

ACUTE PHASE PROTEINS & CYTOKINES

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ACUTE PHASE RESPONSE

Change in plasma concentration of several proteins, called **acute phase reactants**, that occurs as a part of **innate immune response** to infections

ACUTE PHASE RESPONSE

- ▶ Starts within hours or days of the onset of inflammation or infection.
- ▶ endothelial cell, monocyte, macrophage, T-lymphocyte, fibroblast
 - ▶ Release cytokines : (TNF, Interleukin-6)
 - ▶ change the expression of genes
 - ▶ Production of protein (Acute Phase Protein)
 - ▶ Release APP to blood

ACUTE PHASE PROTEINS

- Class of proteins that are synthesized in the liver in response to **inflammation**
- Mediated by inflammatory cytokines
IL-6, Tumor necrosis factor (TNF)

ACUTE PHASE PROTEINS

- ▶ Positive APPs

- Increase during acute phase response

- ▶ Negative APPs

- Decrease during acute phase response

ACUTE PHASE PROTEINS

Positive APPs

- C-reactive protein (CRP)
- Fibrinogen
- Serum Amyloid A protein
- Mannose-Binding Lectin (MBL)
- α_1 Antitrypsin
- Plasminogen

ACUTE PHASE PROTEINS

Negative APPs

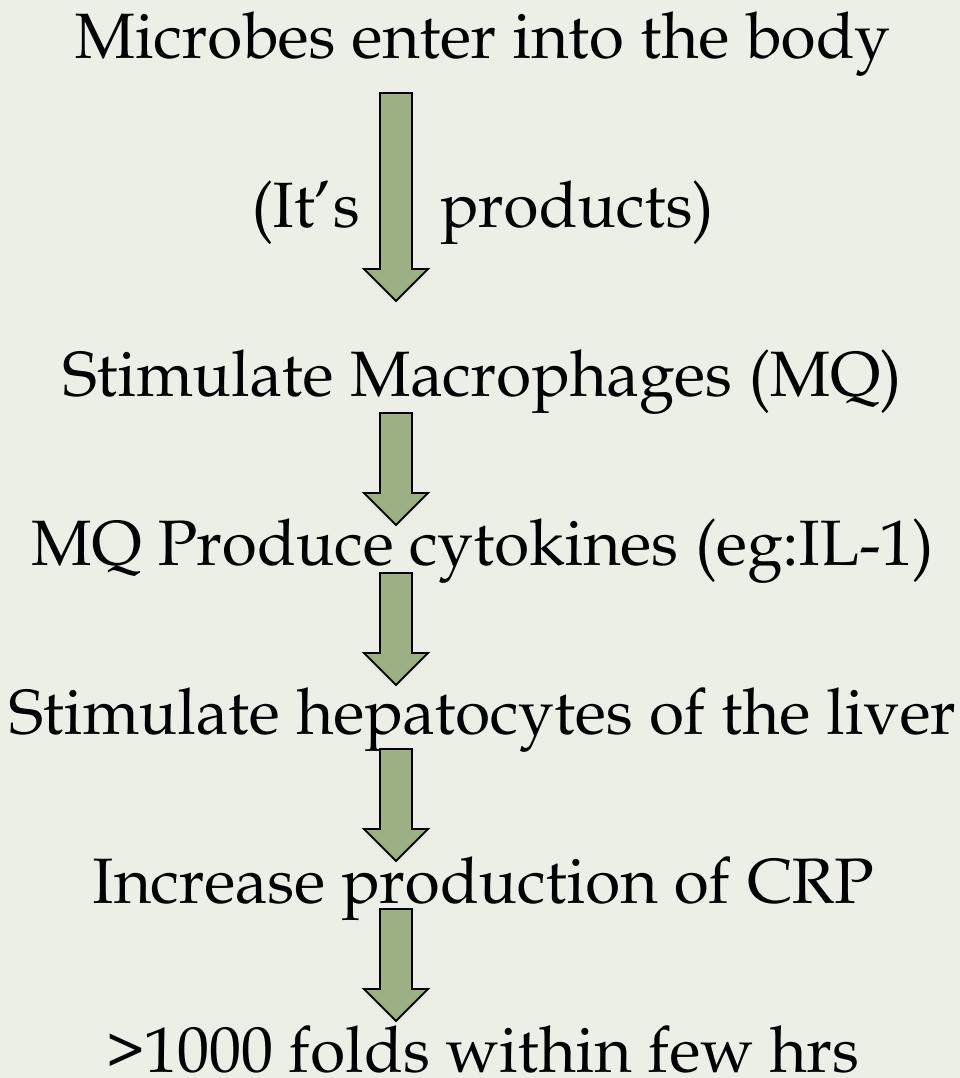
- Albumin
- Transferrin
- Transthyrectin
- Thyroxine-binding globulin

<u>Protein</u>	<u>Function</u>
<u>C-reactive protein</u>	<u>Opsonin on microbes</u>
<u>Serum amyloid A</u>	<ul style="list-style-type: none"> • <u>Recruitment of immune cells to inflammatory sites</u> • <u>Induction of enzymes that degrade extracellular matrix</u>
<u>Complement factors</u>	<u>Opsonization, lysis and clumping of target cells. Chemotaxis</u>
<u>Mannose-Binding Lectin (MBL)</u>	<u>Mannan-binding lectin pathway of complement activation</u>
<u>Fibrinogen, prothrombin, factor VIII, von Willebrand factor</u>	<u>Coagulation factors, trapping invading microbes in blood clots.</u>
<u>Plasminogen</u>	<u>Degradation of blood clots</u>
<u>Ferritin</u>	<u>Binding iron, inhibiting microbe iron uptake</u>
<u>Haptoglobin</u>	<u>Binds hemoglobin, inhibiting microbe iron uptake</u>
<u>Alpha 1-antitrypsin</u>	<u>downregulates inflammation</u>

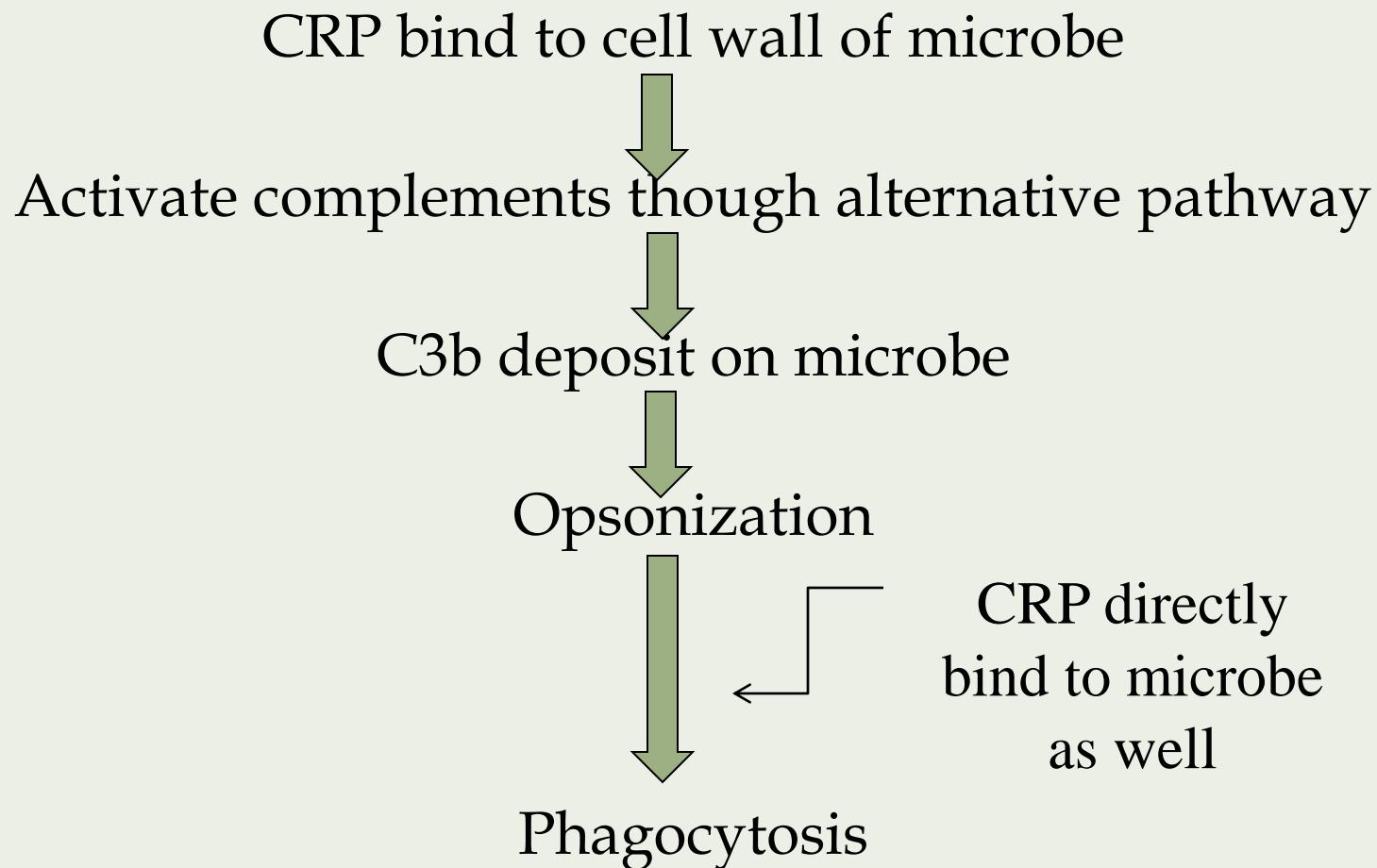
CRP

- Key APP
- Innate defense against infections
- Present in plasma in very low concentration

