

# Basic Immunology

*Lecture 8th*

## Cytokines, cytokine receptors

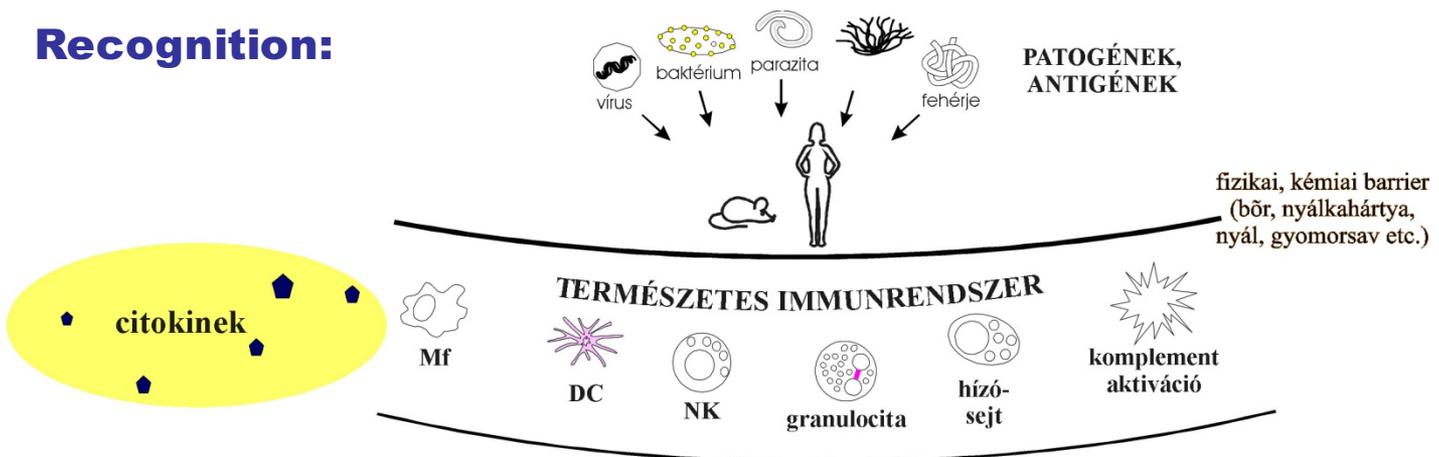
**Timea Berki MD, PhD**

# The interaction among cells of the immune response are mediated by 2 mechanisms:

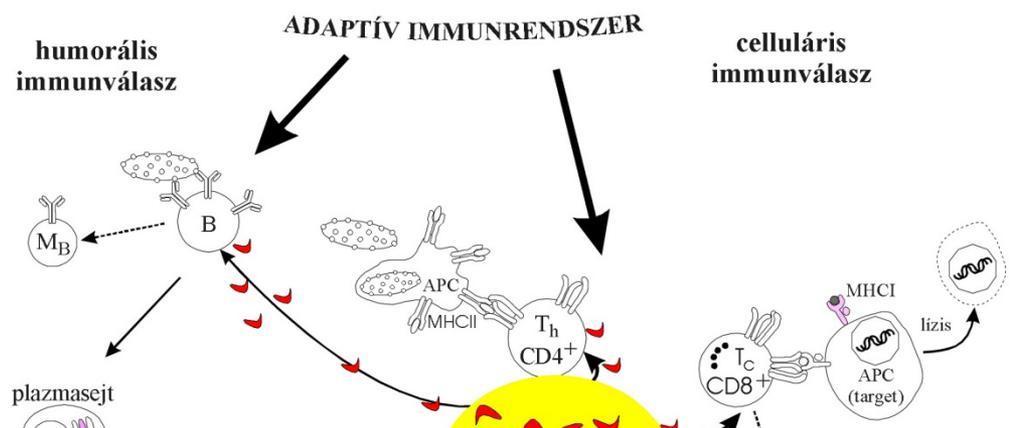
1. By direct cell-cell interactions: through **adhesion molecules**
2. By low MW regulatory proteins, called **cytokines**: messengers of the immune system

# Cytokines act in each phase of the immune response

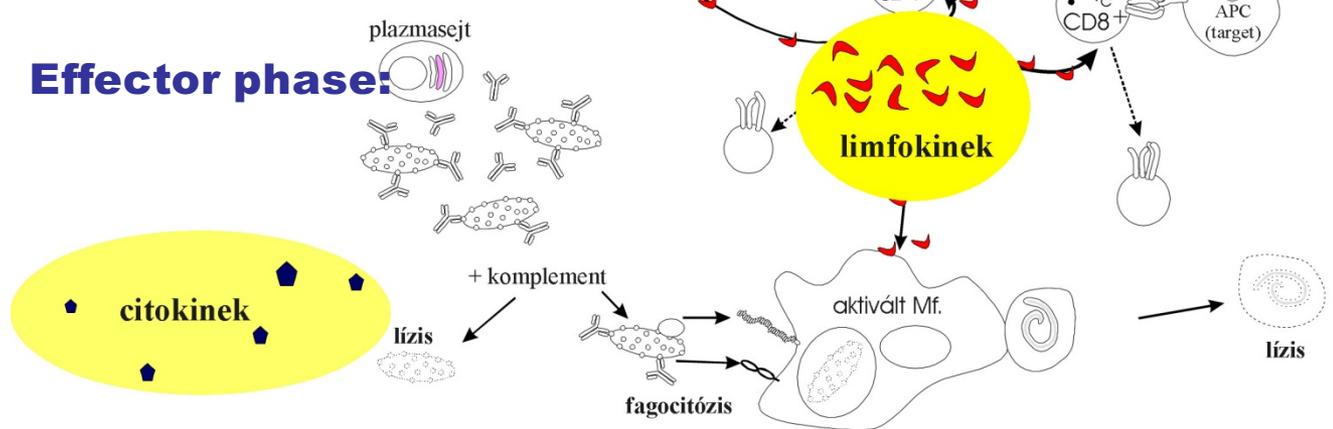
## Recognition:



