



# NOVA

Charting New Horizons in Education

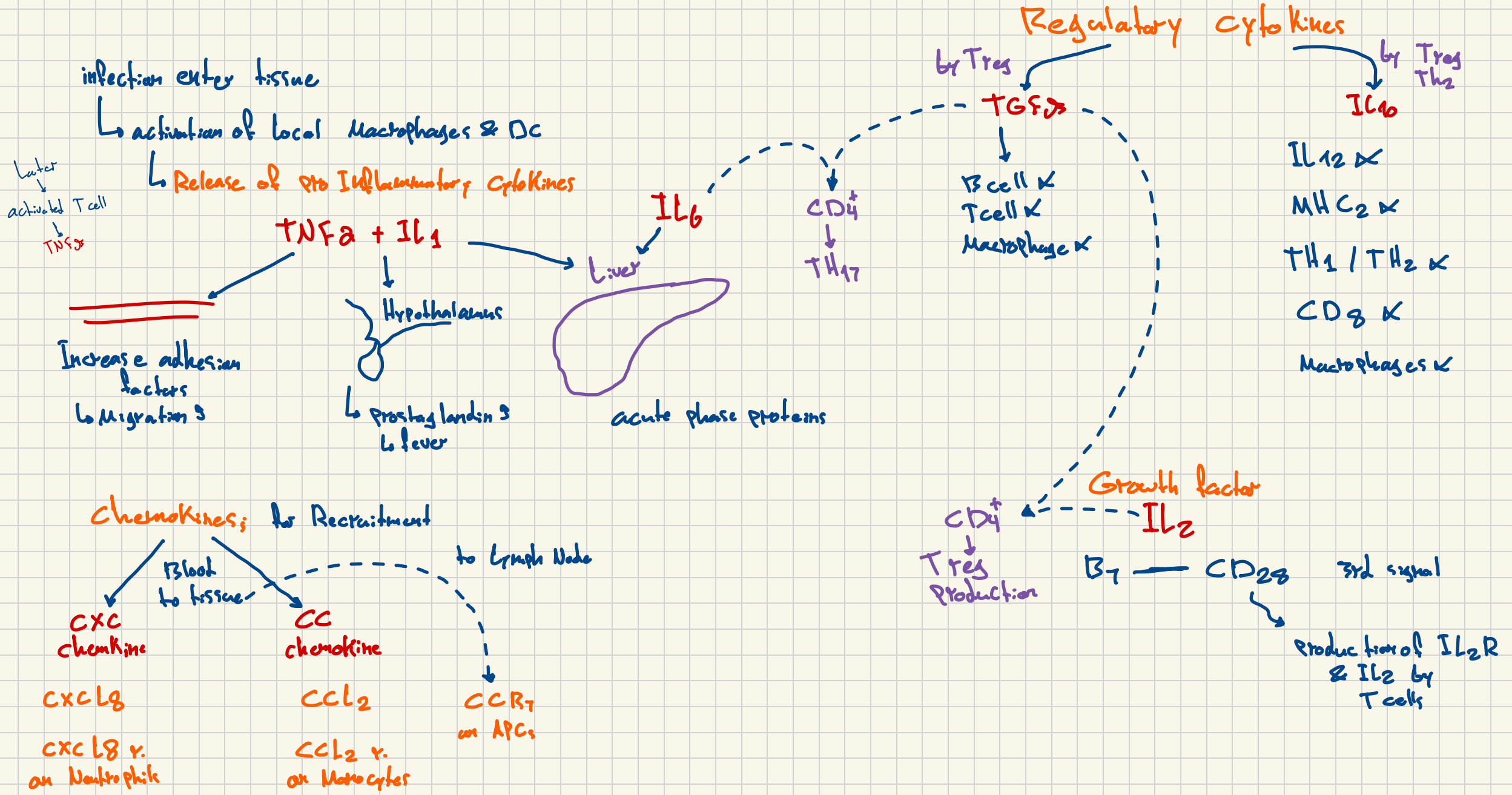
Intro Cytokines Polism

## Cytokines

# 9

Part 2  
Immunology



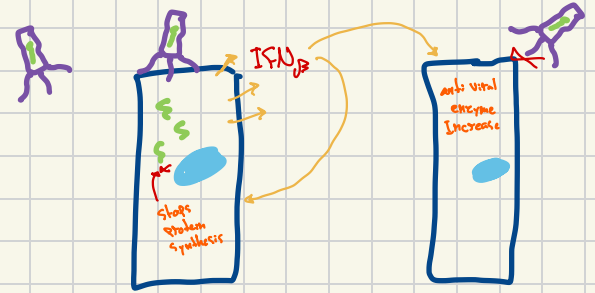


Intra cellular Microbe

Infects cells

↳ activation of DC & Macrophages

↳ stimulate production of



IL12 production

IFN<sub>α</sub> + IFN<sub>β</sub>

CD4<sup>+</sup>

TH<sub>1</sub>

CD8<sup>+</sup>

Cytotoxic

Stimulate secretion

IFN<sub>γ</sub>

activates Macrophages

IgG production

activates NK

extra cellular Microbe

↳ TH<sub>2</sub> activation

IL<sub>4</sub>

B cell growth  
IgE production

IL<sub>13</sub>

eosinophil activation  
against helminths

IL<sub>5</sub>