Mechanism of production of CRP



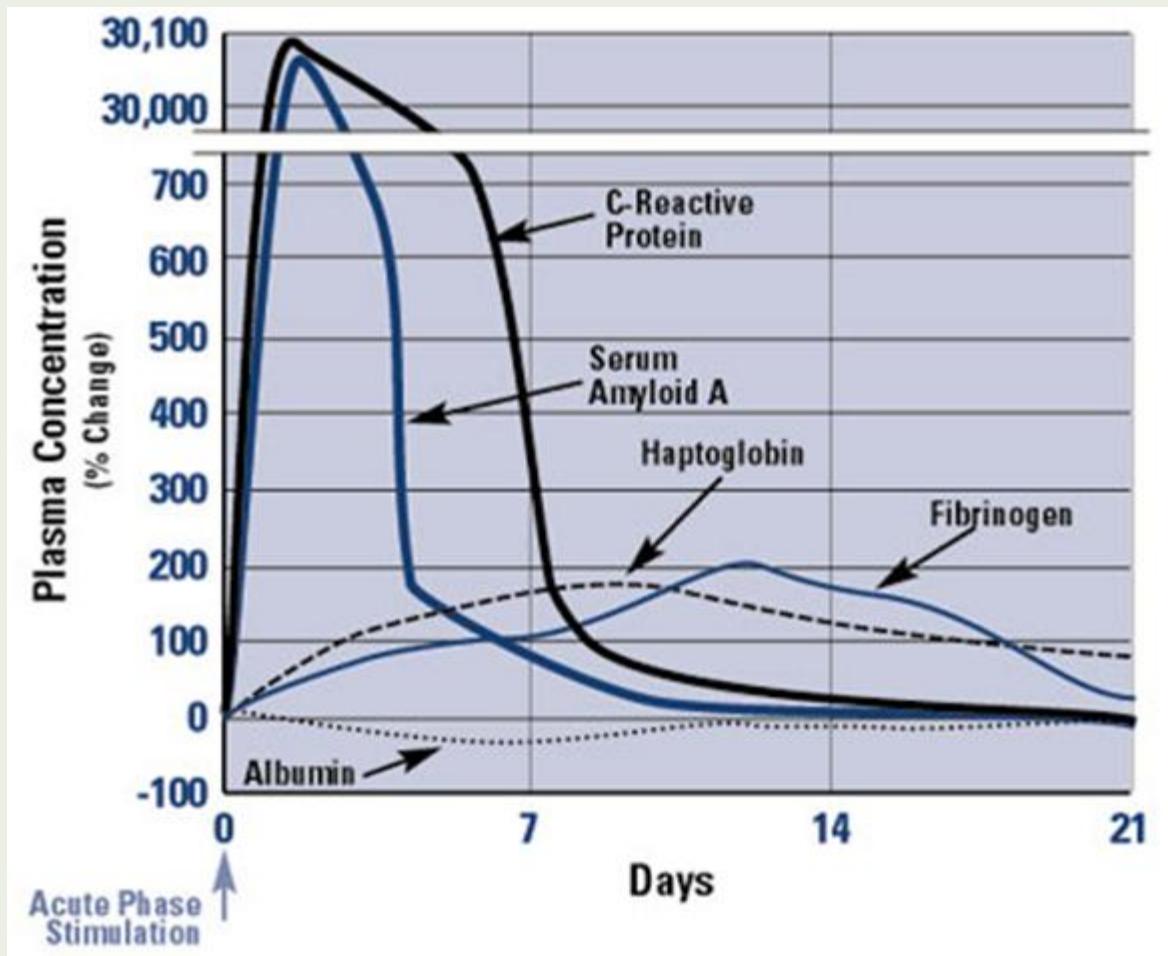
CRP - Mechanism of action



ADVANTAGES / CLINICAL USES OF CRP

- Limit tissue damage
- Maximize complement activation
 - Helps in phagocytosis
- Increased level indicate high level of disease activity
 - bacterial > viral
 - serial measurement - important in disease Mx
 - increase before ESR (depend on elevation of fibrinogen)
 - indicate inflammatory response within 24-48 hrs

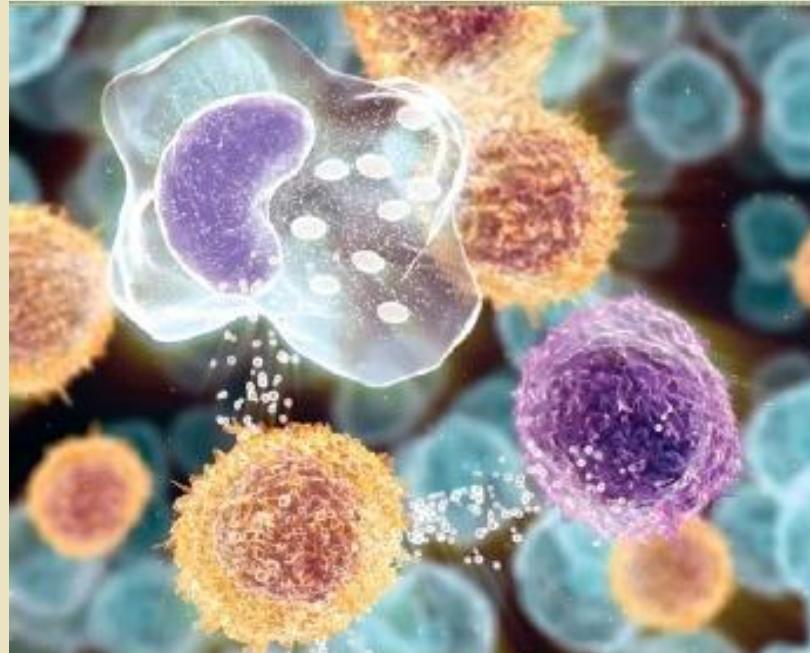
Alterations in some acute phase reactants following tissue injury. Note that CRP levels rise the highest and the fastest.