## Activation:



## Effector phase:

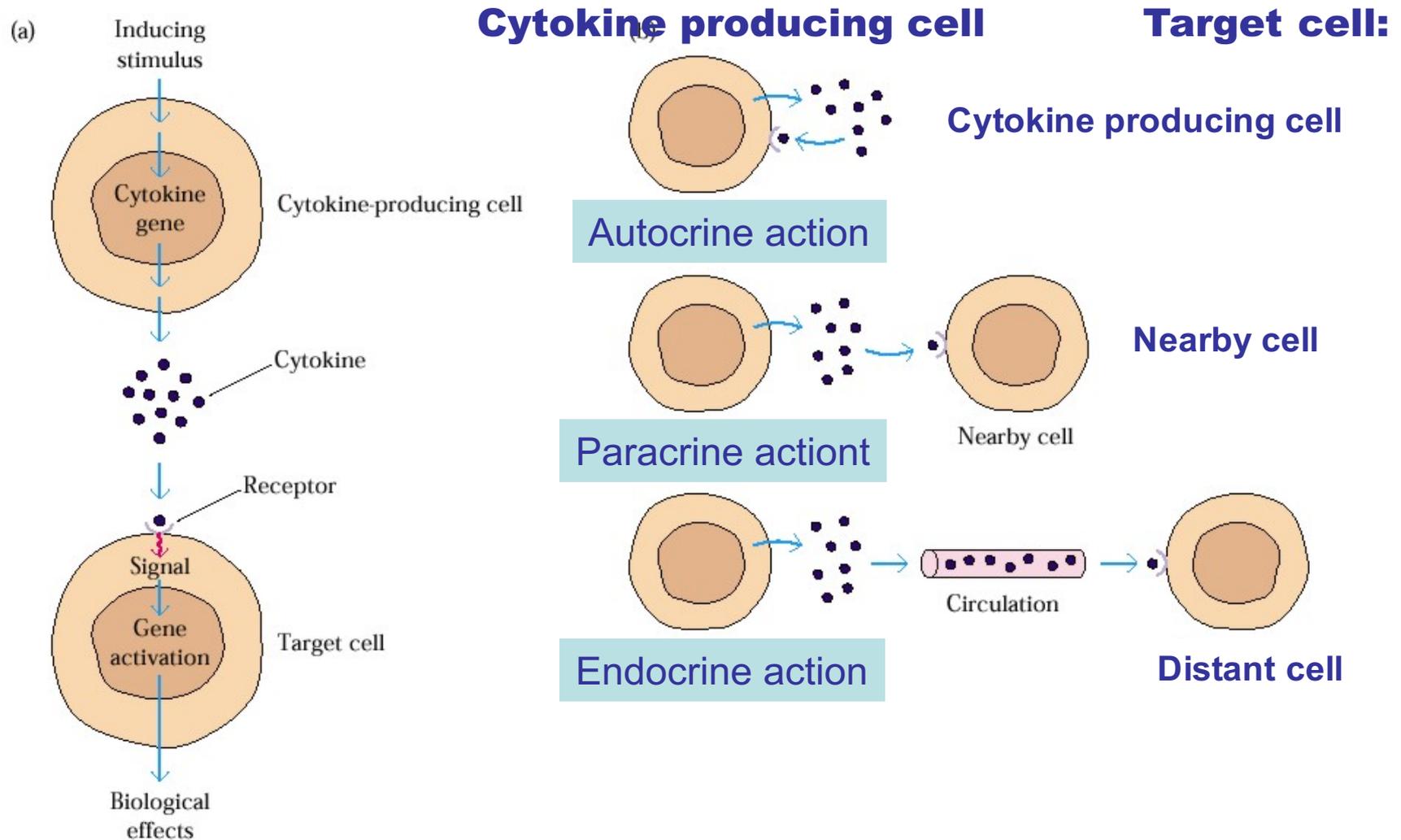


# Basic characteristics of cytokines

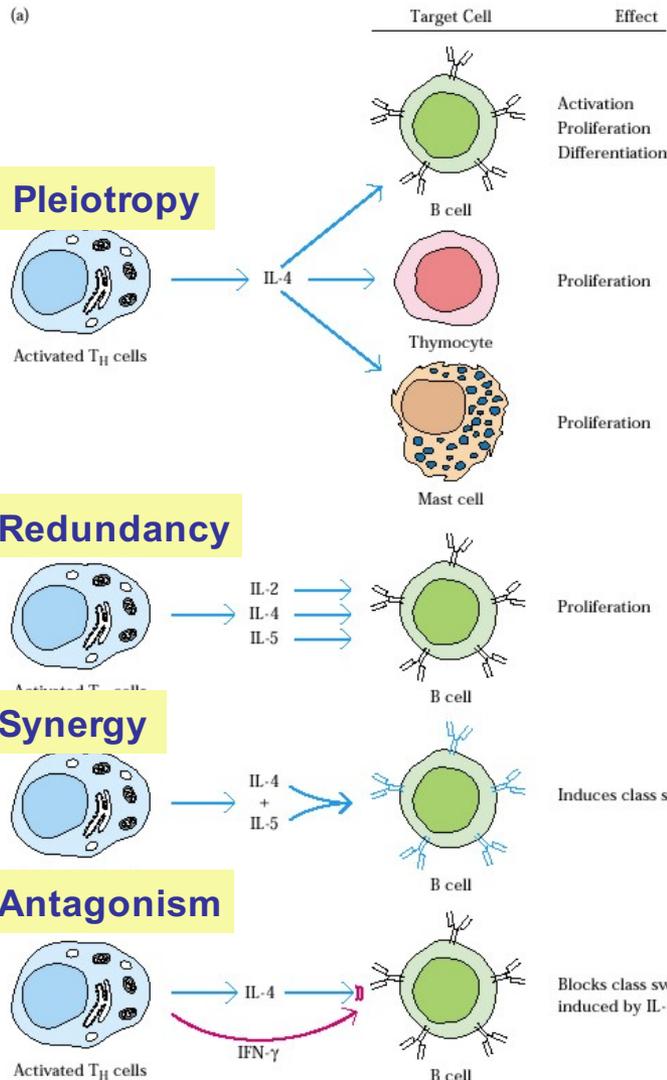
- Low molecular weight (10-40 kDa) glycoproteins
- Isolated cells secrete them, due to gene activation
- They mediate cell-cell interaction:
  - - sending information
  - - regulation of immune response
- Mechanism of action:
  - produced after transient gene activation
  - act through receptors triggering signal-transduction
  - high affinity
  - picomolar concentration

They act mostly locally.

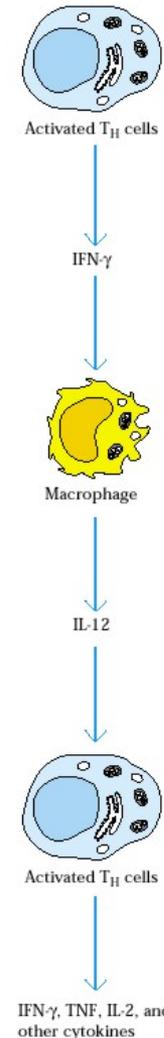
# Mechanism of cytokine action I.:



# Mechanism of cytokine action II.:



## Starting a cascade



A cytokine induces different effects on different target cells

The action of more cytokine on the target cell is similar

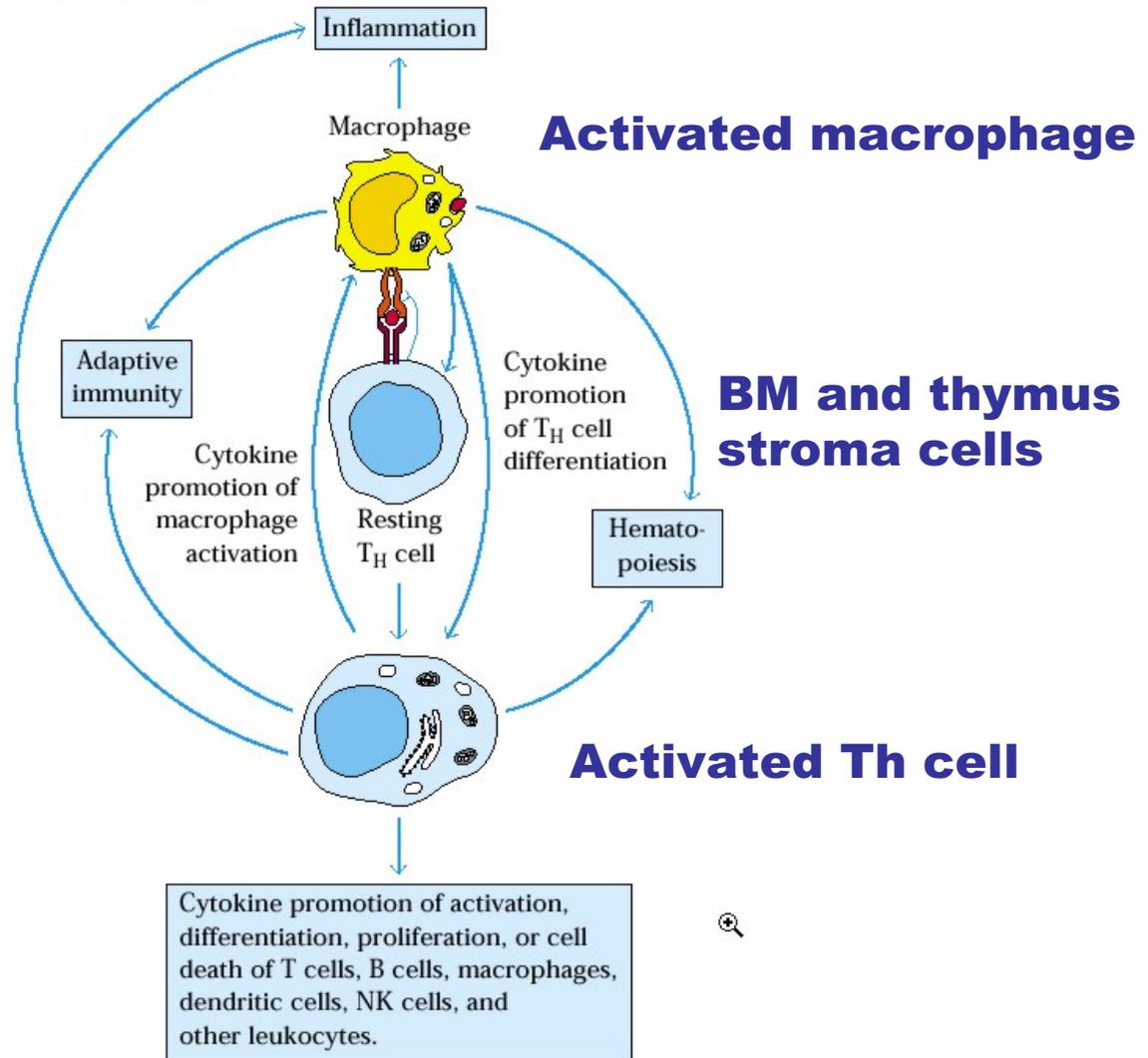
The effect of two cytokines is stronger than their additive effects

One cytokine inhibits the effects of another cytokine

# Cytokine producing cells



VISUALIZING CONCEPTS.