# VA Definition of Cytokines



Cytokines are low molecular weight, soluble proteins produced in response to an **antigen**, functioning as chemical messengers that regulate the **innate** and **adaptive immune systems**.

- Production:** Produced by virtually all cells involved in **innate** and **adaptive immunity**.
- Mechanism:** Cytokines bind to specific **cytokine receptors** on other immune cells to influence their activity.

## Characteristics of Cytokines:

- Pleiotropic:** A particular cytokine can act on multiple cell types, not just a single cell type.
- Redundant:** Different cytokines can perform the same function.
- Multifunctional:** A single cytokine can regulate various functions.
- Cytokines can act **locally** or **at a distance**.

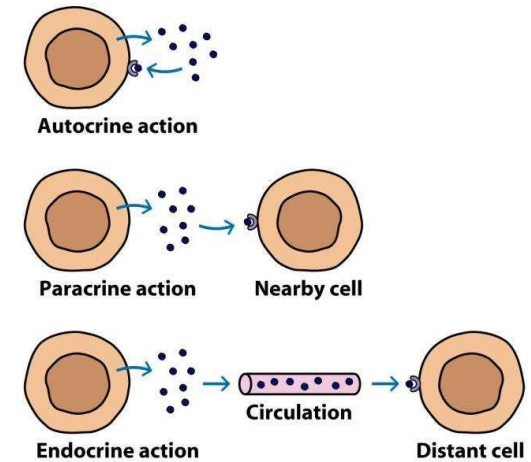
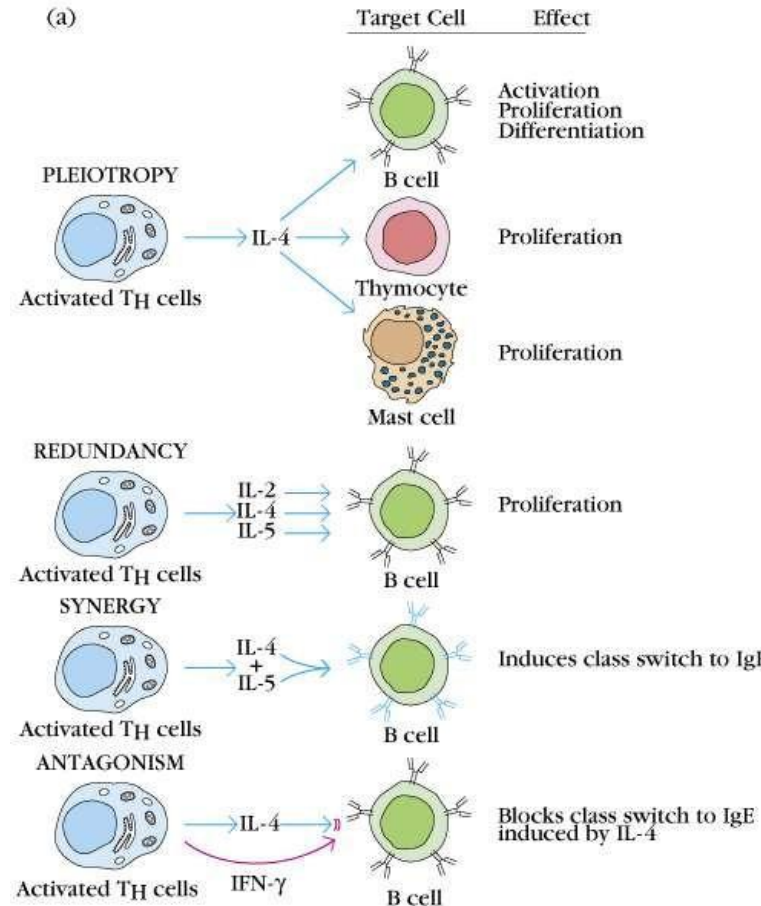