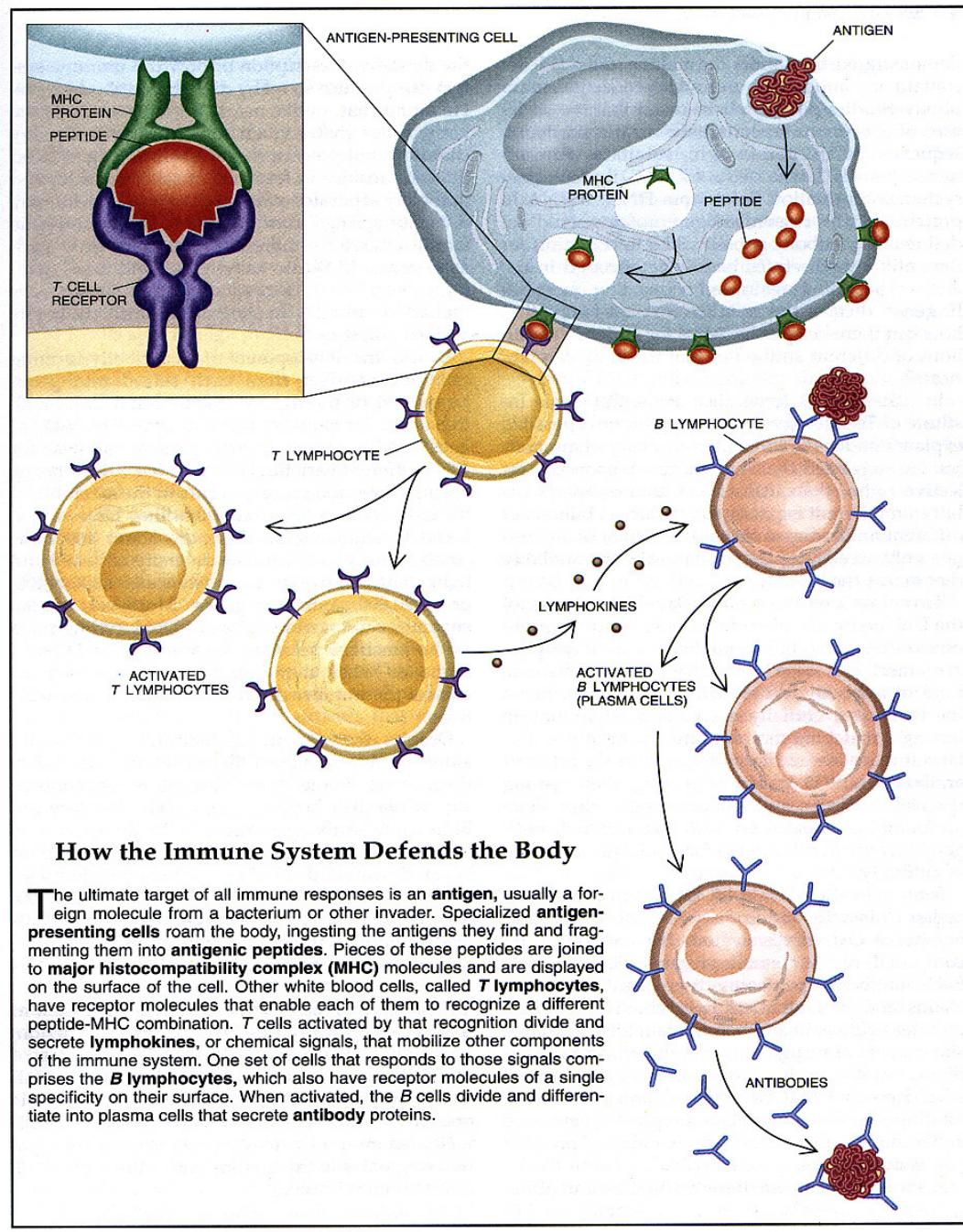


CYTOKINES

Cytokines

Secretory **proteins** that function as **mediators** of immune and inflammatory reactions.





Features

- Low molecular weight proteins
- Potent
- Bind receptors
- Alter gene expression
- Do cell-to-cell communication

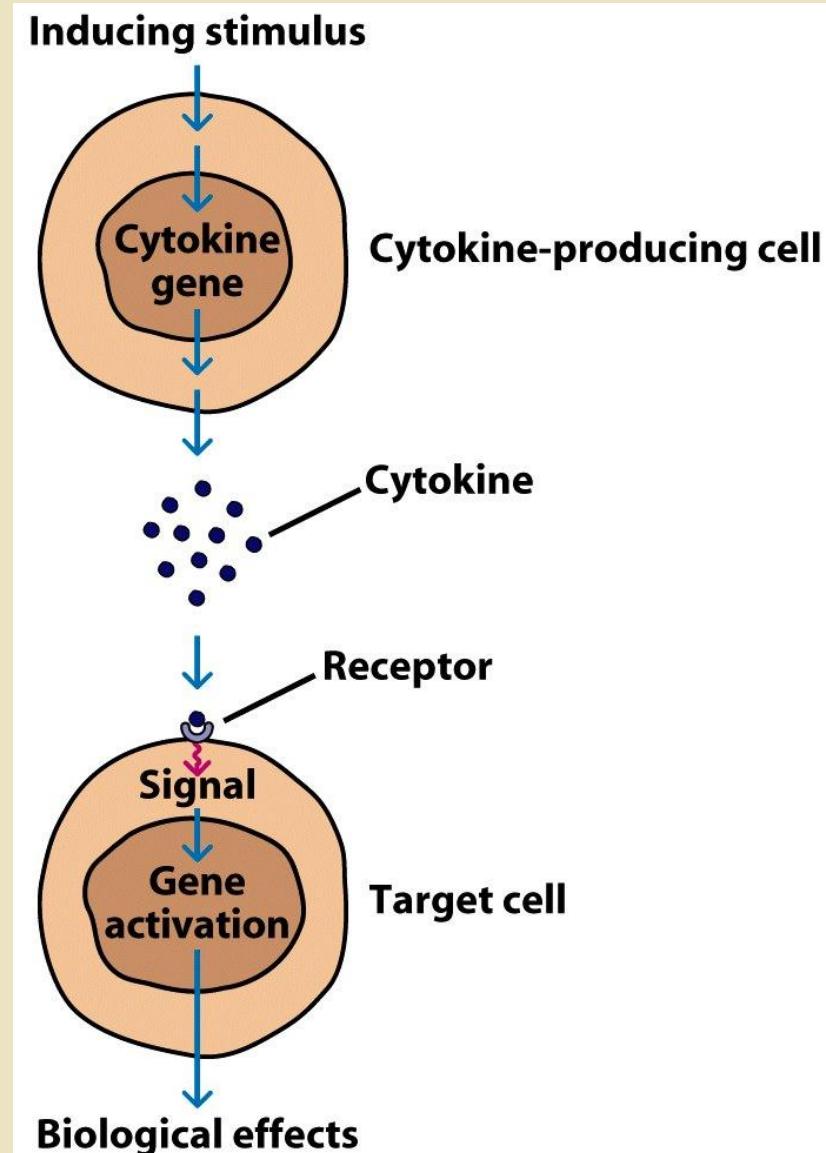
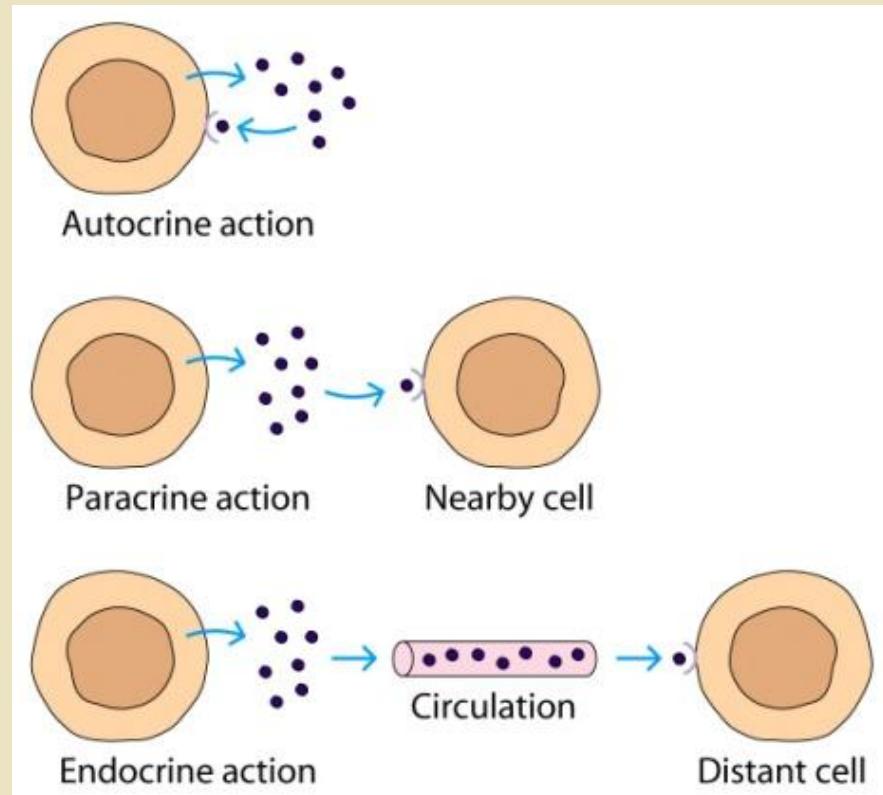


Figure 12-1a
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Features...

exert variety of effects on lymphocytes and other effector cells

- Can bind the secreting cell (autocrine)
- Can bind another cell close by (paracrine)
- Few cases bind another cell far away (endocrine)
- regulate the **intensity** and **duration** of the immune response