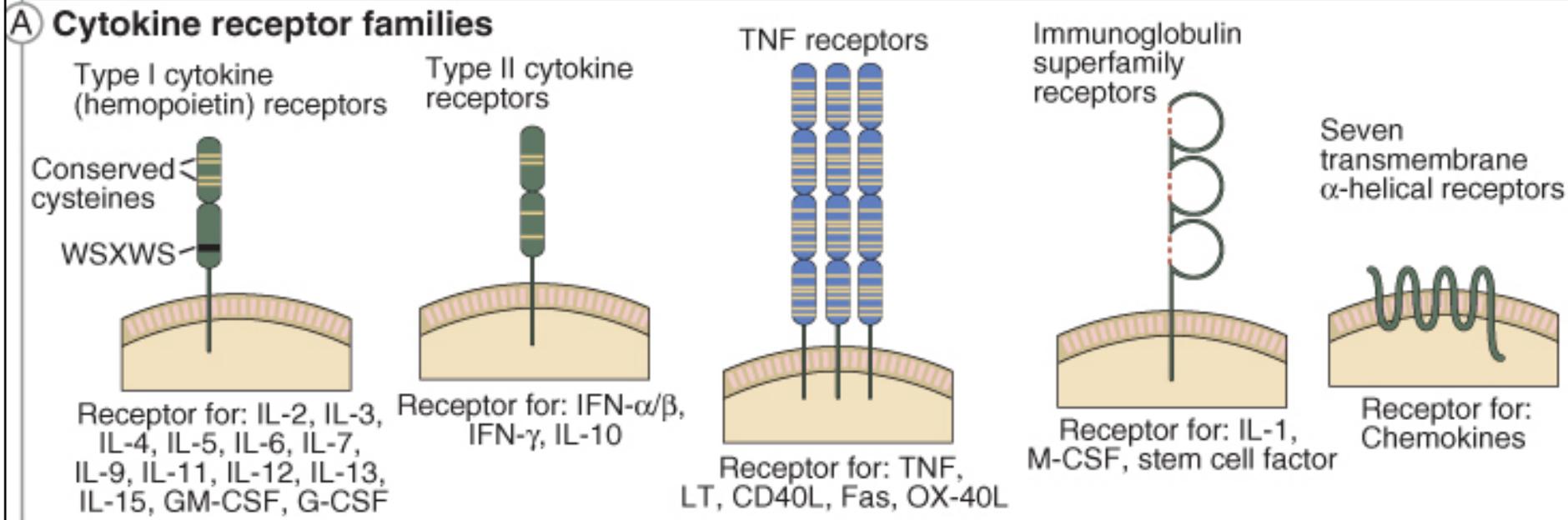


# Functional groups of cytokines

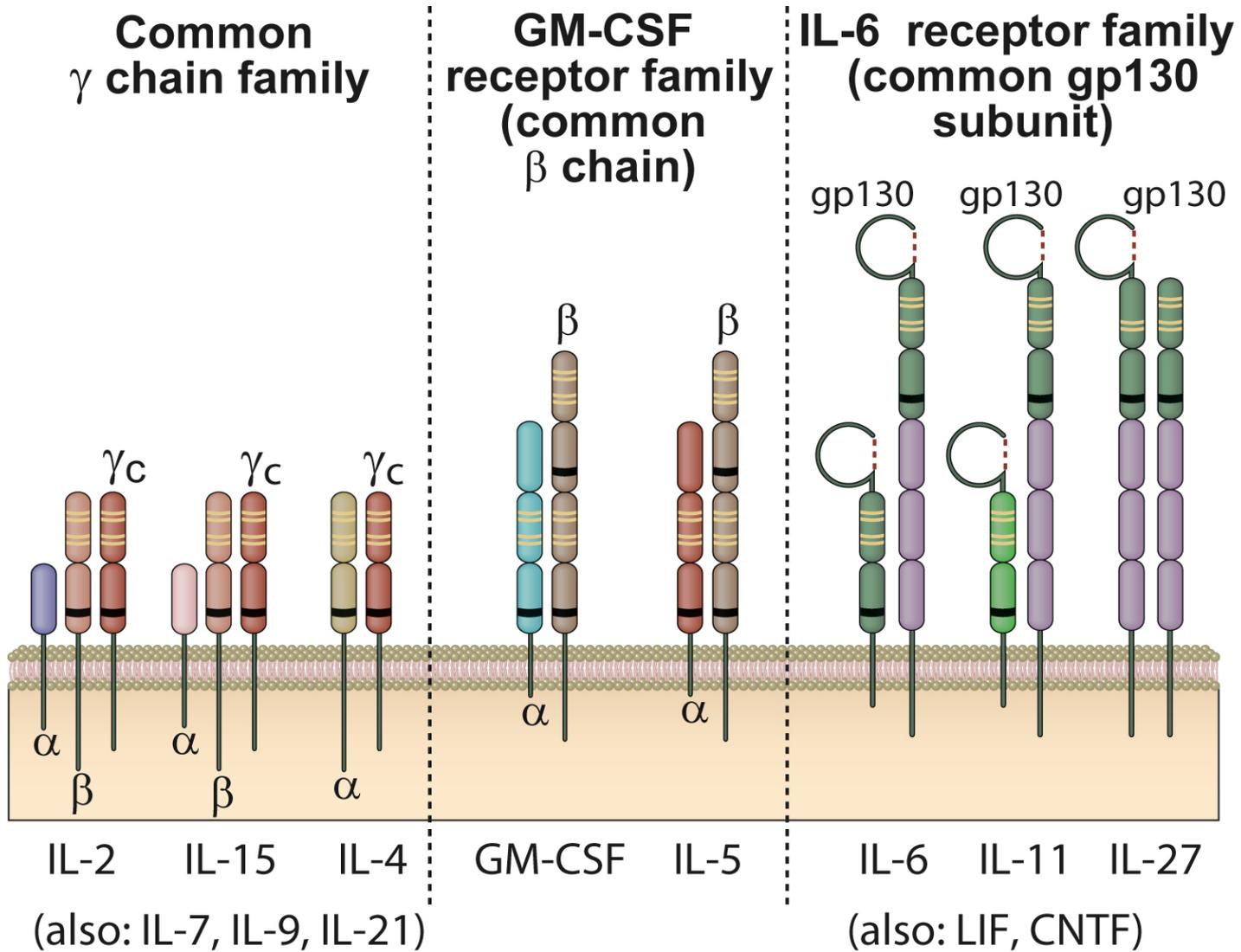
<p>I. Regulators of natural immunity and inflammation</p>	<p>IFN<math>\alpha</math>, IFN<math>\beta</math>, IL-1<math>\alpha</math>, IL-1<math>\beta</math>, IL-6, TNF<math>\alpha</math> IL-12,  Chemokines: CXCL8 (IL-8), CCL3,4 (MCP, MIP-1)</p>
<p>II. Regulators of lymphocyte activation and differentiation</p>	<p>TH1: IL-2, INF<math>\gamma</math>, TNF<math>\beta</math> (LT) TH2: , IL-4, IL-5, IL-6, IL-13, IL-15  Treg: IL-10 and TGF<math>\beta</math></p>
<p>III. Regulators of haematopoiesis</p>	<p>IL-3, IL-7, GM-CSF, SCF</p>

# **Cytokine receptors**

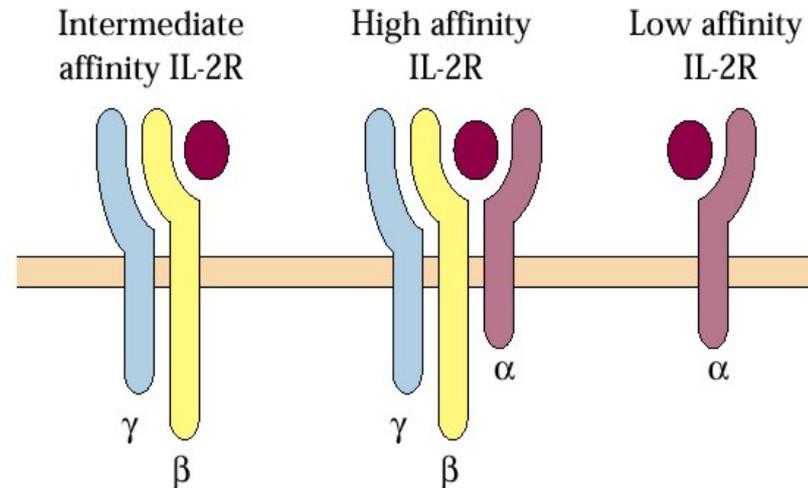
# Cytokine receptor families



# Characteristics of multichain cytokine receptors



# IL-2 receptor chains:



Subunit composition:	IL-2R $\beta$ IL-2R $\gamma$	IL-2R $\alpha$ IL-2R $\beta$ IL-2R $\gamma$	IL-2R $\alpha$
Affinity constant ( $K_a$ ):	$10^7 M$	$10^{11} M$	$10^8 M$
Dissociation constant ( $K_d$ ):	$10^{-9} M$	$10^{-11} M$	$10^{-8} M$
Cells expressed by:	NK cells Resting T cells (low numbers)	Activated CD4 <sup>+</sup> and CD8 <sup>+</sup> T cells Activated B cells (low numbers)	