Figure 12-1b  
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# cytokine superfamily



- **Interleukins:** Act as mediators between **leukocytes** and are primarily produced by **T-helper cells**.
- **Lymphokines:** Produced by **lymphocytes**.
- **Monokines:** Produced exclusively by **monocytes**.
- **Interferons:** Involved in **antiviral responses**.
- **Colony-Stimulating Factors (CSF):** Support the growth of **blood cells**.
- **Chemokines:** Mediate **chemoattraction (chemotaxis)** between cells

- Functional Categories of Cytokines;
  1. Cytokines produced by innate immune responses
  2. Cytokines produced by adaptive immune responses
  3. Cytokines that stimulate hematopoiesis

Features	Innate immunity	Adaptive immunity
Examples	TNF- $\alpha$ , IL-1, IL-12, IFN- $\gamma$ *	IL-2, IL-4, IL-5, IFN- $\gamma$ *
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- $\gamma$ )	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 Produced by Innate Immune Responses

These cytokines are primarily produced by mononuclear phagocytes, dendritic cells, and natural killer (NK) cells. Some are referred to as pro-inflammatory cytokines

# Interleukin 1 (IL-1) and Tumor Necrosis Factor (TNF-alpha)



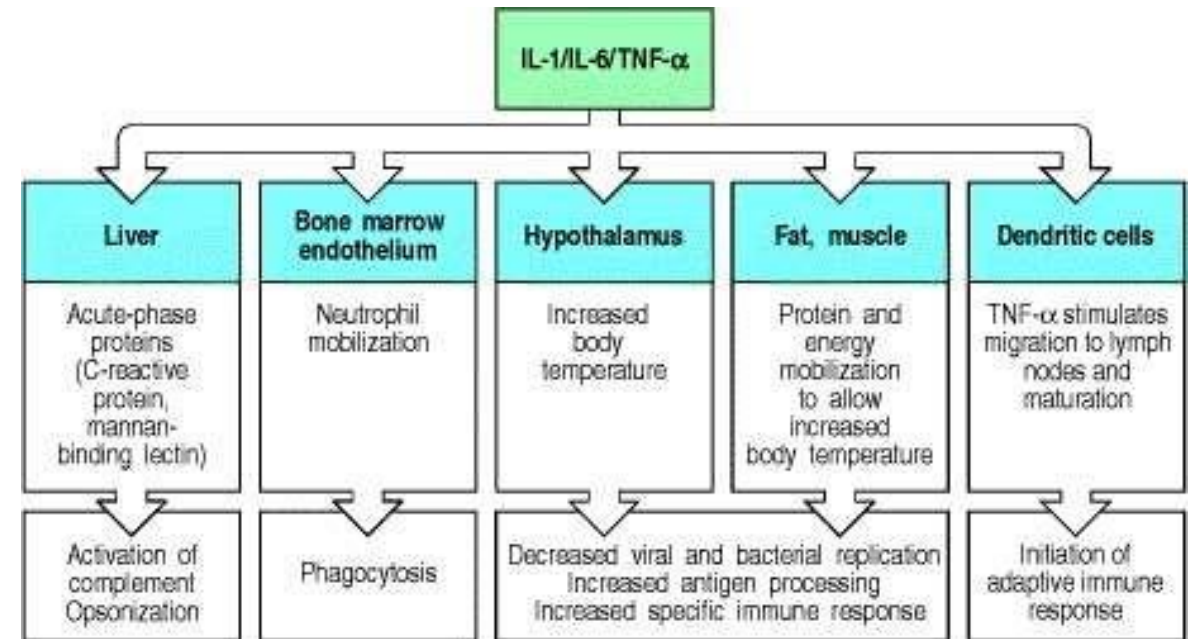
These are **pro-inflammatory cytokines** with overlapping functions, as **IL-1** mediates acute inflammatory responses similarly to **TNF-alpha**. Together, they work synergistically to enhance inflammation.