Features

Pleiotropy

- exerting multiple actions

Redundancy

- Multiple cytokines act on same cell type

Synergy

- Cytokines acting in concert on the same cell

Antagonism

- Competing actions

Cascading

- Cytokines acting sequentially

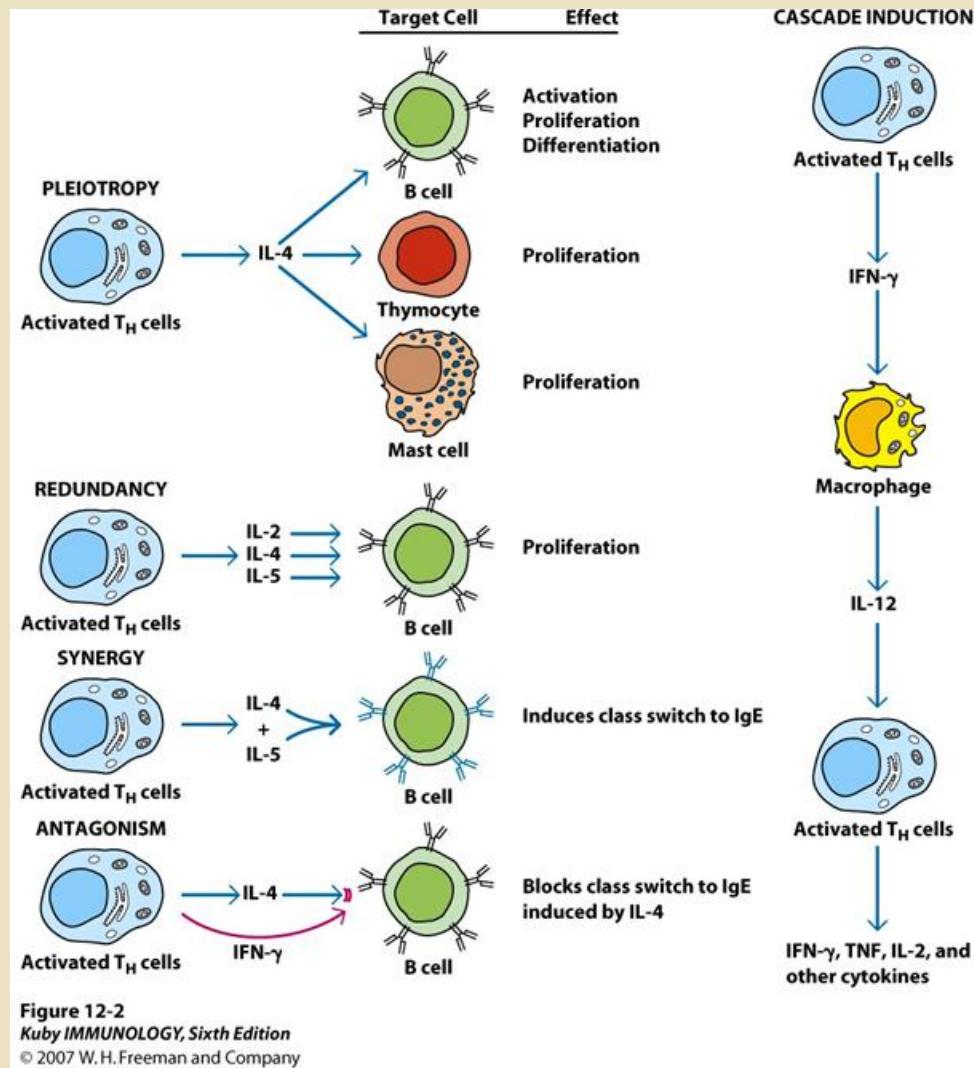


Figure 12-2
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Cytokine nomenclature

- Interleukins

- produced by leukocytes

- Monokines

- produced by myeloid cells

- Lymphokines

- produced by lymphocytes

Cytokine nomenclature

■ Chemokines

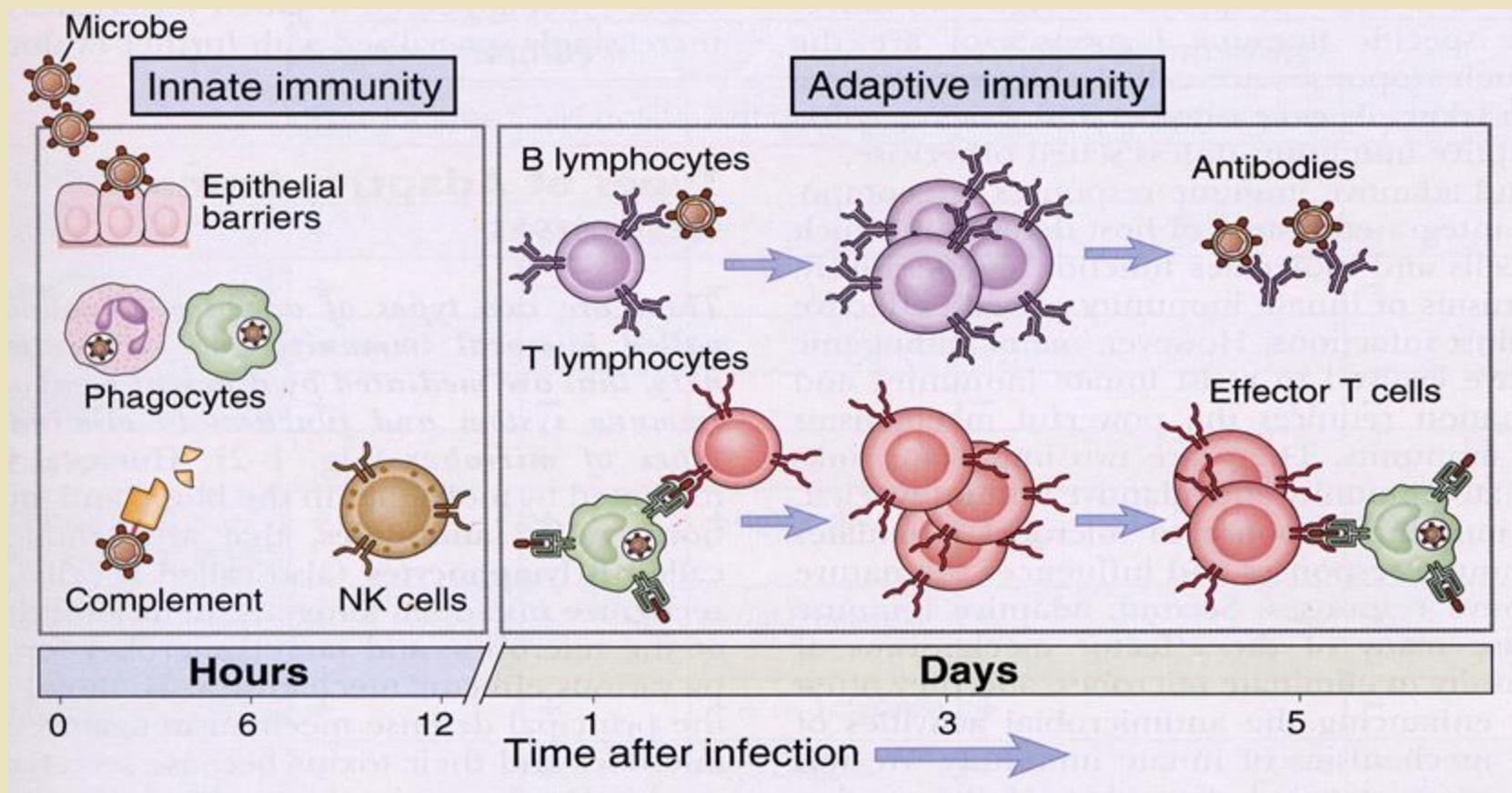
- direct cell migration
- activate cells

■ Interferon

- activation & modulation of immunity
- defense against viral infection

Source of cytokines

- Innate immune response
 - Macrophages
 - Natural Killer cells
- Acquired immune response
 - Lymphocytes



