokinemia: The Cytokine Storm

- **Definition**: Cytokine interactions regulate immunity. Excess cytokine production can lead to inappropriate immune responses.
- **What Happens?**
  - Overproduction of cytokines → Immune hyperstimulation → **Cytokine Storm**
  - Can cause **shock, multiorgan failure, or death**.
- **Pathogen Examples**: superantigens
  - Viruses: Influenza A, SARS-CoV-2.
  - Bacteria: Streptococcus spp., Staphylococcus spp.
- **Clinical Implication**:
  - Cytokine storms disrupt immunity, turning protective mechanisms into harmful ones.

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)

Cytokine as a biologic therapy

- Suppression of TH1 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
- Anti-IL2 R in treat T cell leukemia
- Anti-IL2 R to reduce graft rejection
- Anti-TNF and anti-IL6 in autoimmune rheumatoid arthritis
- Anti-IL4 as trial in allergy
- Interferons in Kaposi sarcoma and hepatitis b and hairy cell leukemia

Autoreactive TH1 cell destruction

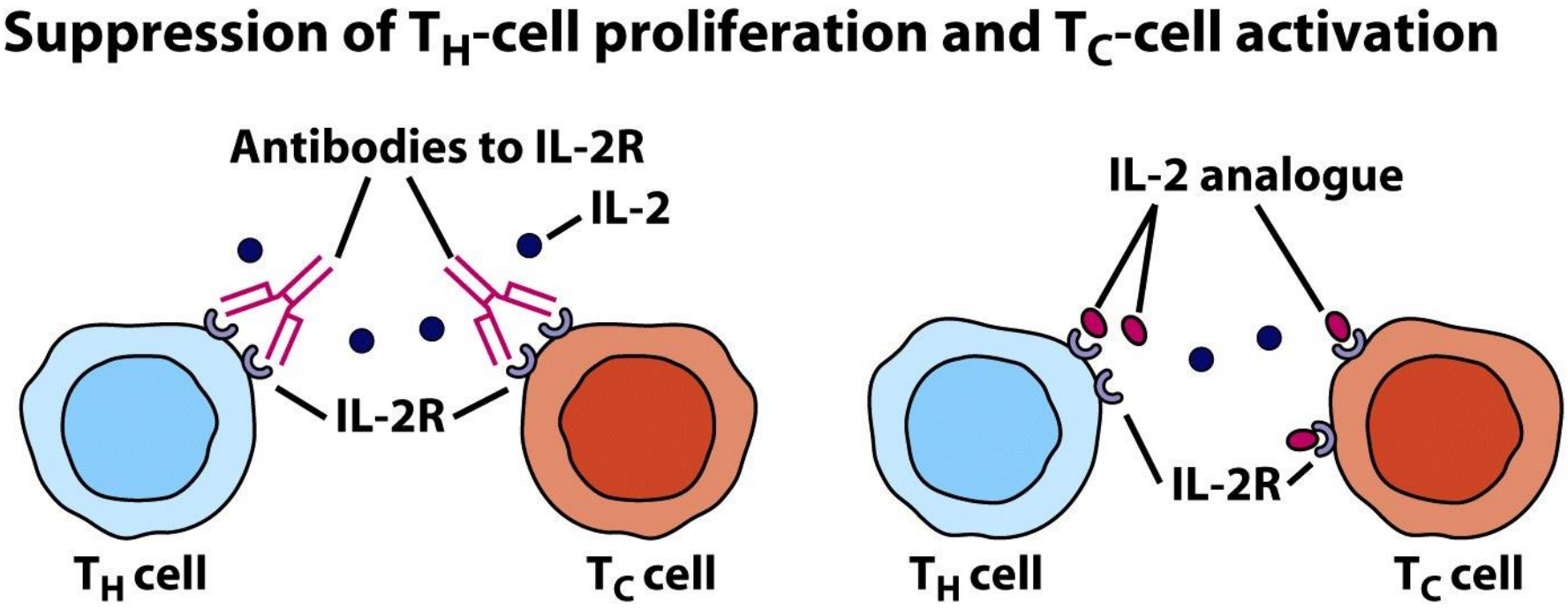


Figure 12-15a
Kuby IMMUNOLOGY, Sixth Edition

Autoreactive TH1 cell destruction

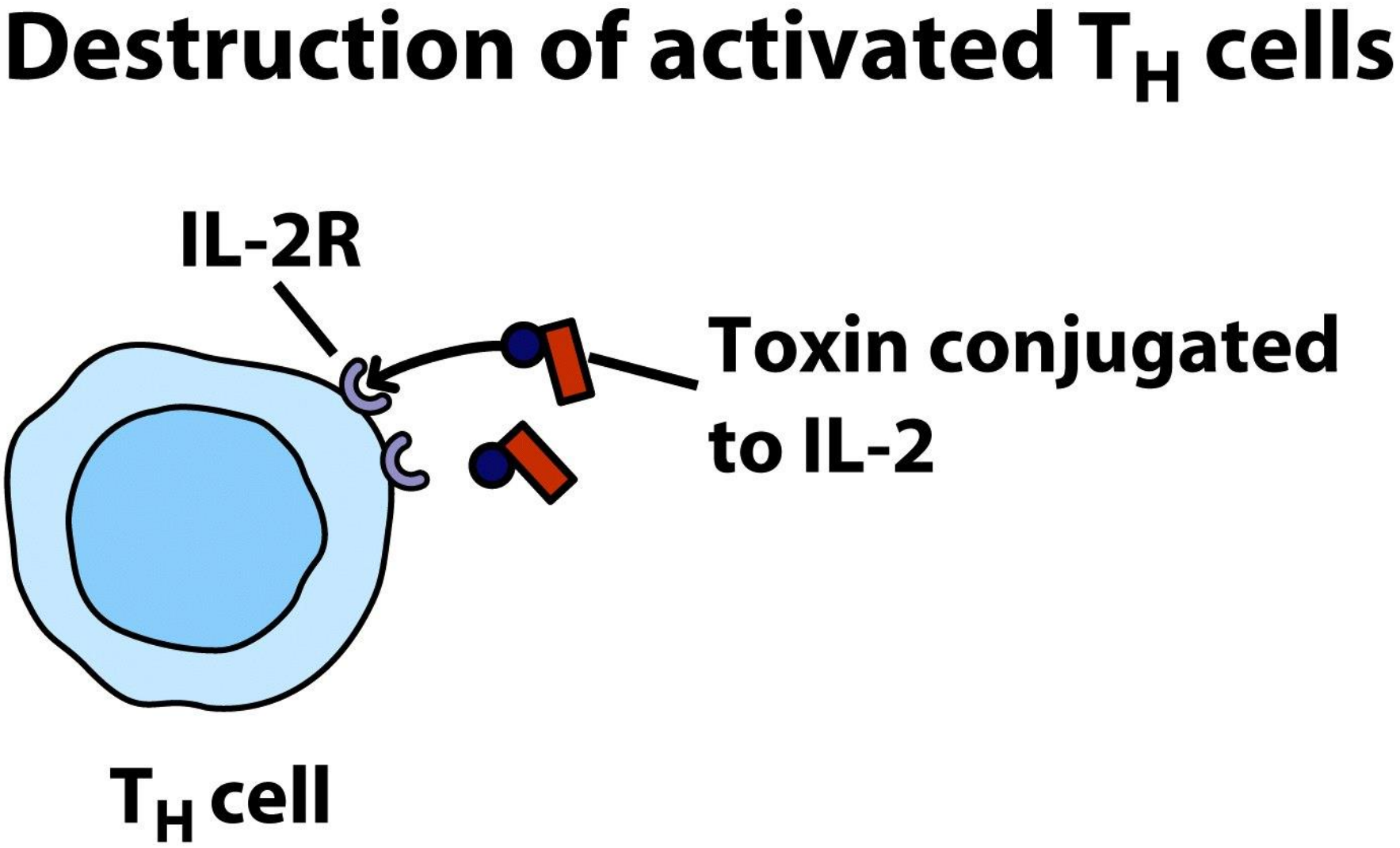


Figure 12-15b
Kuby IMMUNOLOGY, Sixth Edition