

# Definition and general properties of Cytokines

## I . Definition

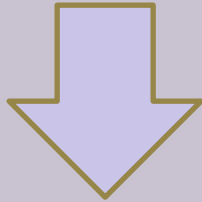
A

group of low molecular weight polypeptides or proteins which are secreted by activated immunocytes or some matrix cells and possess high activity and various functions.

Their major functions are to mediate and regulate immune response and inflammatory reactions.

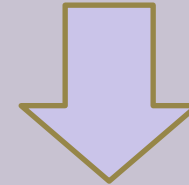
Cytokines are produced by lymphocytes known as lymphokines. where as produced by monocytes or macrophages are called as monokines.

# Release of Cytokines



## **Peripherally**

Mast cell  
Glial cell  
Monocytes  
Macrophages  
Lymphocytes

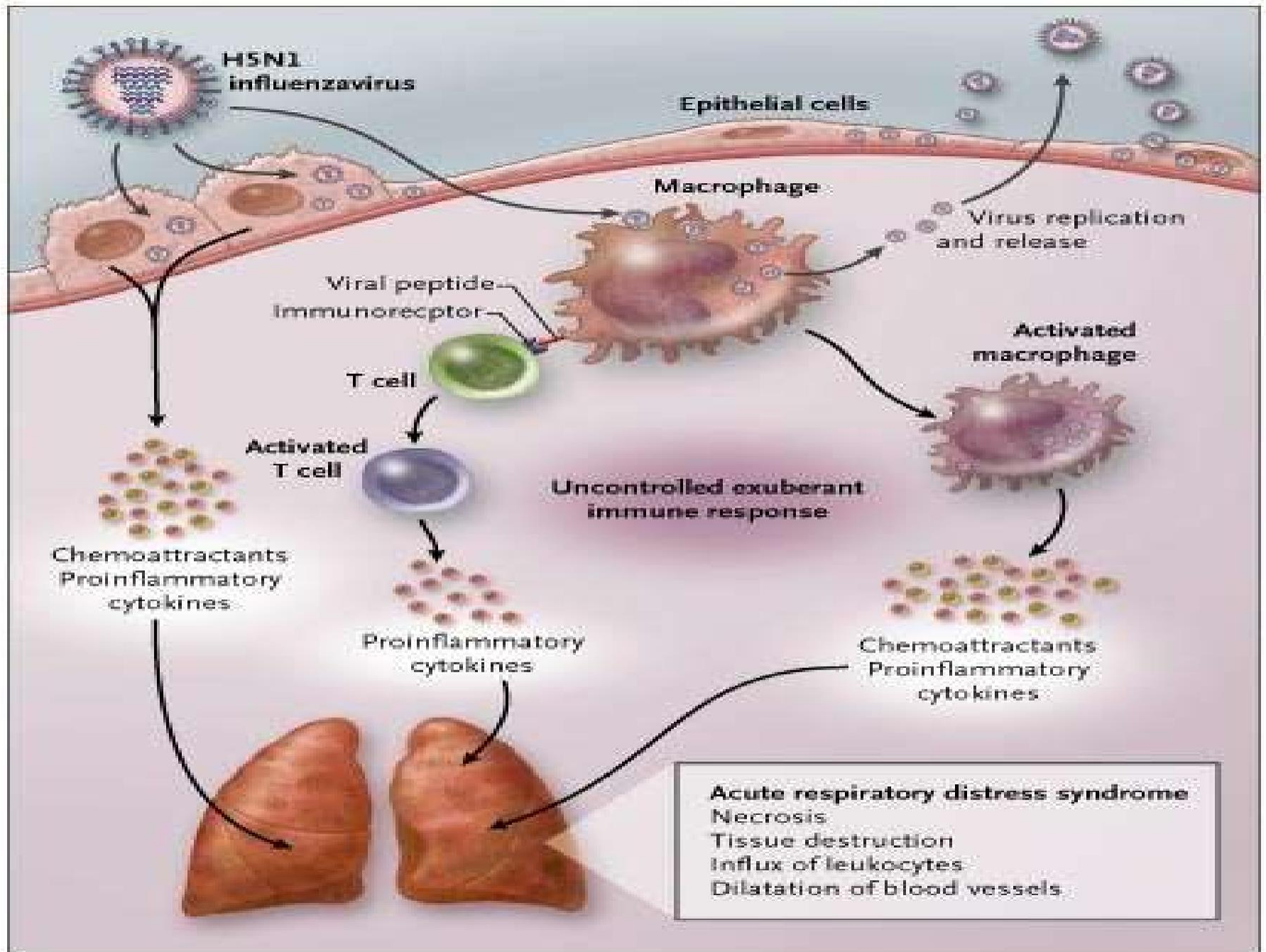


## **Centrally**

Non neuronal cell  
Microglia  
Astrocytes  
Schwan Cells

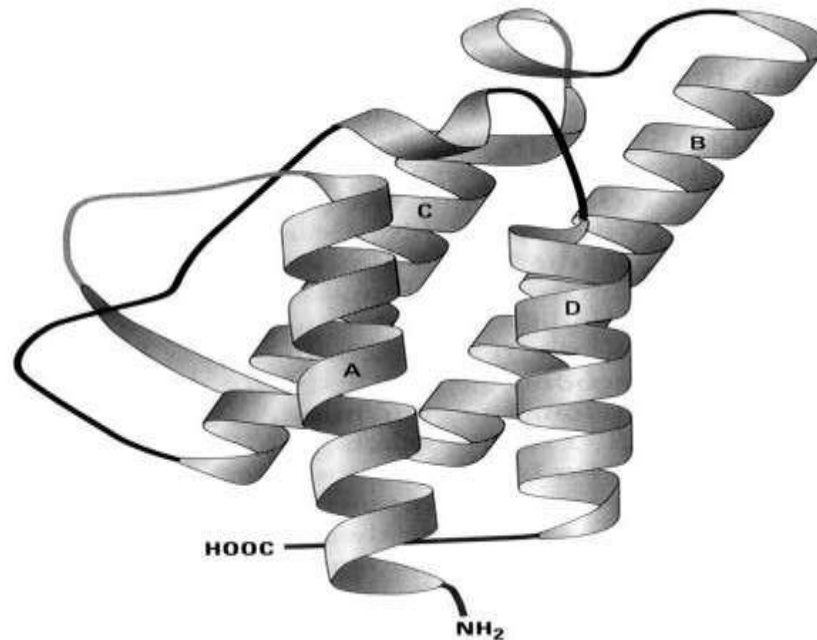