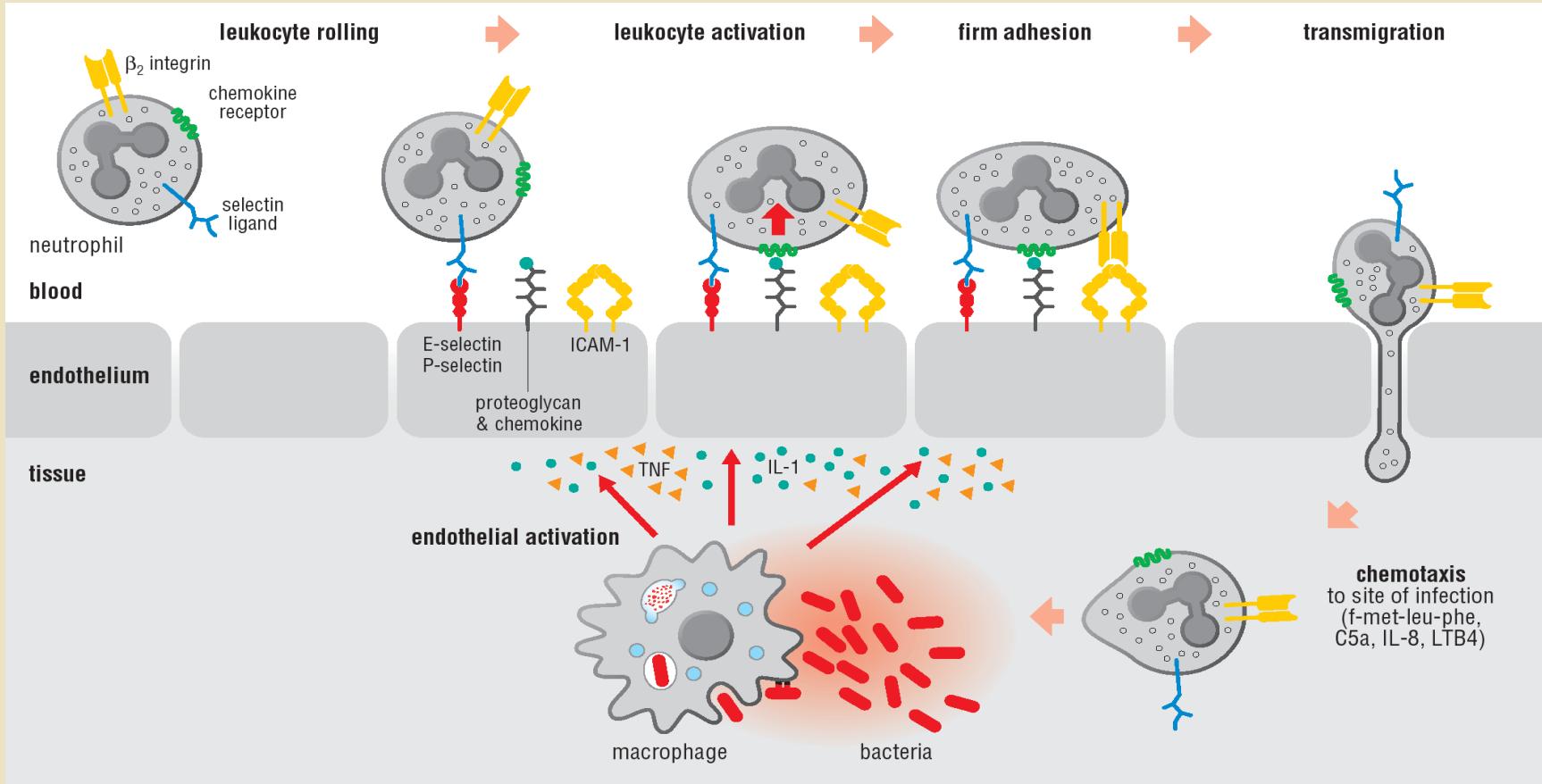
Functional groups of selected cytokines*		
Cytokine†	Secreted by‡	Targets and effects
SOME CYTOKINES OF INNATE IMMUNITY		
Interleukin 1 (IL-1)	Monocytes, macrophages, endothelial cells, epithelial cells	Vasculature (inflammation); hypothalamus (fever); liver (induction of acute phase proteins)
Tumor 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 _H 1 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 _H 2 cells, mast cells	Promotes T _H 2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T _H 2 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 _H 1 cells, CD8 $^{+}$ cells, NK cells	Activates macrophages; increases expression MHC class I and class II molecules; increases antigen presentation

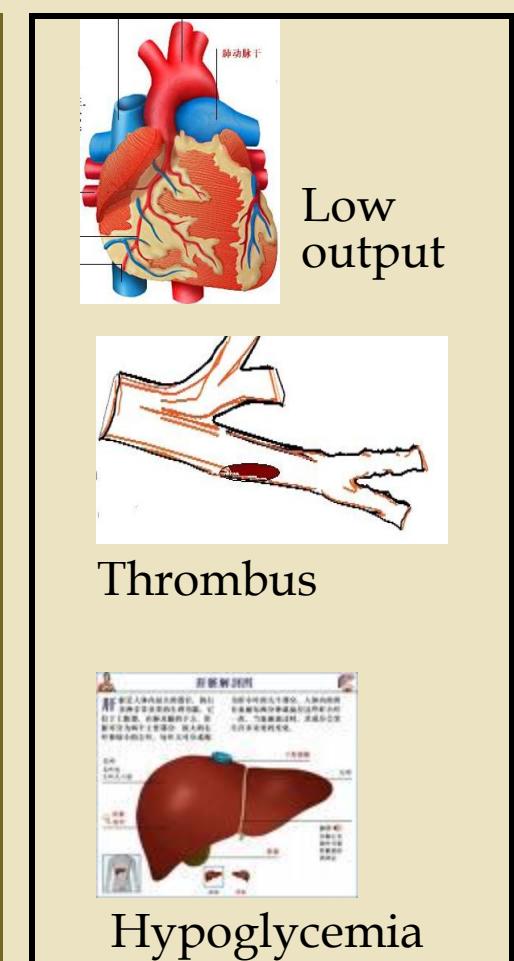
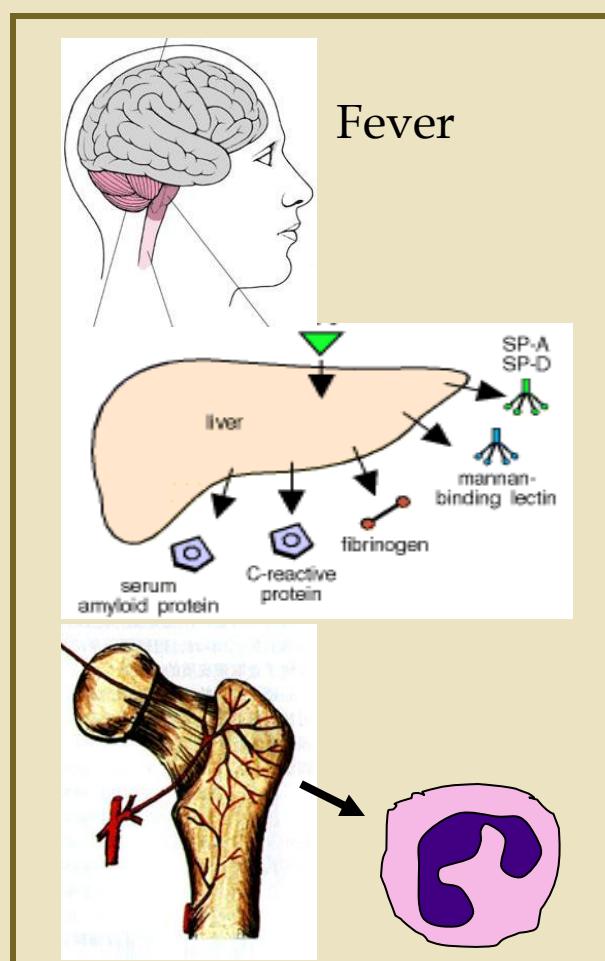
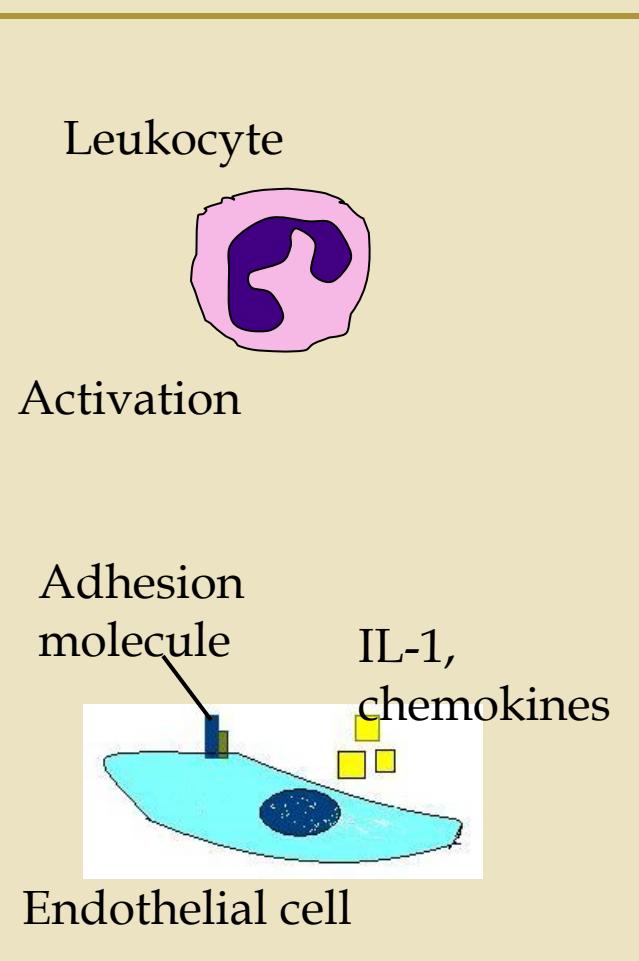
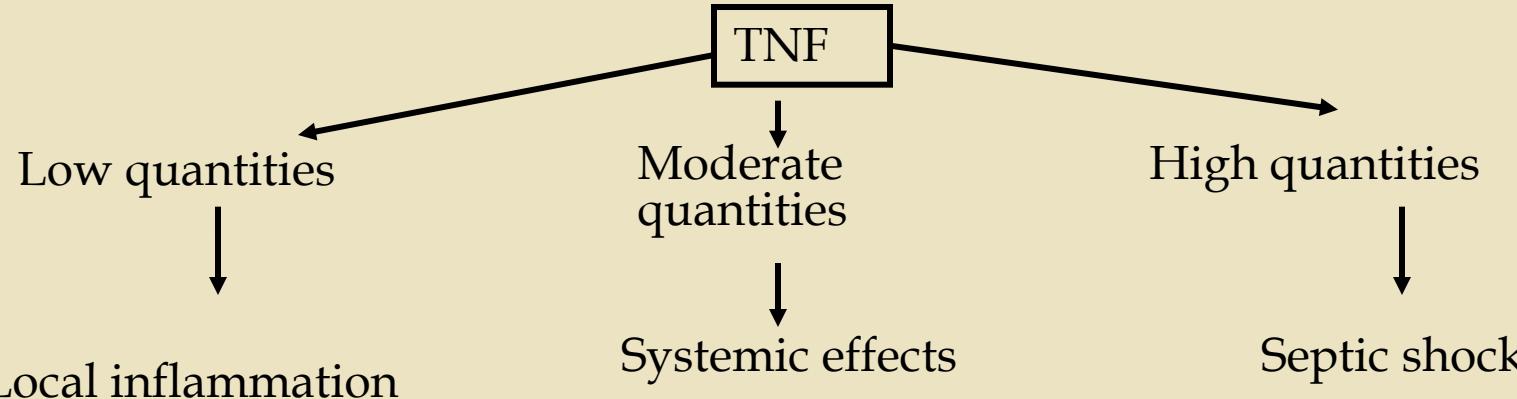
FUNCTIONS OF CYTOKINES