# Cytokine Induction of JAK-STAT Signaling

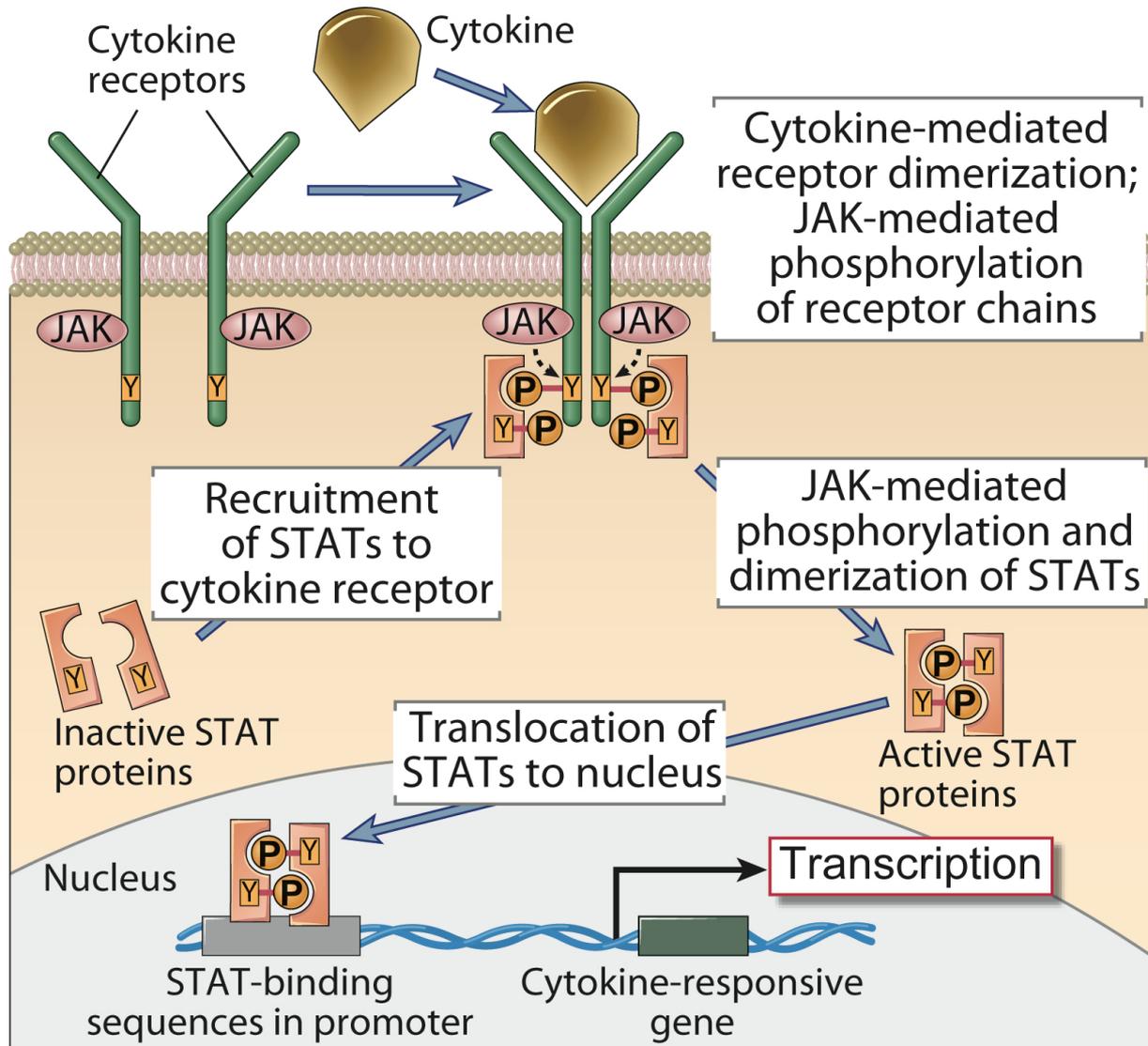


Fig. 7-25

# TNF Receptor Signaling

Cross-linking of TNF-R1 by TNF

Binding of adaptor protein

Binding of signaling intermediates

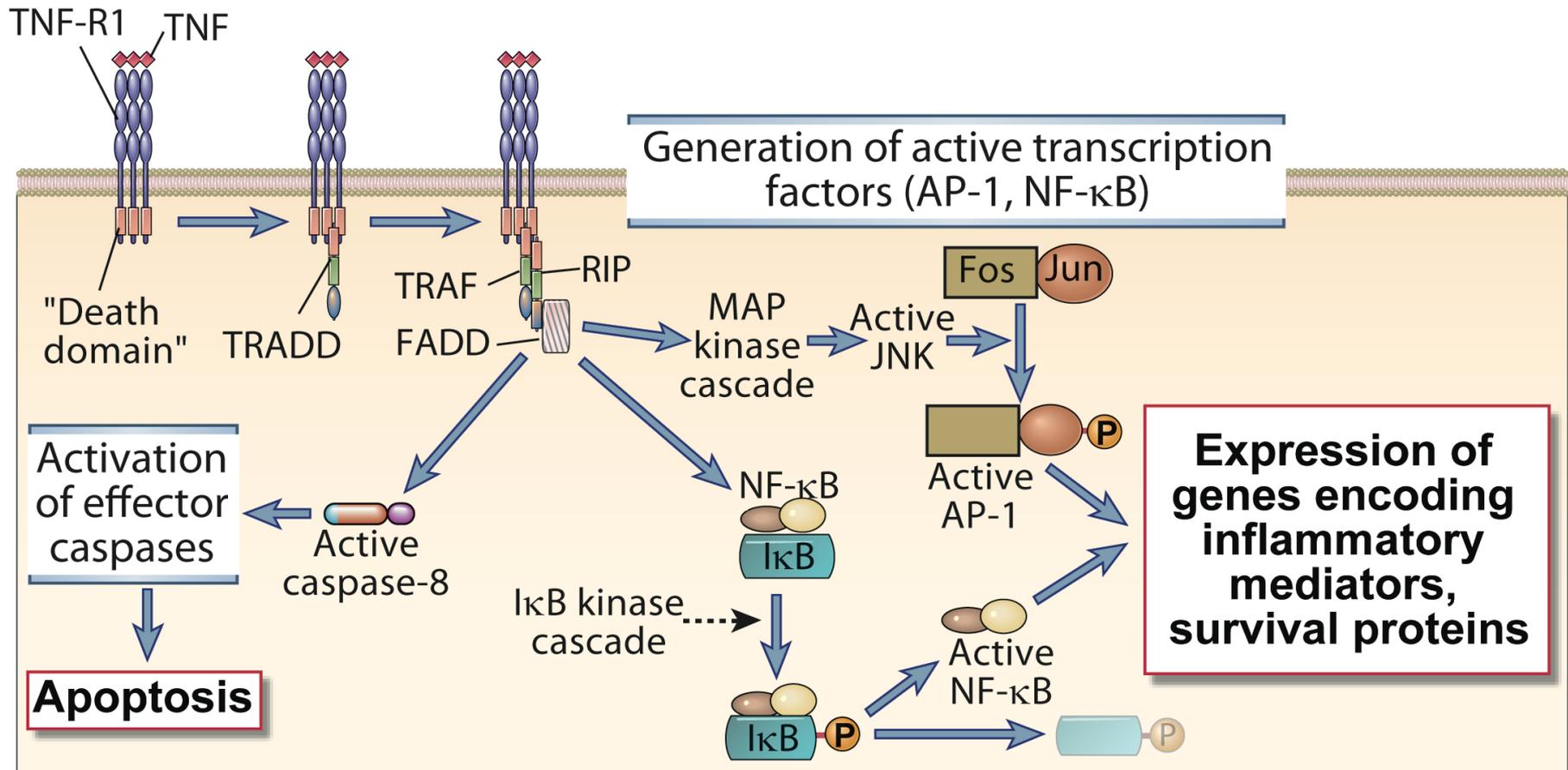
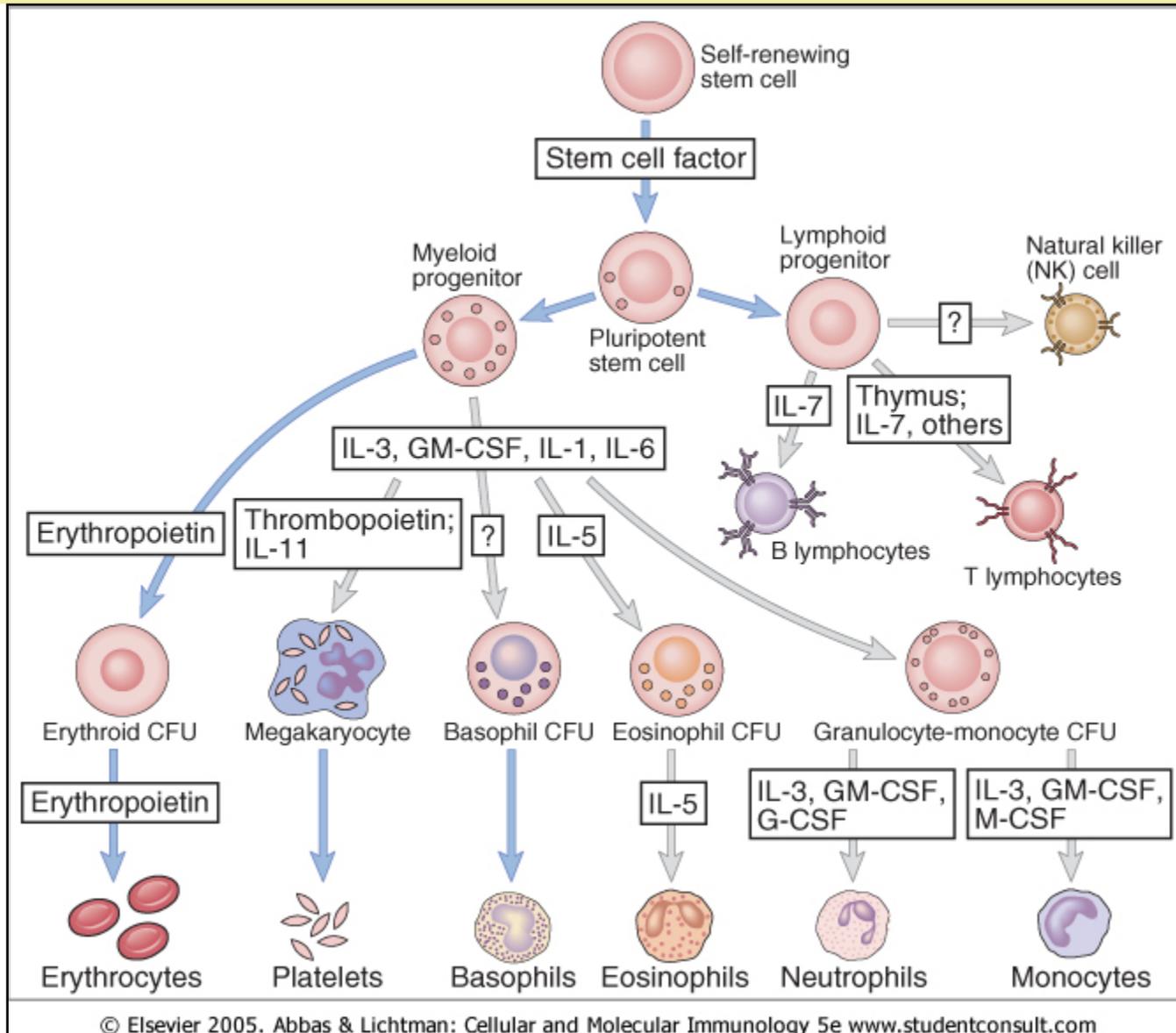