## •Functions:

- Stimulate the synthesis of adhesion factors on endothelial cells and leukocytes to aid in cell migration.
- Affect the hypothalamus to increase prostaglandin synthesis, causing **fever** (acting as **endogenous pyrogens**), a process inhibited by **aspirin**.
- Stimulate the production of **acute phase proteins** from the liver.

## •Sources:

- Both are produced primarily by locally activated **monocytes, macrophages, and neutrophils**.



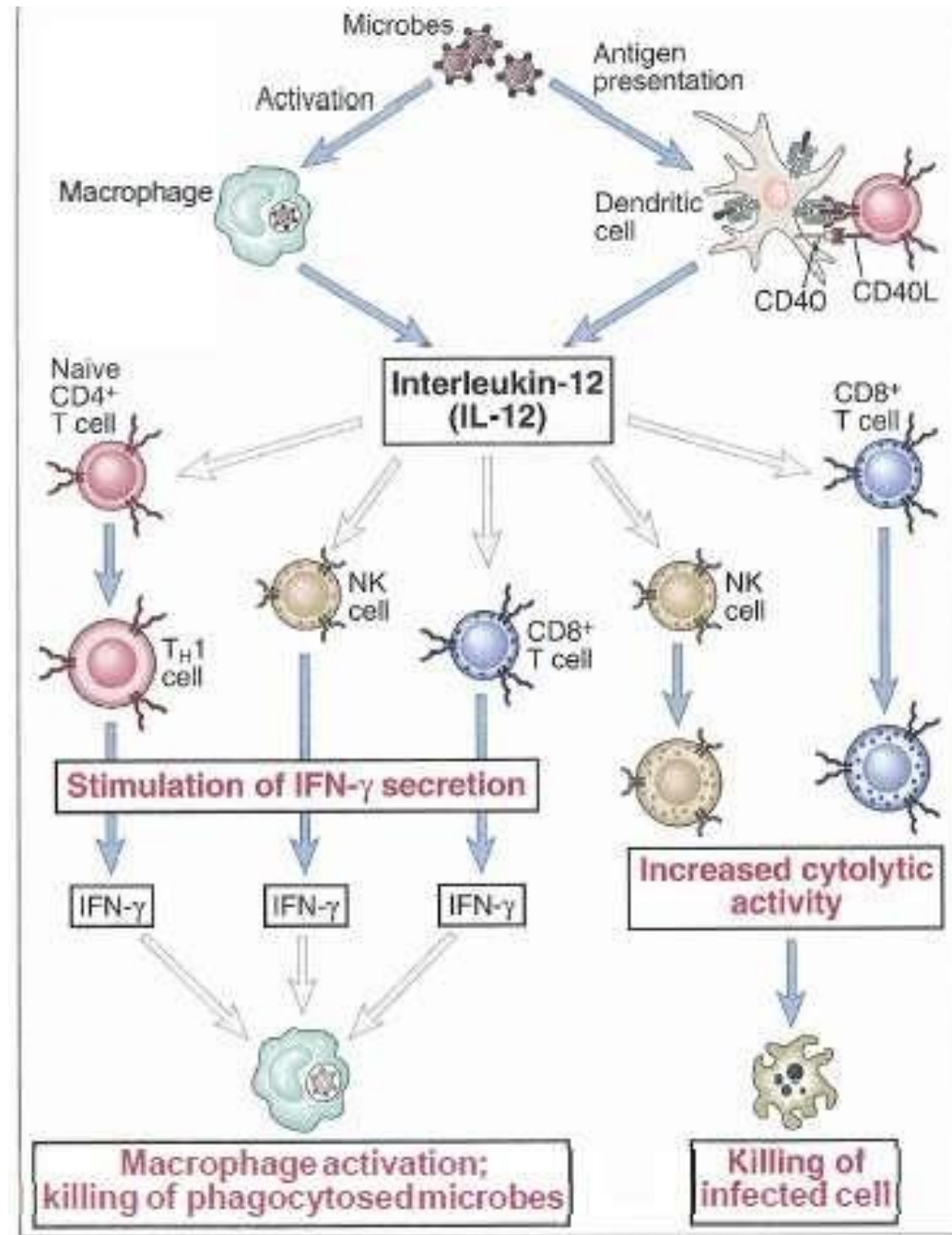
# IL-12

## Interleukin-12 (IL-12)

IL-12 is a primary mediator of immune responses to **intracellular microbes** (such as **Listeria**, **mycobacteria**, and **viruses**), produced by **dendritic cells (DC)** and **macrophages**.

### •Functions:

- Activates **CD8 T cell** differentiation.
- Promotes **TH1 cell** differentiation.
- Activates **CD8, TH1, and NK cells**.
- Stimulates **interferon-gamma** production from these cells.





# VA Chemokines



Although there are exceptions, immune cell recruitment is generally mediated as follows:

- **Neutrophil recruitment:** Primarily mediated by **CXC chemokines**.
- **Monocyte recruitment:** More dependent on **CC chemokines**.
- **Lymphocyte recruitment:** Mediated by both **CXC** and **CC chemokines**.

• **Chemokines** are required for the migration of immune cells from sites of infection into **draining lymph nodes**, facilitated by **CC-chemokine receptor 7 (CCR7)**.

• **Neutrophils** express receptors for **CXCL8 (IL-8)**, produced by tissue-resident macrophages, which is the major chemokine supporting neutrophil migration into tissues.

• **Classical monocytes** express **CCR2**, which binds **CCL2**, the primary chemokine for monocyte recruitment.

# VA Type I Interferons



**Type I interferons** include 13 subtypes of **interferon-alpha**, **interferon-beta**, and others. *(Note: There is only one Type II interferon, interferon-gamma, which is involved in both innate and adaptive immune responses.)*

• **Stimulus:** The most powerful stimulus for Type I interferons is the initial immune response to **viral infection**.