- Mediate and Regulate Innate Immunity
- Mediate and Regulate Adaptive Immunity
- Stimulate Hematopoiesis

Cytokines in Innate Immunity

- Proinflammatory cytokines
 - Tumor necrosis factor (TNF)
 - IL-1
 - IL-6
- Chemokines (eg: IL-8)
- Type I IFNs
- IL-12
- IL-15
- IL-18





Type I IFNs

- **Major cellular sources**

IFN- α : mononuclear phagocytes

IFN- β : fibroblasts

- **Potent stimulus**

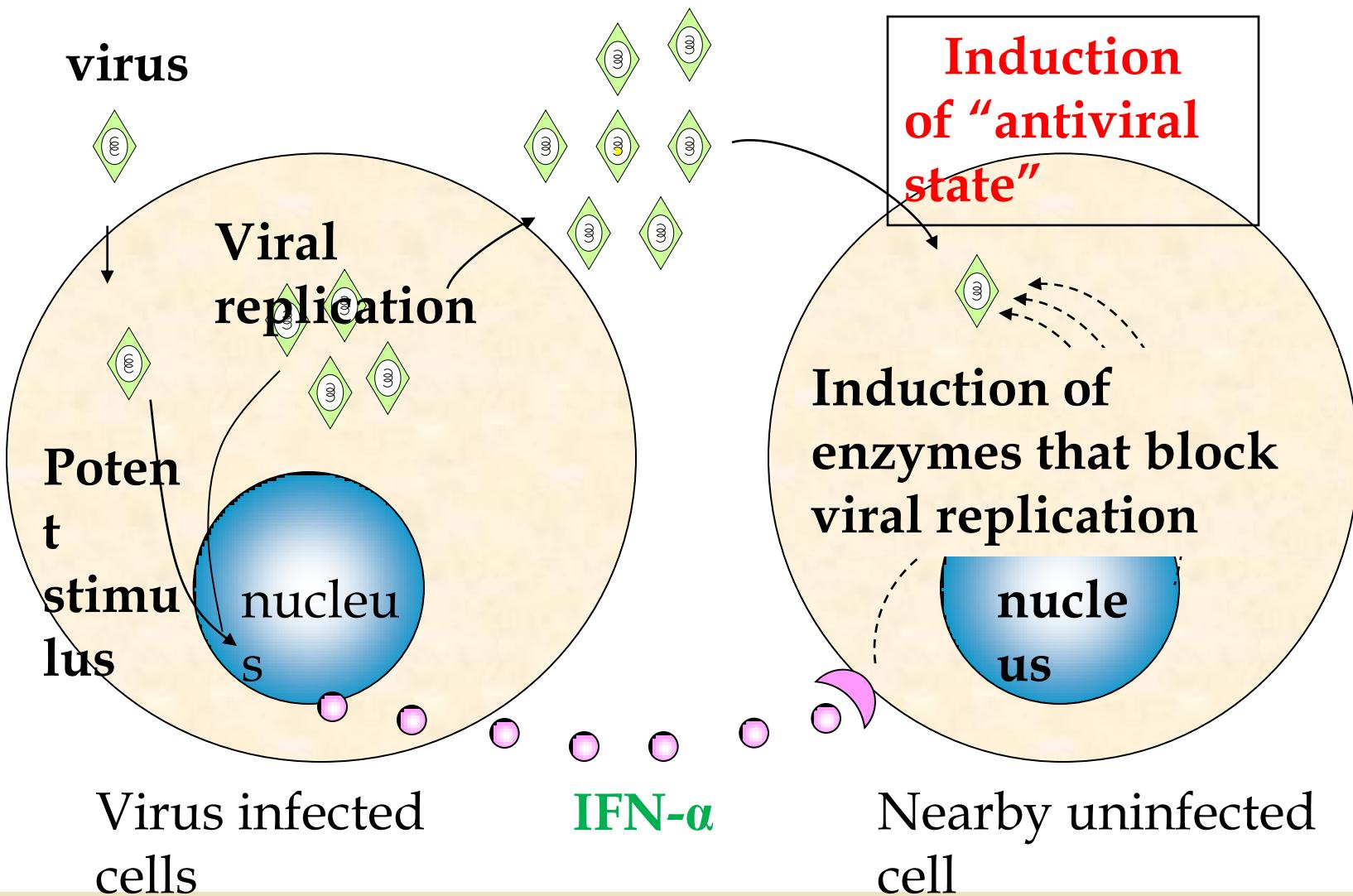
viral infection

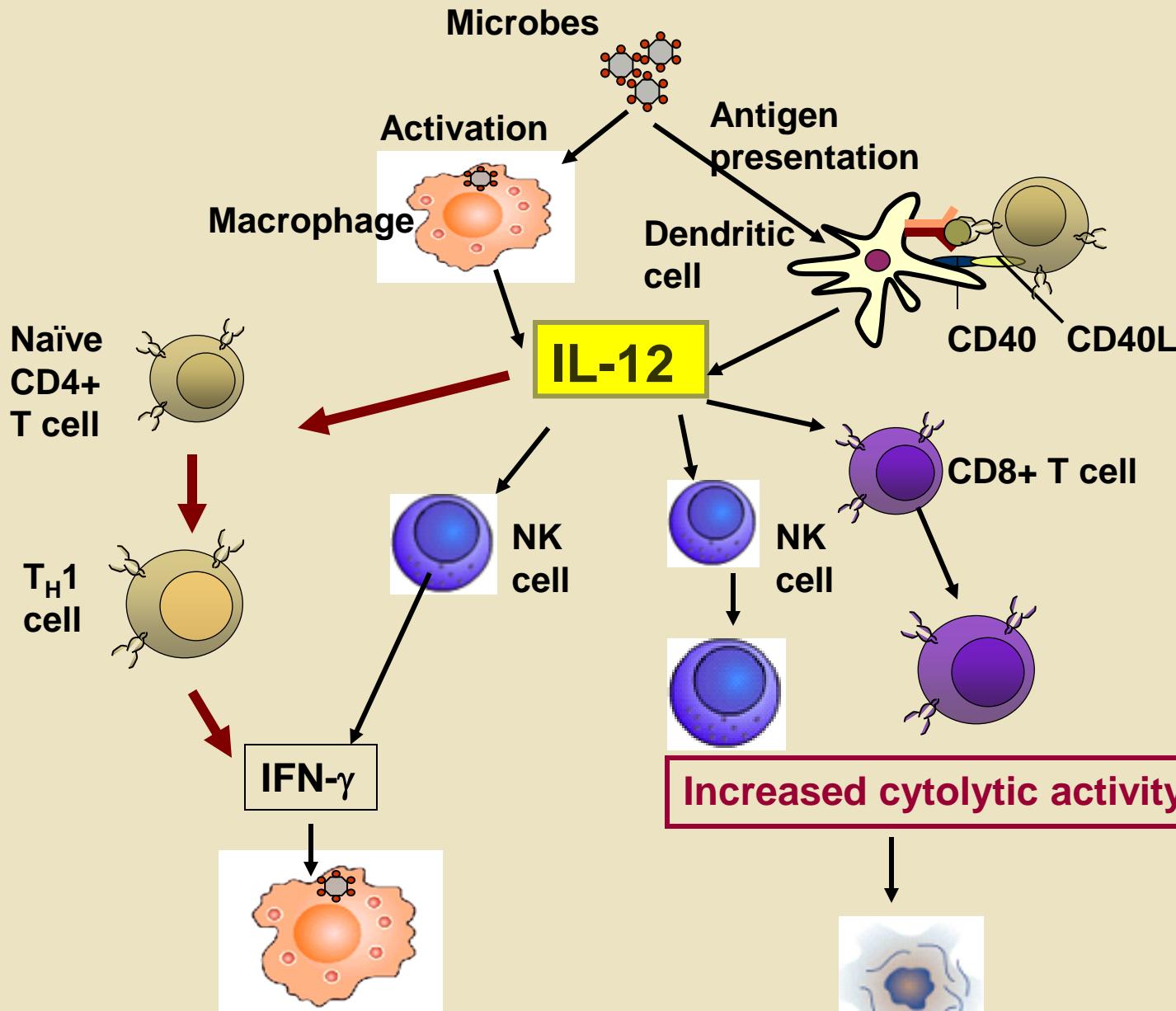
- **Function**

mediate the early innate immune response to viral infections

- Inhibits viral replication
- Increase expression of class I MHC molecules
- Stimulates the development of Th1 cells in human