Fig. 7-24

# **Functional groups of cytokines:**

- 1. Haematopoietic cytokines –  
growth factors**

# Haematopoietic cytokines – growth factors



# Haemopoietic growth factors

CSF: Colony Stimulating Factor

SCF: stem cell factor

GM-CSF

multi-lineage

IL-3

M-CSF

**CSF= Colony Stimulating Factor**

G-CSF

Lineage-specific

EPO

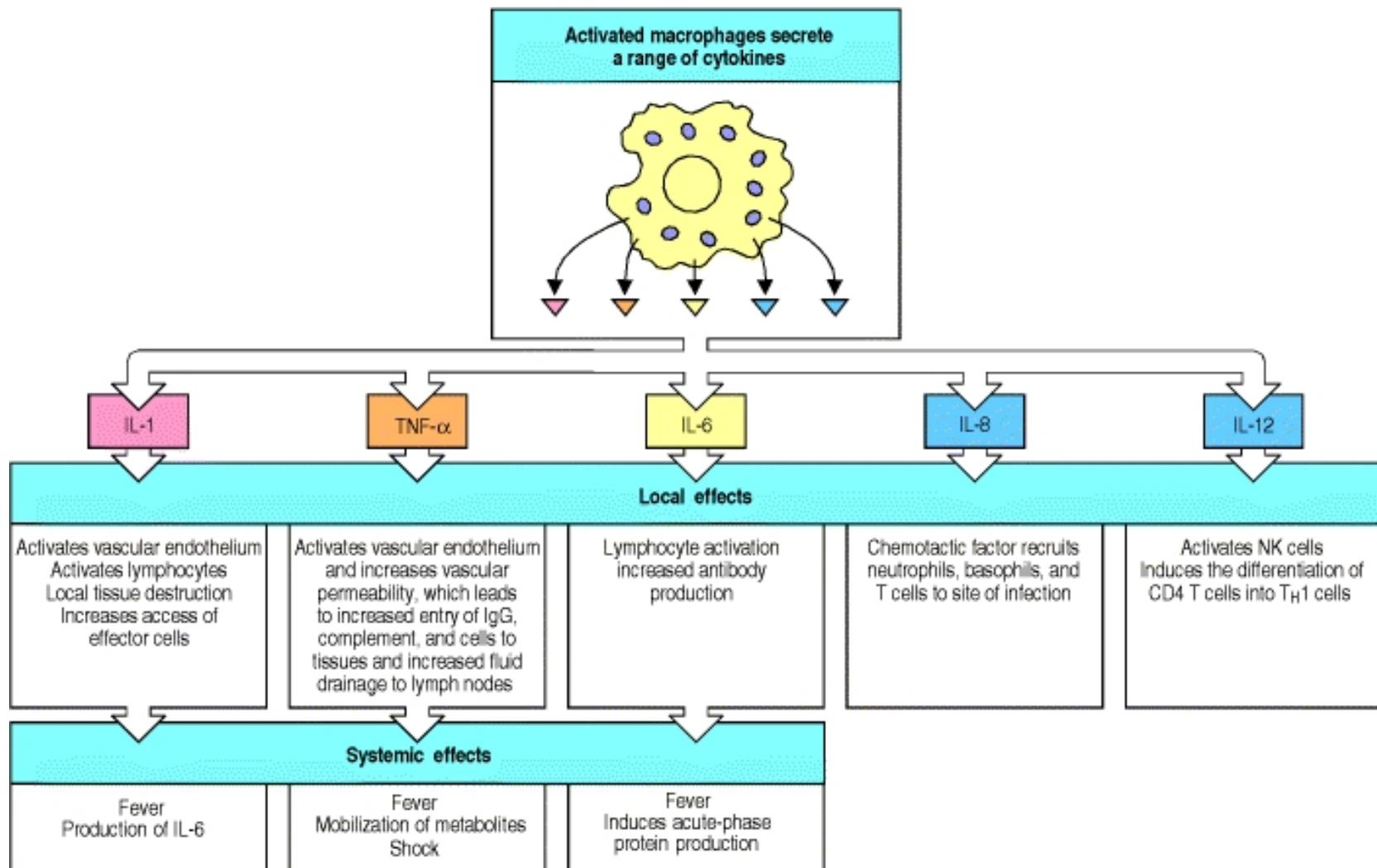
TPO

IL-5

IL-7 : T and B cell maturation

# Functional groups of cytokines:

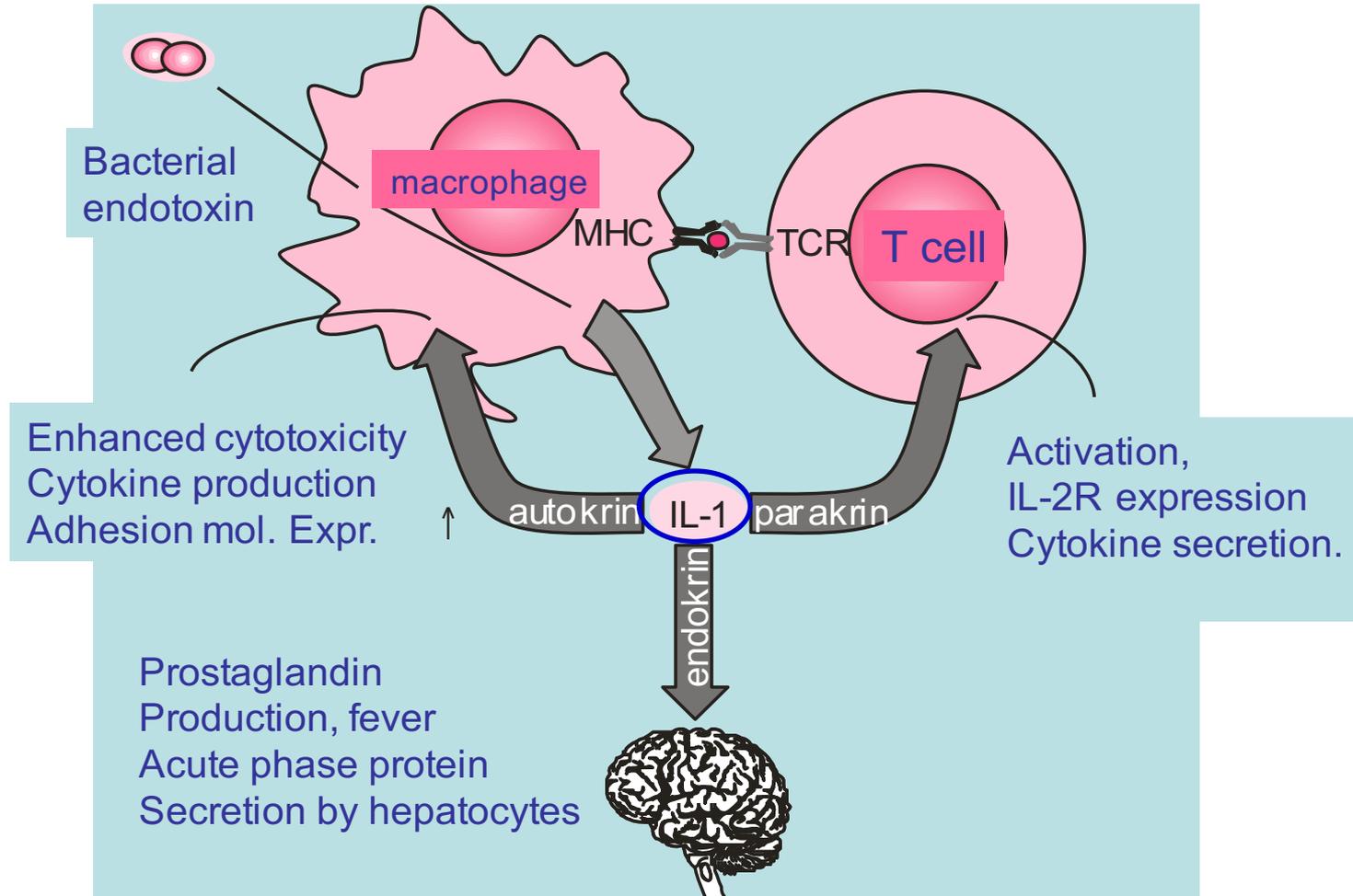
## 2. Inflammatory cytokines, chemokines



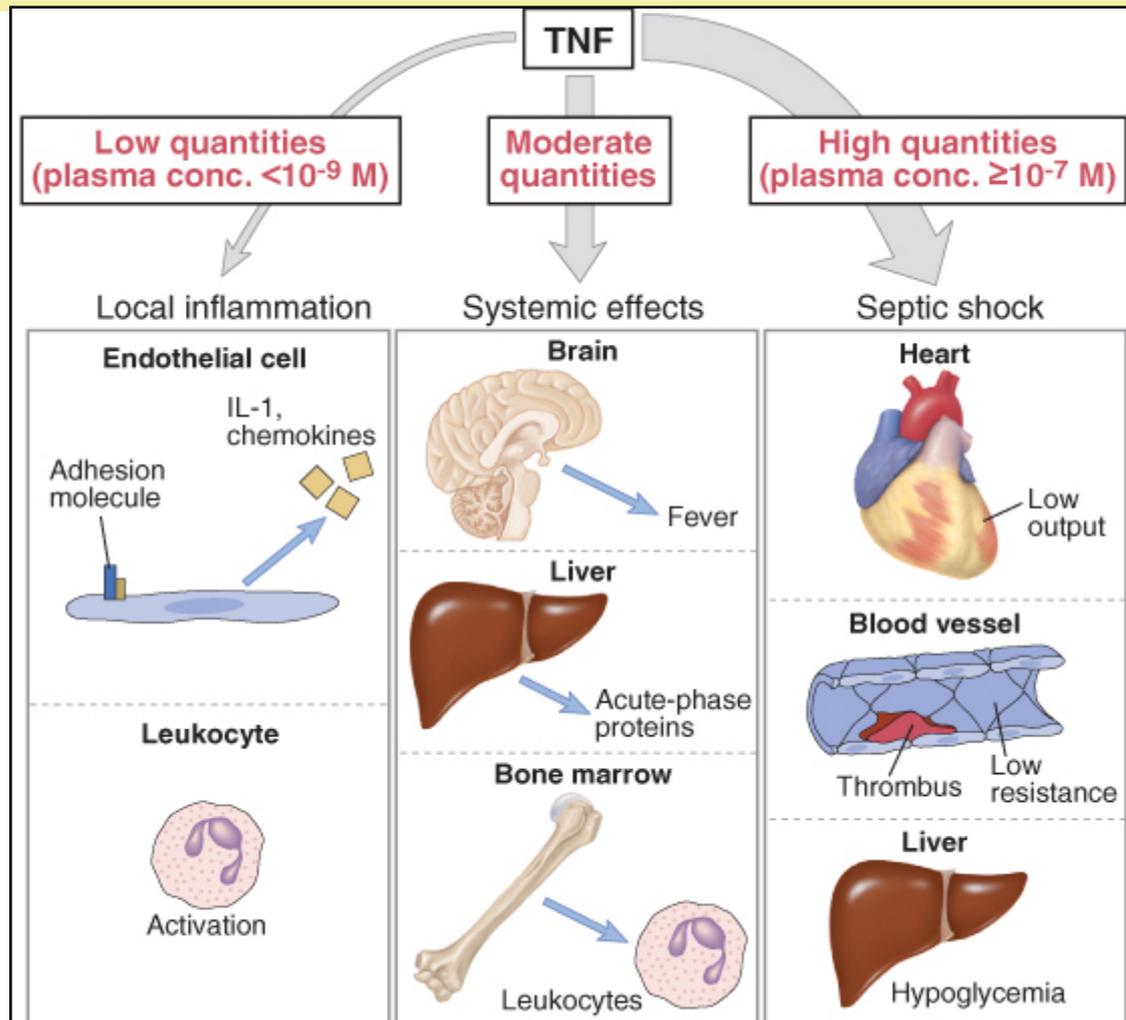
IMPORTANT CYTOKINES SECRETED BY MACROPHAGES IN RESPONSE TO BACTERIAL PRODUCTS INCLUDE IL-1, IL-6, IL-8, IL-12, AND TNF- $\alpha$

**TNF- $\alpha$**  is an inducer of a local inflammatory response that helps to contain infections; it also has systemic effects, many of which are harmful (see [Section 2-23](#)). **IL-8** is also involved in the local inflammatory response, helping to attract neutrophils to the site of infection. **IL-1**, **IL-6**, and **TNF- $\alpha$**  have a critical role in inducing the [acute-phase response](#) in the liver (see [Section 2-24](#)) and induce fever, which favors effective host defense in several ways. **IL-12** activates natural killer (NK) cells and favors the differentiation of [CD4 T cells](#) into the TH1 subset during adaptive immunity.

# Autocrine, paracrine and endocrine action of IL-1



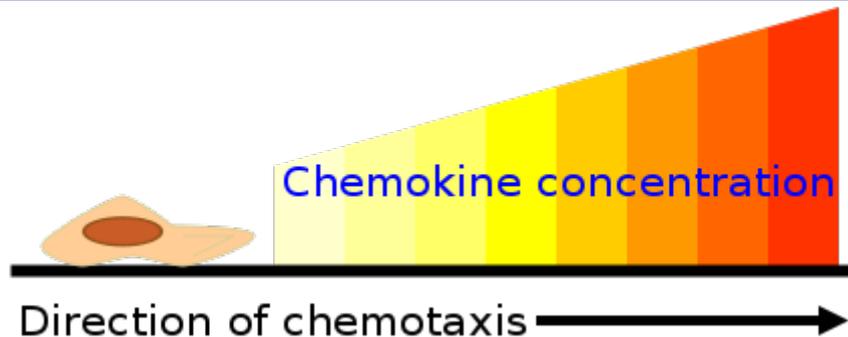
# Concentration dependent effects of TNF $\alpha$



# Chemokines

## Functions:

- Chemotaxis for different leukocytes
  - regulation of normal leukocyte traffic
  - recruitment of cells to inflammatory sites
- Enhancement of cell adhesion
- Activation of effectors leukocytes
- Development of inflammatory reaction
- Development of normal lymphoid tissues

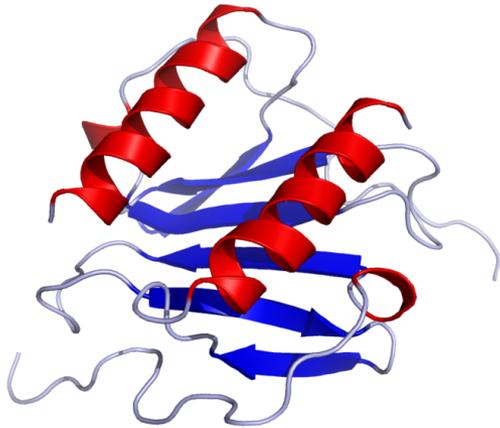


- Chemokines possess 4 conserved cysteine residues:

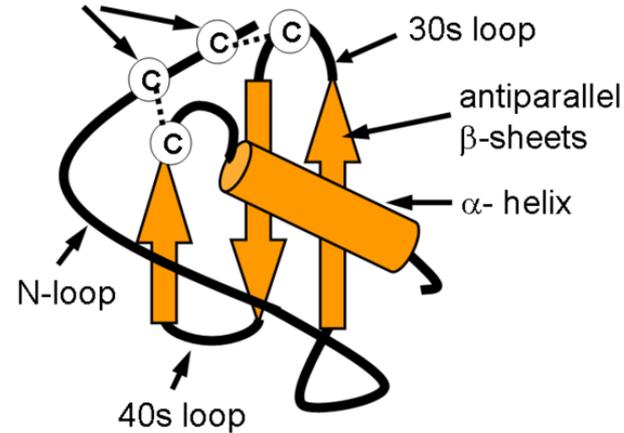
$\alpha$  Chemokines: C-X-C

$\beta$  Chemokines: C-C

$\delta$  Chemokines

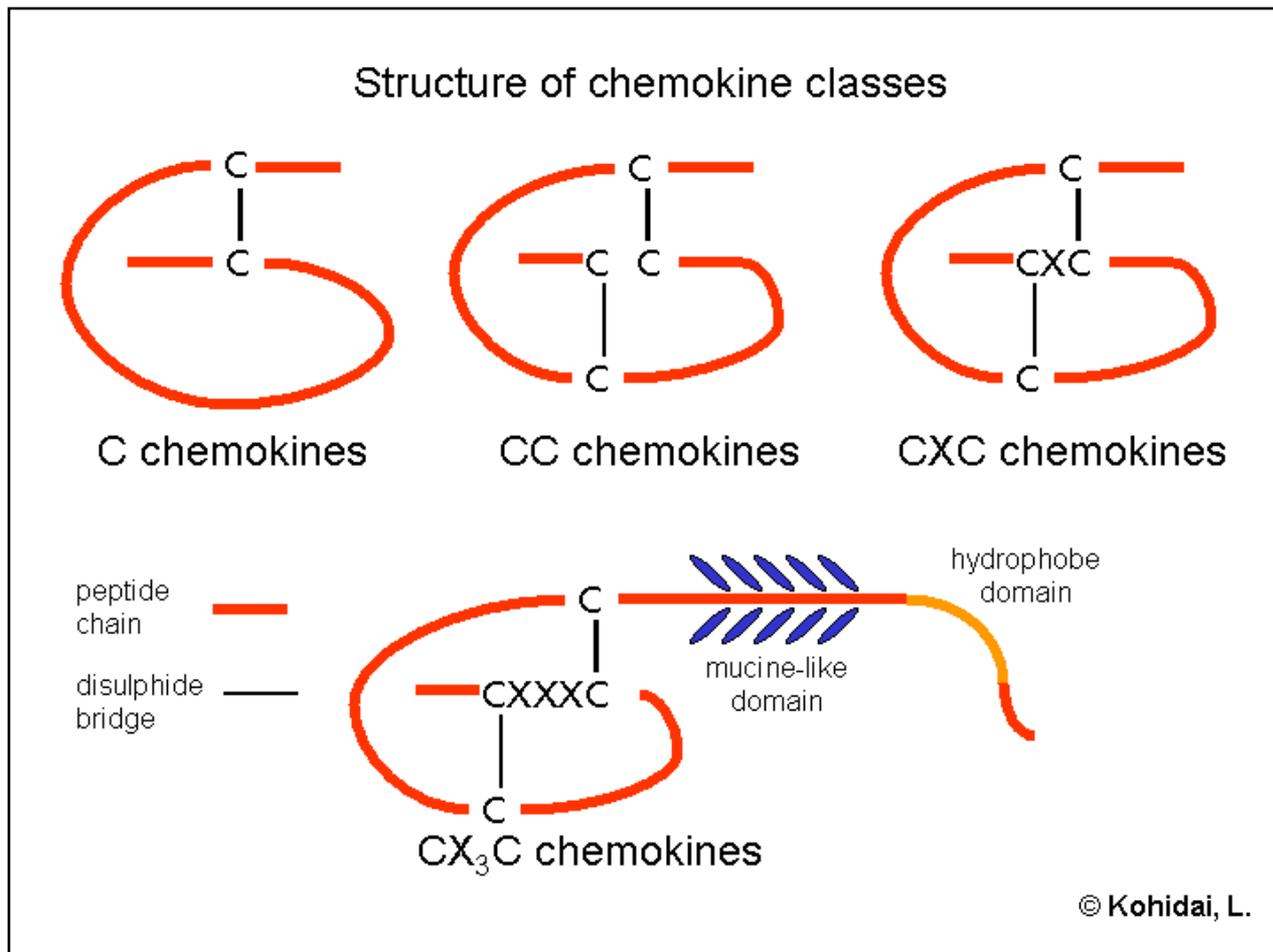


Three dimensional structure of chemokines  
disulphide bridges of Cys-Cys



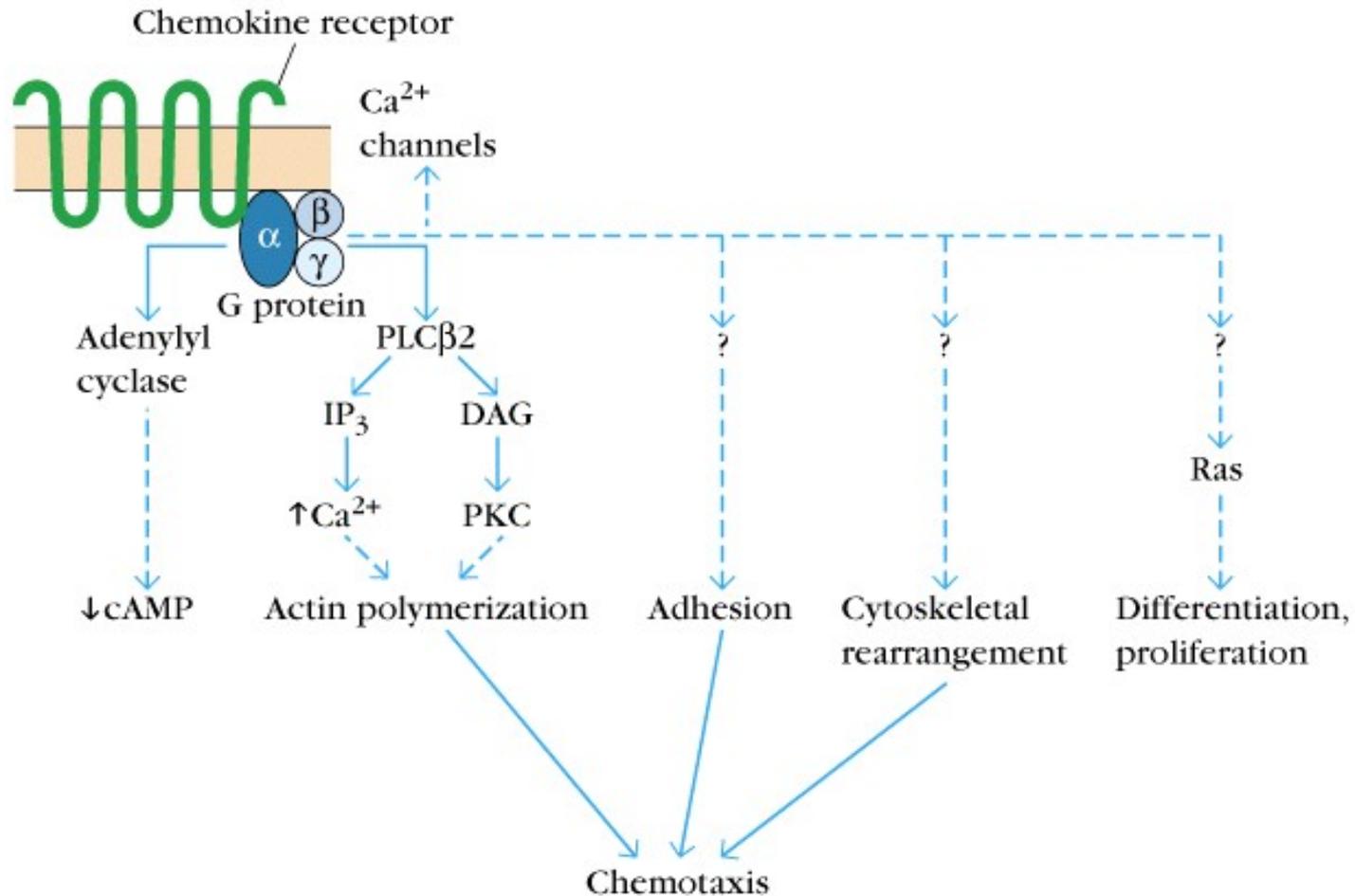
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- „small cytokines”: MW: 8-10 kD
- special structure

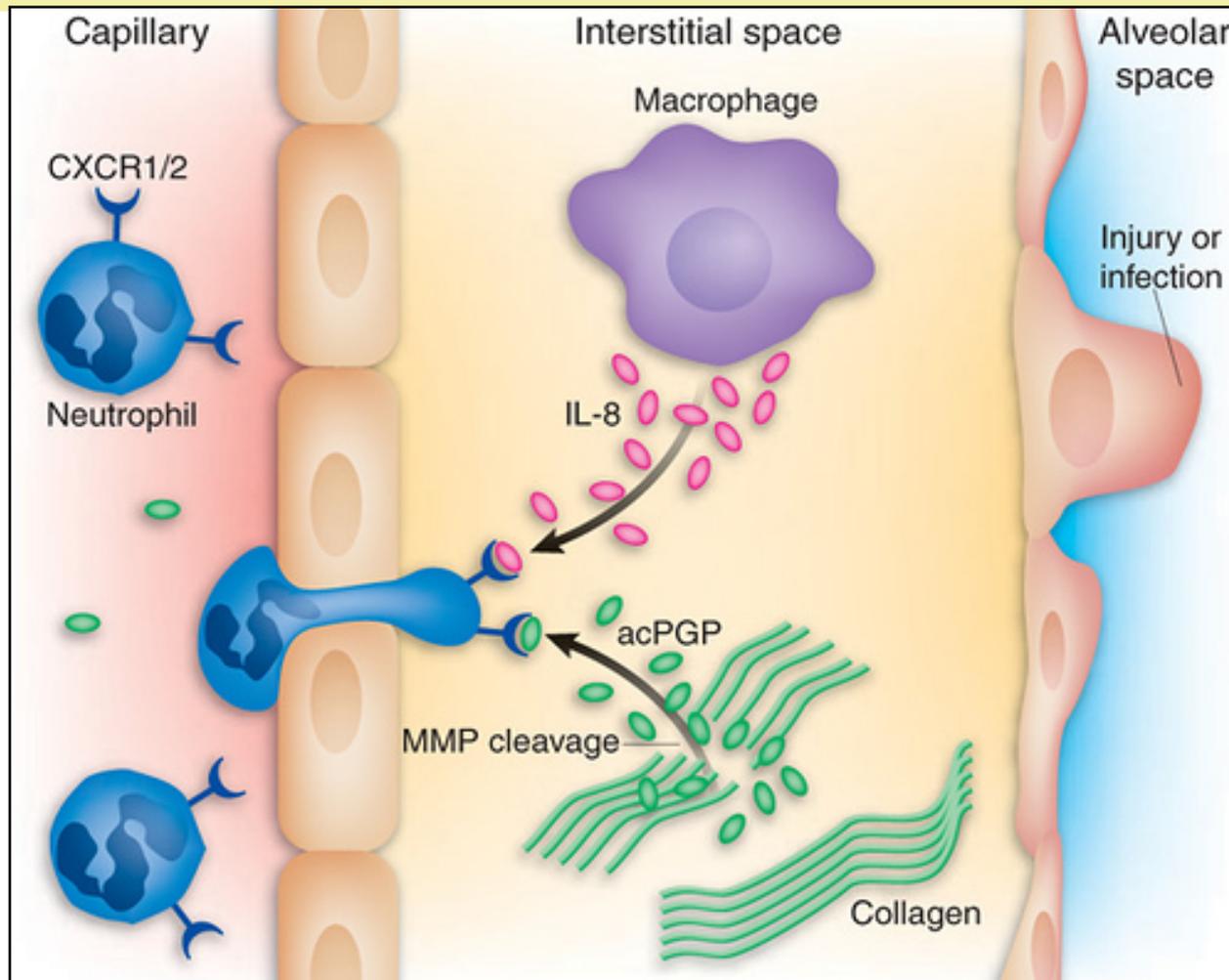


They all possess conserved **cytseins** that are important for creating their 3-dimensional structure: 4 cysteins interact with each other in pairs to create a **Greek key shape** that is a characteristic of chemokines. **Intramolecular S-S bonds** typically join the first to third, and the second to fourth cysteine residues