• **Production and Action:**

- Produced by any virus-infected cell.
- Acts **paracrine**: Induces uninfected cells to produce enzymes capable of degrading viral **mRNA**, rendering them virus-resistant.
- Acts **autocrine**: Blocks viral protein synthesis and replication within the infected cell.

• **Functions:**

- Aids in **CD4** differentiation into **TH1 cells**.
- Assists in **CD8 cell** activation to kill virus-infected cells.
- Activates **NK cells** to target the virus.
- Stimulates production of **IFN-gamma** by activated **T cells**.

• **Types:**

- **Interferon-alpha** (leukocyte): Produced by **monocytes/macrophages**.
- **Interferon-beta** (fibroblast): Produced by **virus-infected cells** and **fibroblasts**



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

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

# IL- 2, 4, 5 and 13



- **Interleukin-2 (IL-2):**
  - IL-2 is a **growth factor** produced by **DC**, **T** cells, and **B** cells.
  - It is a growth factor for **Th1**, **Th2**, and **CD8**-lymphocytes upon activation (3rd signal).
  - **B7** ligates the **T-cell CD28**, activating the T cell to produce **IL-2** and its receptor (**IL-2R**).
  - The cytokine acts in an autocrine fashion, causing the cell to divide and differentiate into an effector T cell.
- **Interleukin-4 (IL-4):**
  - **IL-4** is a major stimulus for the production of **IgE** in **B** cells and promotes **B-cell growth**.
  - It also antagonizes the effects of **interferon-gamma**, thereby inhibiting **cell-mediated immunity**.
  - **IL-4** is mainly produced by **Th2 cells** and **B cells**.
- **Interleukin-5 (IL-5)**
  - **IL-5** is a growth and activating factor for **eosinophils**, playing a role in defense against **helminths**.
  - It also stimulates the proliferation and differentiation of antigen-activated **B-lymphocytes**.
  - **IL-5** is mainly produced by **Th2 cells**.
- **Interleukin-5 (IL-13)**
  - produced by **Th2 cells**, acts on **B cell**