Type I IFN inhibits viral replication



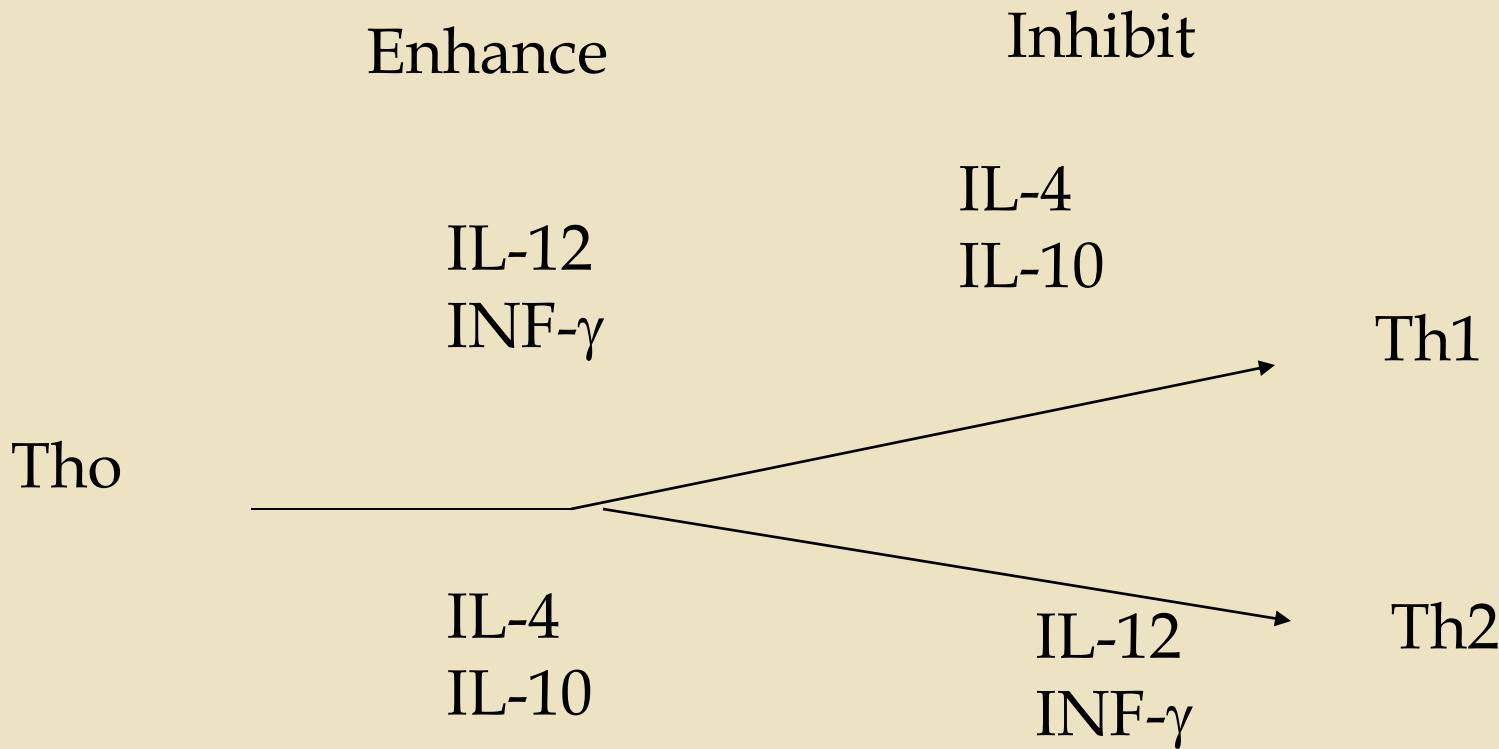


Macrophage activation;
killing of phagocytosed microbes

Killing of infected cell

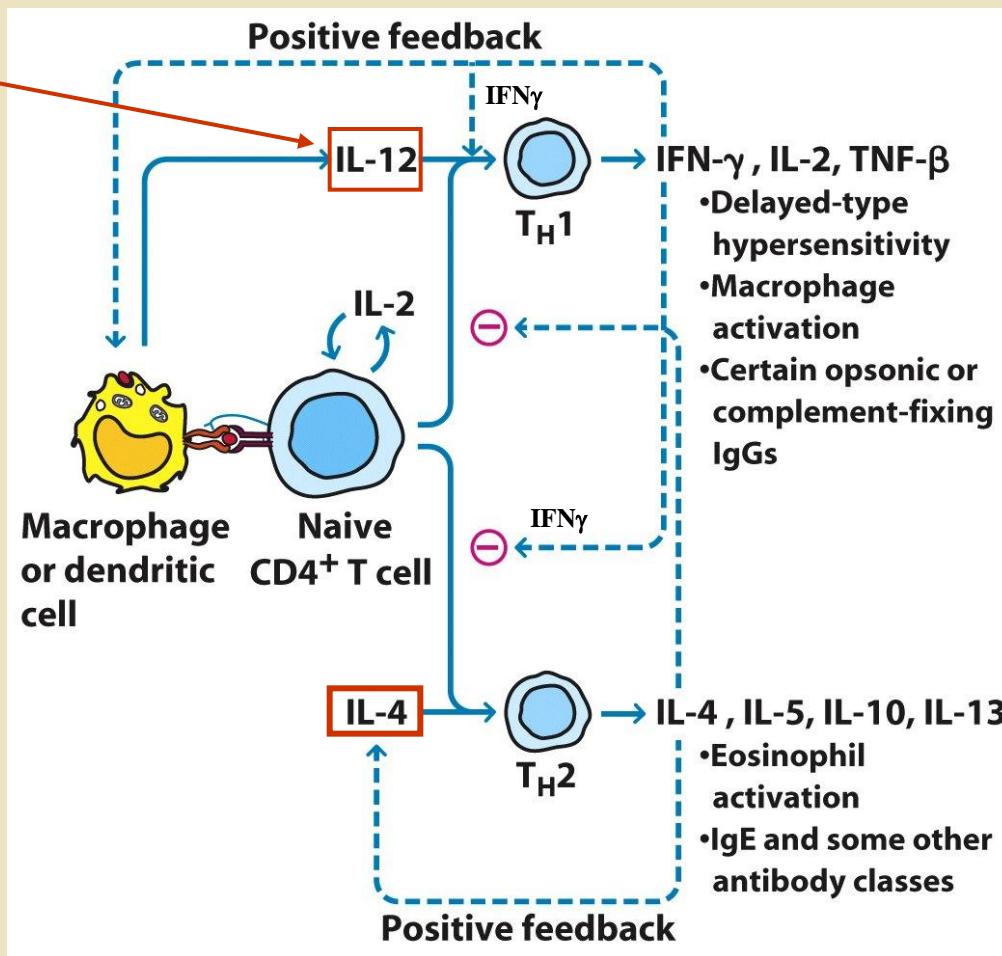
Cytokines in Adaptive Immunity

Cytokine effects on Th1 and Th2 immune response



Cytokines Determine the Development of T_H1 and T_H2 Responses

activated by intracellular pathogens and LPS



cross regulation

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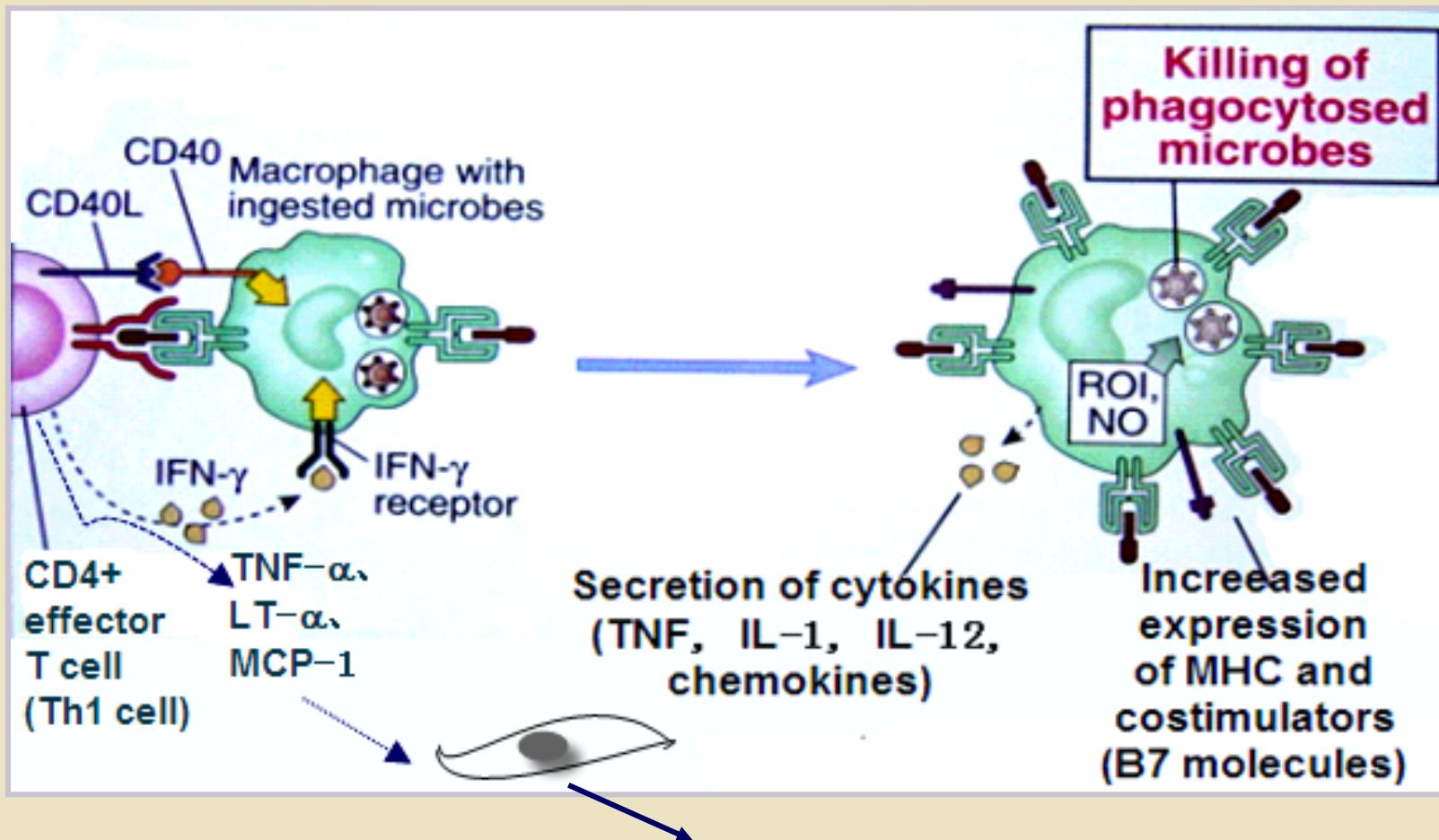
Cytokine effects on Th1 and Th2 immune response

Cell	Cytokines produced	Effect
Th1	INF- γ	Help for CTL and IgG antibody response
	IL-2	
Th2	IL-4	IL-5
	IL-6	IL-10
	IL-13	

Type II Interferon

- **IFN- γ**
- produced by Th1 cells & NK cells
- activates macrophages & PMNs for enhanced killing
- induces the development of Th1 cells that are critical to CTL & IgG production

IFN- γ : A principal macrophage-activating cytokine