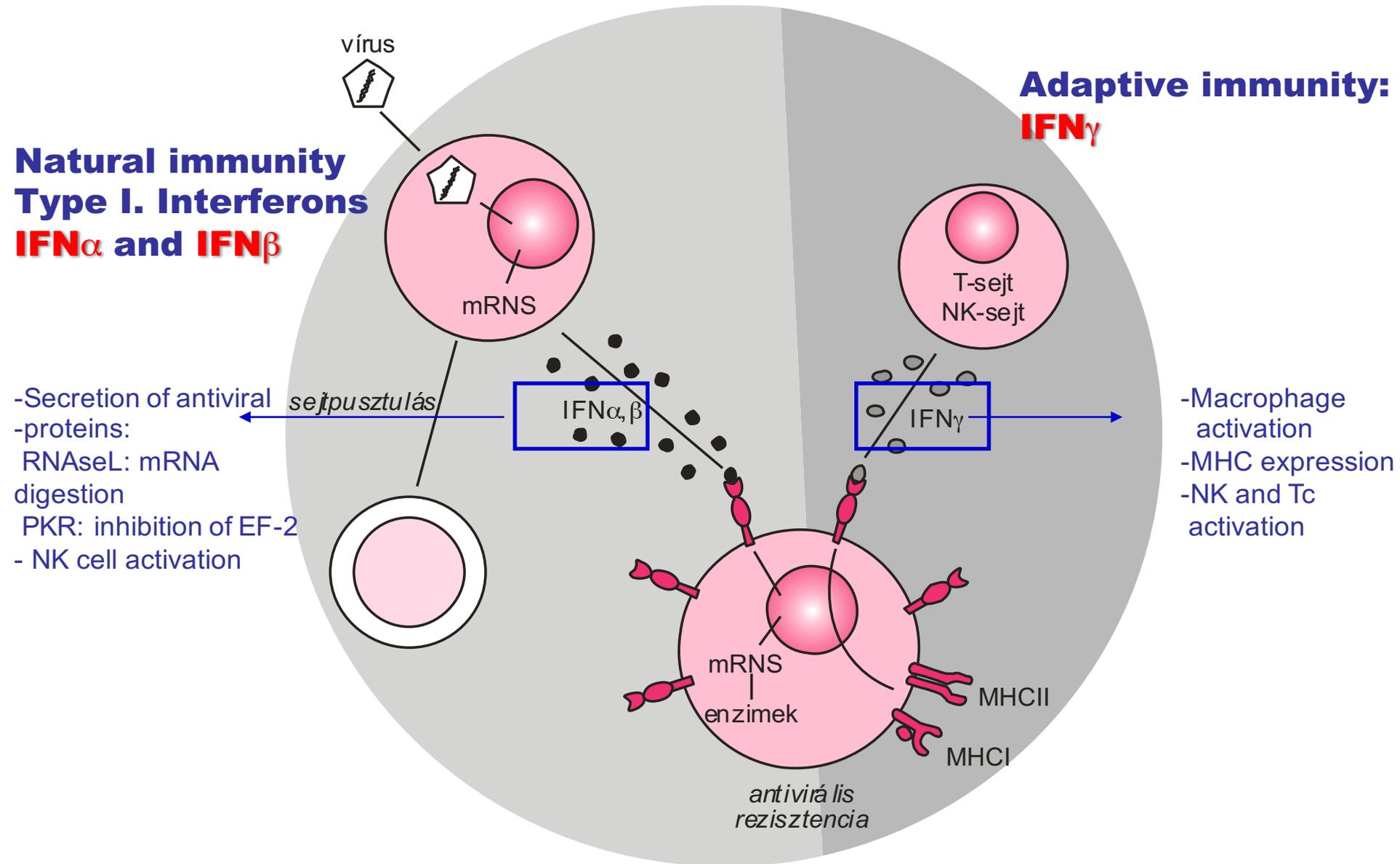
# Chemokines signal through receptors coupled with G-proteins



# Recruitment of neutrophil granulocytes to the site of inflammation

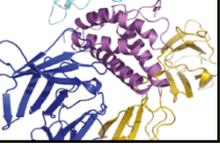


# Antiviral effects of interferons:



## Functional groups of cytokines:

### **3. Cytokines, regulating specific immune response**



# $T_H1$ , $T_H2$ , and $T_H17$ Subsets of $CD4^+$ T Cells

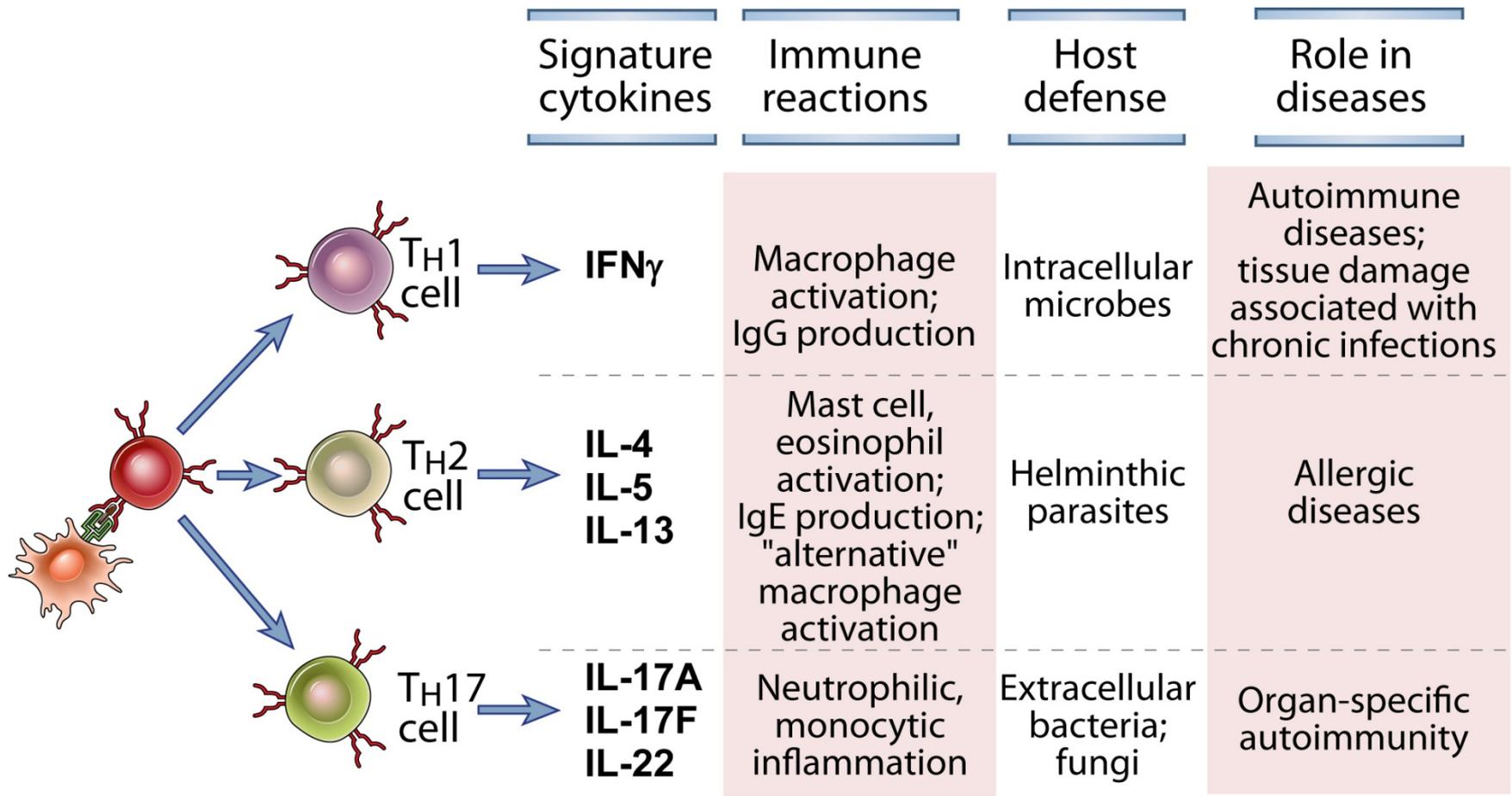
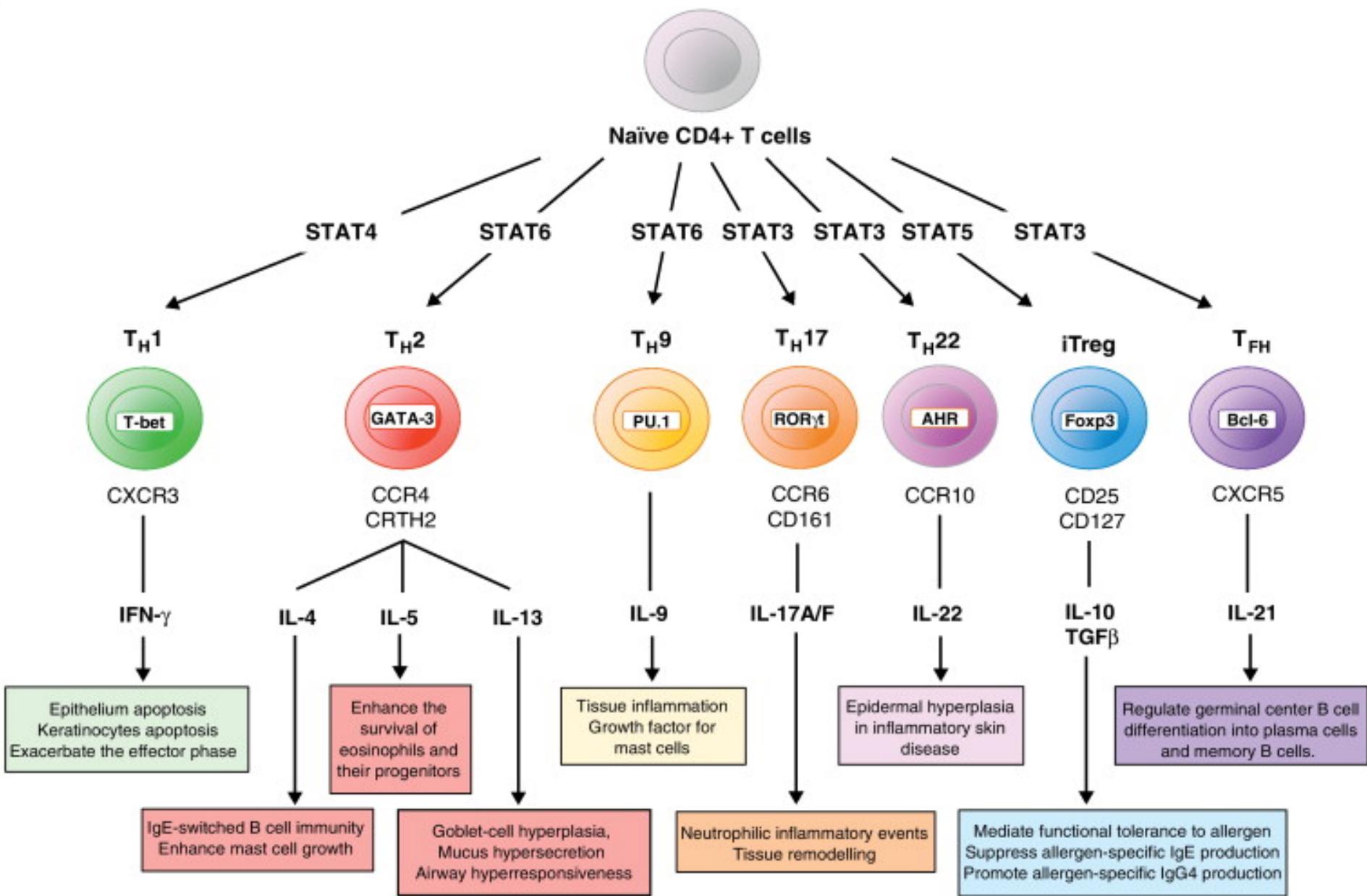
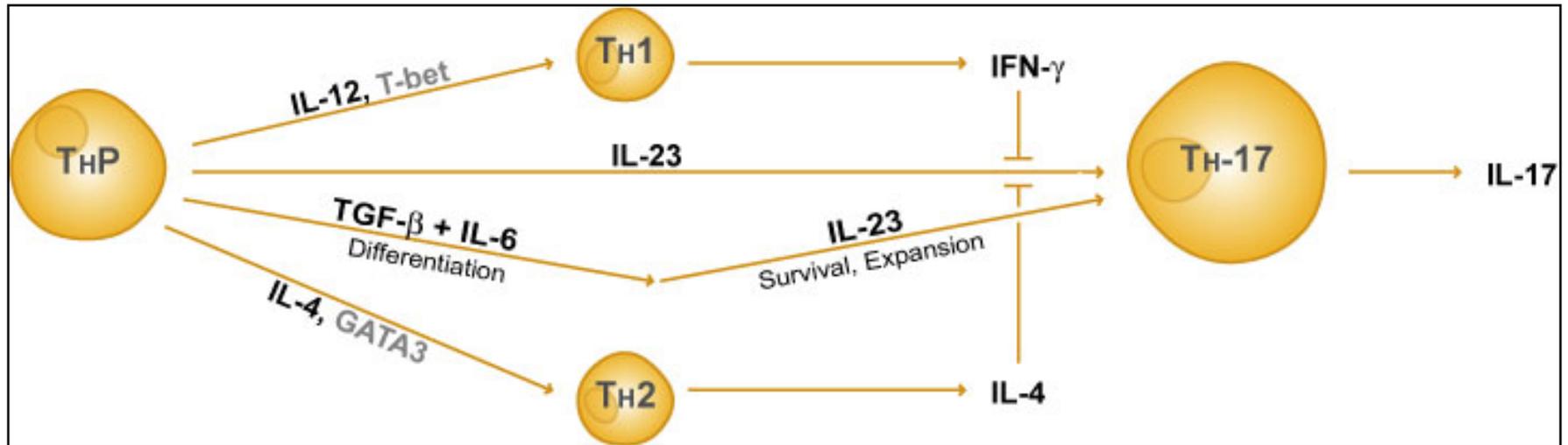