# ❖ Interferon-gamma (IFN-gamma) - Type II Interferon



- **Type II interferon** is produced by both innate and adaptive immune responses. It is produced by macrophages and dendritic cells (DC) during intracellular infections, as well as by activated **TH1**, **NK**, and **CD8** cells to promote the activity of the cell-mediated immune system against intracellular pathogens.
- **IFN-gamma** is the principal cytokine for activating macrophages. It also promotes cell-mediated immunity by activating **CD8** and **NK** cells.
- Inhibits the proliferation of **Th2** cells.
- Stimulates the production of **IgG** subclasses that activate the complement pathway and promote opsonization.

# VA Transforming Growth Factor-beta (TGF-beta)



- **TGF-beta** is a **regulatory cytokine** that functions to:
  - Inhibit the proliferation and effector function of **T-lymphocytes**.
  - Inhibit the proliferation of **B-lymphocytes**.
  - Inhibit **macrophage** function.
- **TGF-beta** is produced by **T-reg** cells.
- The generation of some regulatory T cells from **CD4** cells requires the cytokines **TGF-beta** and **IL-2**.
- **TGF-beta** with **IL-6** leads to the differentiation of **TH17** cells.

# VA Lymphotoxin (TNF-beta)



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

# VA IL-6 and IL-10



•**IL-6**: Produced by both innate and adaptive immune functions, IL-6 is produced by macrophages and monocytes. It is a **pro-inflammatory cytokine** that:

- Stimulates the liver to produce acute-phase proteins.
- Stimulates the differentiation and growth of B-lymphocytes, from **TH2**.
- Helps in the differentiation of **TH17** if **TGF-beta** is present.

•**IL-10**: Known as a **pan-regulatory cytokine**, IL-10 is an inhibitor of activated macrophages and dendritic cells. It inhibits the production of **IL-12** and co-stimulator molecules like **MHC2**, thus inhibiting **TH1**, **TH2**, and **CD8**. Additionally, it:

- Regulates innate immunity, as well as cell-mediated and humoral immunity.
- Is mainly produced by **Treg** and **Th2** cells.



## *Other....*

### # Type-1 & Type-2

- ▶ Type-1 cytokines are cytokines produced by Th1 T-helper cells.
- ▶ Include IL-2 (IL2), IFN-gamma (IFN-G), IL-12 (IL12) & TNF-beta (TNF-b).
- ▶ Type-2 cytokines are those produced by Th2 T-helper cells.
- ▶ Include IL-4 (IL4), IL-5 (IL5), IL-6 (IL6), IL-10(IL10), and IL-13 (IL13).

### # Mediators of natural immunity.

- ▶ TNF- $\alpha$ , IL-1, IL-10, IL-12, type I interferons (IFN- $\alpha$  and IFN- $\beta$ ), IFN- $\gamma$ , and chemokines.

### # Mediators of adaptive immunity.

- ▶ IL-2, IL-4, IL-5, TGF- $\beta$ , IL-10 and IFN- $\gamma$ .