Cytokines that Stimulate Hematopoiesis

Induce growth and differentiation

■ Colony-stimulating factors (CSFs)

drive the development, differentiation & expansion of cells of immature leukocytes

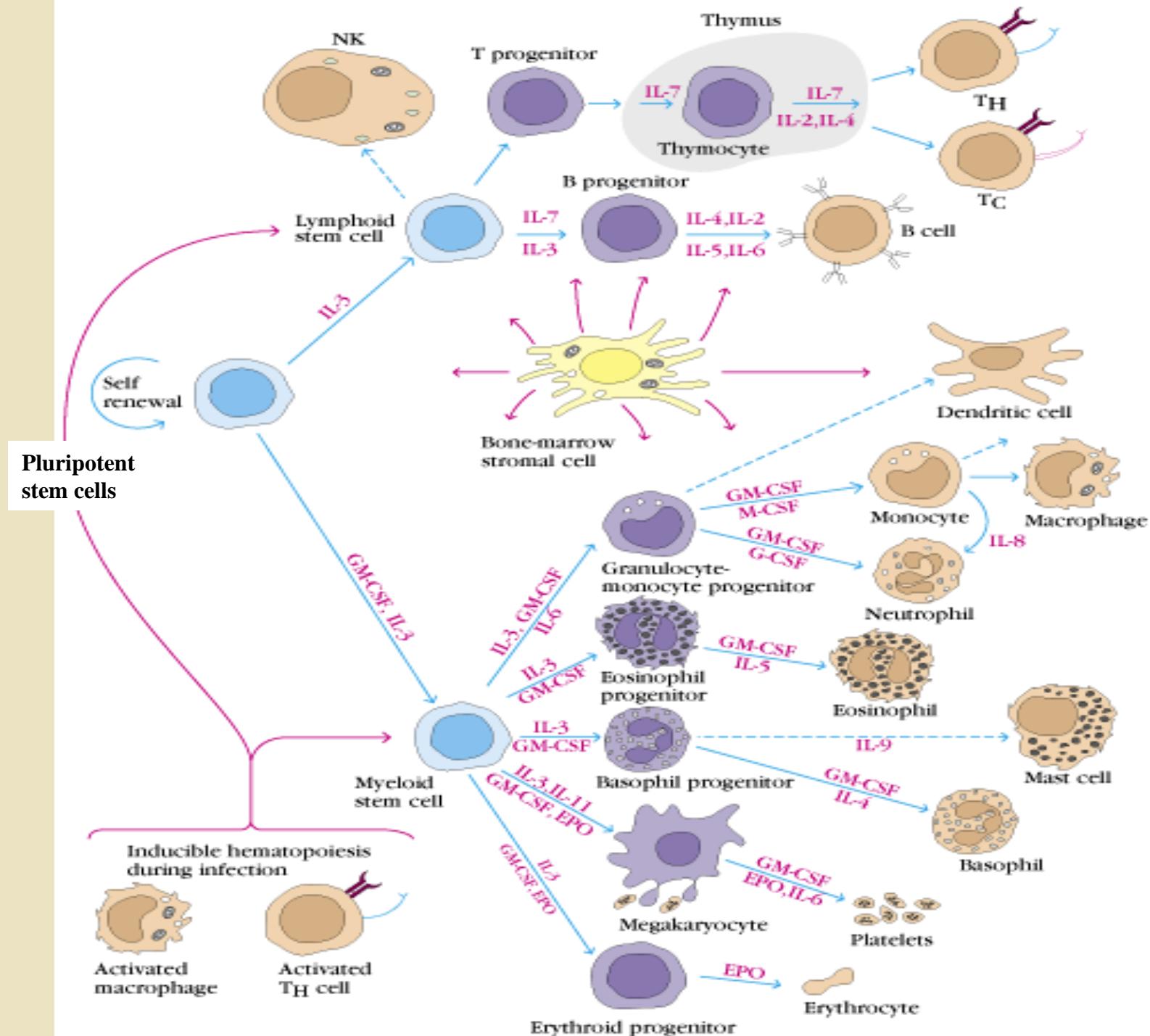
■ Members

granulocyte-macrophage-CSF, GM-CSF)

induces commitment of progenitor cells to the monocyte / granulocyte lineage

granulocyte-CSF, G-CSF

macrophage-CSF, M-CSF



Cytokines in the clinic

■ Cytokine treatment

- enhance immune system
 - IL-2, INF γ & INF α
 - Rx of certain tumours
- enhance haemopoiesis
 - G-CSF
 - Rx of low PMN counts resulting from chaemotherapy or irradiation

- ▶ INF- α --> some infections
- ▶ INF- γ --> Rx of patients with CGD
- ▶ G-CSF --> Rx of low granulocyte count
- ▶ IL-2 --> Renal cell carcinoma
- ▶ INF- α --> Hairy cell leukemia

Cytokine receptor targeting

- blocking of pro-inflammatory cytokine receptors
 - Eg TNF- α and IL-1
 - TNF- α receptor blockers in Rheumatoid Arthritis