Fig. 9-13

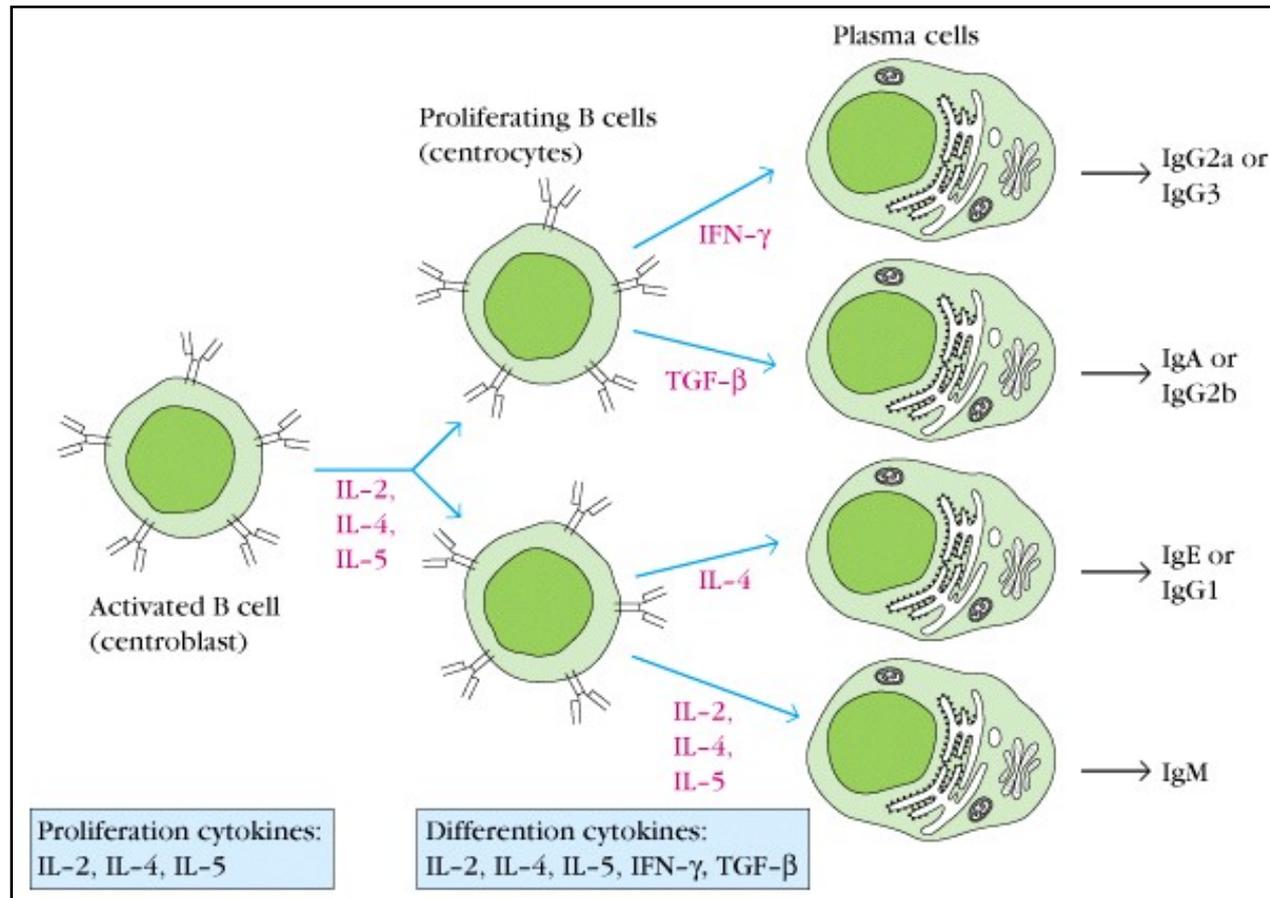


# Development of CD4+ Th17 cells



The Th17 derived IL-17 induces inflammation. It correlates with the severity of different immunological diseases: rheumatoid arthritis, asthma, multiple sclerosis, psoriasis, transplant rejection.

# Cytokines regulate B cell activation, proliferation and isotype (class) switching



# Viral mimics of cytokines and cytokine receptors

Virus	Product
Leporipoxvirus (a myxoma virus)	Soluble IFN- $\gamma$ receptor
Several poxviruses	Soluble IFN- $\gamma$ receptor
Vaccinia, smallpox virus	Soluble IL-1 $\beta$ receptor
Epstein-Barr	IL-10 homolog
Human herpesvirus-8	IL-6 homolog; also homologs of the chemokines MIP-I and MIP-II
Cytomegalovirus	Three different chemokine receptor homologs, one of which binds three different soluble chemokines (RANTES, MCP-1, and MIP-1 $\alpha$ )

## Cytokine-Based Therapies In Clinical Use

Agent	Nature of agent	Clinical application
Enbrel	Chimeric TNF-receptor/IgG constant region	Rheumatoid arthritis
Remicade	Monoclonal antibody against TNF- $\alpha$ receptor	Rheumatoid arthritis
Interferon $\alpha$ -2a	Antiviral cytokine	Hepatitis B Hairy cell leukemia Kaposi's sarcoma
Interferon $\alpha$ -2b	Antiviral cytokine	Hepatitis C Melanoma
Interferon $\beta$	Antiviral cytokine	Multiple sclerosis
Actimmune	Interferon $\gamma$	Chronic granulomatous disease (CGD) Osteopetrosis
Neupogen	G-CSF (hematopoietic cytokine)	Stimulates production of neutrophils Reduction of infection in cancer patients treated with chemotherapy
Leukine	GM-CSF (hematopoietic cytokine)	Stimulates production of myeloid cells after bone-marrow transplantation
Neumega	Interleukin 11 (IL-11), a hematopoietic cytokine	Stimulates production of platelets
Epogen	Erythropoietin (hematopoietic cytokine)	Stimulates red-blood-cell production

# Cytokine balance of inflammation