# Cytokines that Stimulate Hematopoiesis

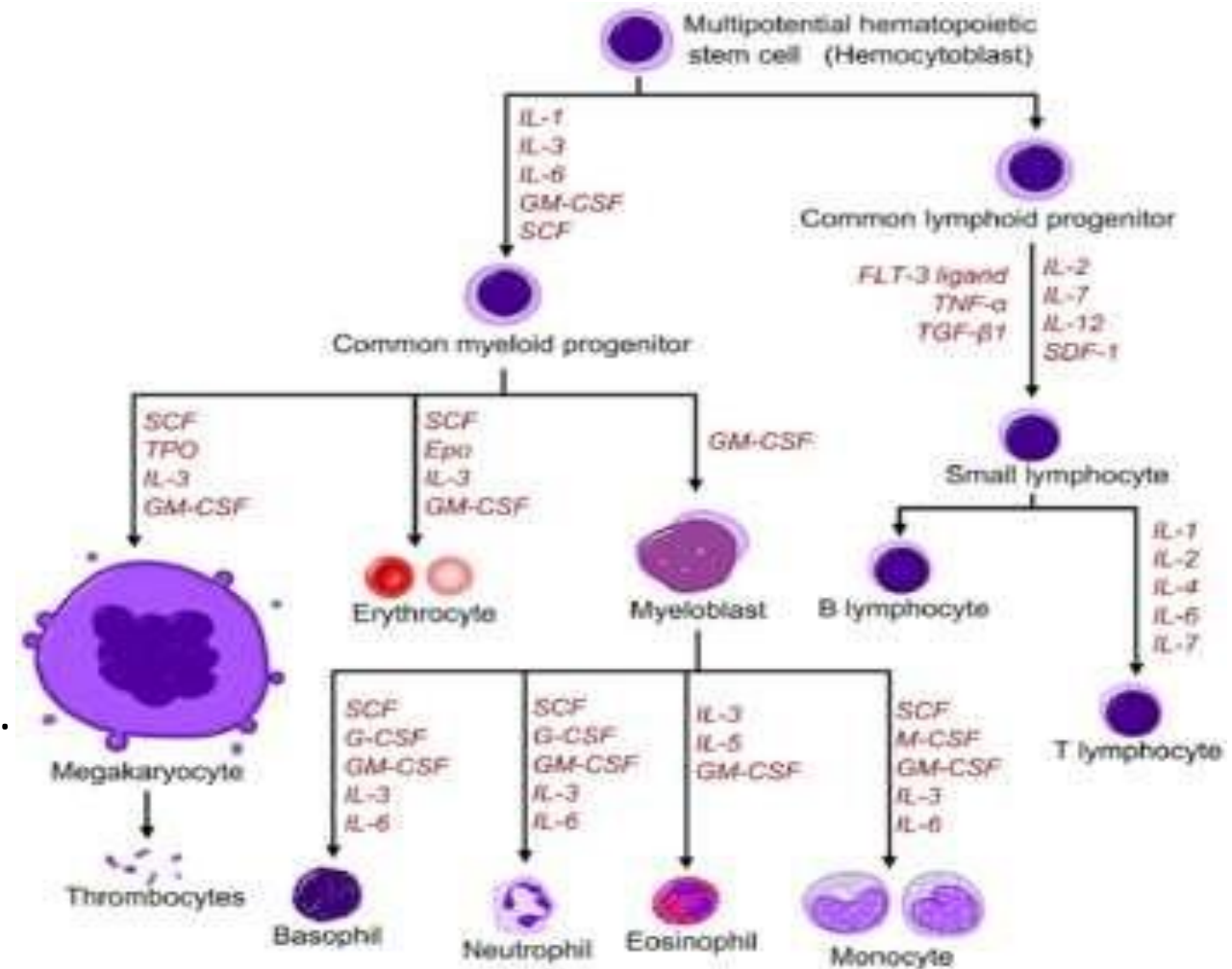
Produced by bone marrow stromal cells, these cytokines stimulate the growth and differentiation of immature leukocytes

# VA Cytokines of hematopoiesis



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

- **Colony-stimulating factors (CSF):** These promote the production of colonies of different leukocytes in the bone marrow and enhance their activity. Examples include:
  - **Granulocyte-macrophage colony-stimulating factor (GM-CSF):** Stimulates the production of granulocytes (neutrophils, eosinophils, and basophils) and monocytes.
  - **Granulocyte colony-stimulating factor (G-CSF).**
  - **Macrophage colony-stimulating factor (M-CSF).**
- **Stem cell factor:** This makes stem cells in the bone marrow more responsive to the various CSFs.
- **Interleukin-3 and IL-7:** These support the growth of multi-lineage bone marrow stem cells.



# VA Cytokine Receptors



There are **5 major families** of cytokine receptors:

## 1. Immunoglobulin Superfamily

## 2. Hematopoietin Receptor Family (Class I)

## 3. Interferon Receptor Family (Class II)

## 4. TNF Receptor Family

## 5. Chemokine Receptor Family

• **Class I** and **Class II** are the majority of the 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 $\beta_c$ (common beta chain)
		Receptors for IL-2, IL-4, IL-7, IL-9 and IL-15 share a common chain CD132 or $\gamma_c$ (common gamma chain). IL-2 receptor also has a third chain, a high-affinity subunit IL-2R $\alpha$ (CD25)
Class II cytokine receptor		Interferon- $\alpha$ , - $\beta$ , and - $\gamma$ 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

# Immune Modulation



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** (by increasing **TH2** response) or in **allergy** (by increasing **TH1** response), 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 Biologic Therapy

- Suppression of TH1 and Tc in autoimmune diseases** can be achieved by:

- Blocking antibodies against **IL-2R**.
- Using **IL-2** analogs that prevent **IL-2** binding.

- Using IL-2** to activate lymphocytes to attack cancer in a patient

## Suppression of $T_H$ -cell proliferation and $T_C$ -cell activation

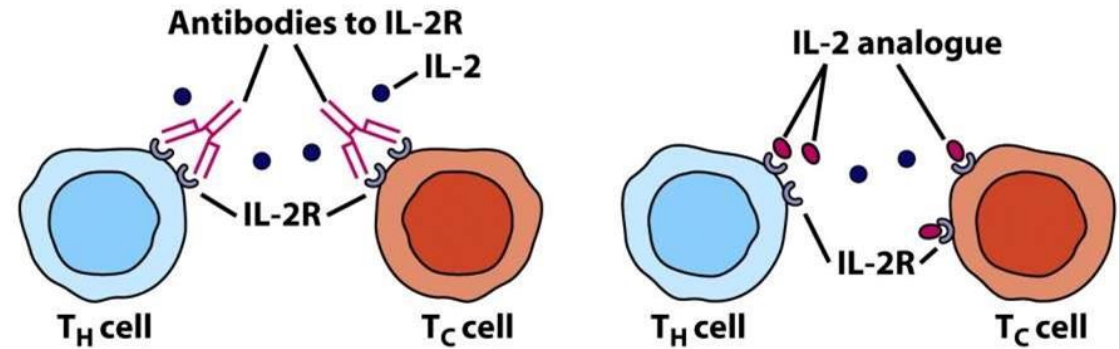


Figure 12-15a  
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## Destruction of activated $T_H$ cells

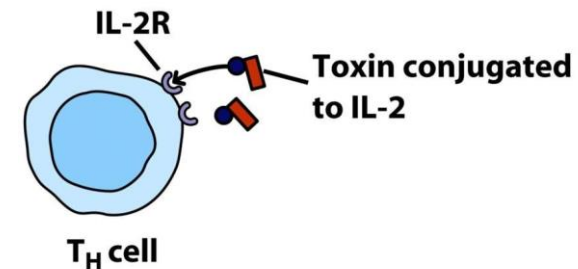


Figure 12-15b  
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## Therapeutic Uses of Cytokines

- 1) Interferon in treatment of viral diseases, cancer.
- 2) Several cytokines are used to enhance T-cell activation in immunodeficiency diseases, e.g. IL-2, IFN- $\gamma$ , TNF- $\alpha$ .
- 3) IL-2 and lymphokine activating killer cells (LAK) in treatment
- 4) Anti-cytokines in management of autoimmune diseases :
  - a)- Anti-TNF in treatment rheumatoid arthritis
  - b)- Anti-IL2R to reduce graft rejection.
- 5) Anti-TNF antibodies in treating septic shock.
- 6) Anti-IL-2R  $\alpha$  in treating adult T-cell leukemia.
- 7) Anti-IL-4 is under trial for treatment of allergies.



«Wherever the art of medicine is loved,  
there is also a love of humanity.»

- Hippocrates-