# Cytokine -mediated effects

- ❖ **Cell growth**
- ❖ **Cell differentiation**
- ❖ **Cell death**
- ❖ **Induce non-responsiveness to other cytokines/cells**
- ❖ **Induce responsiveness to other cytokines/cells**
- ❖ **Induce secretion of other cytokines**



# II. General properties of cytokines

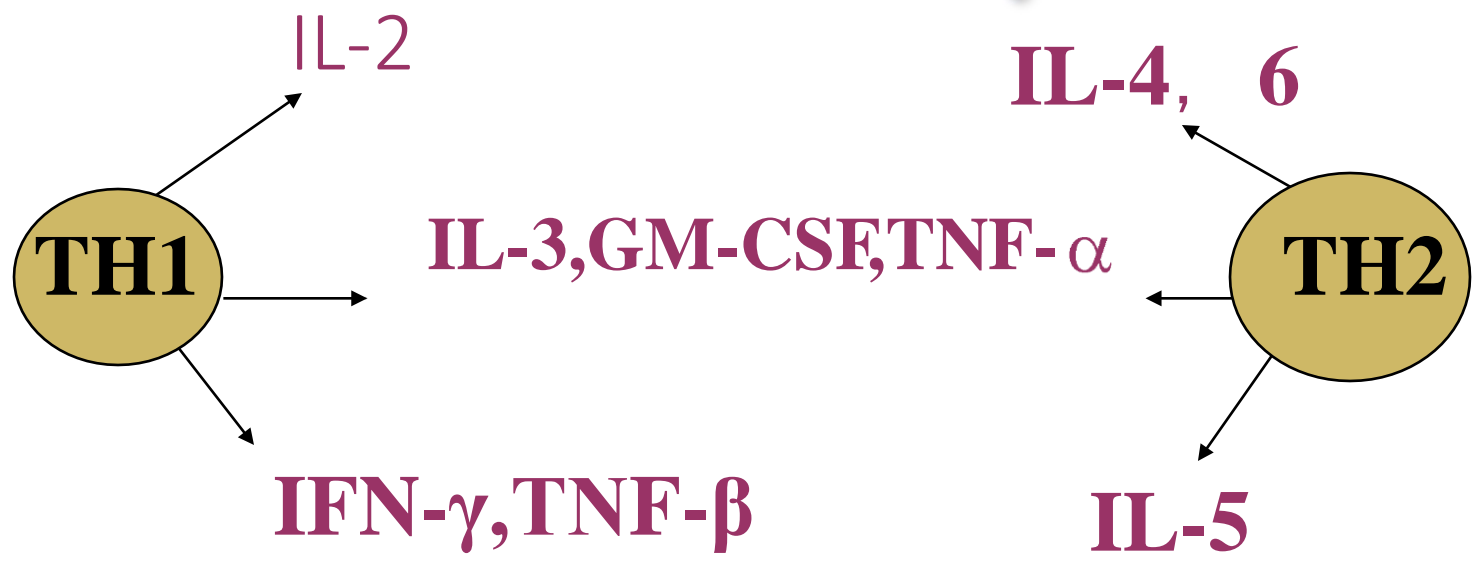
1. Most cytokines are low molecular weight polypeptides or glycoprotein(8~80 KD), and most of them are monomer.



## 2. Natural cytokines are secreted by activated cells

Such as activated immune cells, matrix cells and some tumor cells.

**3. One kind of cytokines can be produced by different cells. One kind of cells can secrete different cytokines.**



# Cytokines can act in three different manners

- **Autocrine**

**Cytokine binds to receptor on cell that secreted it.**

- **Paracrine**

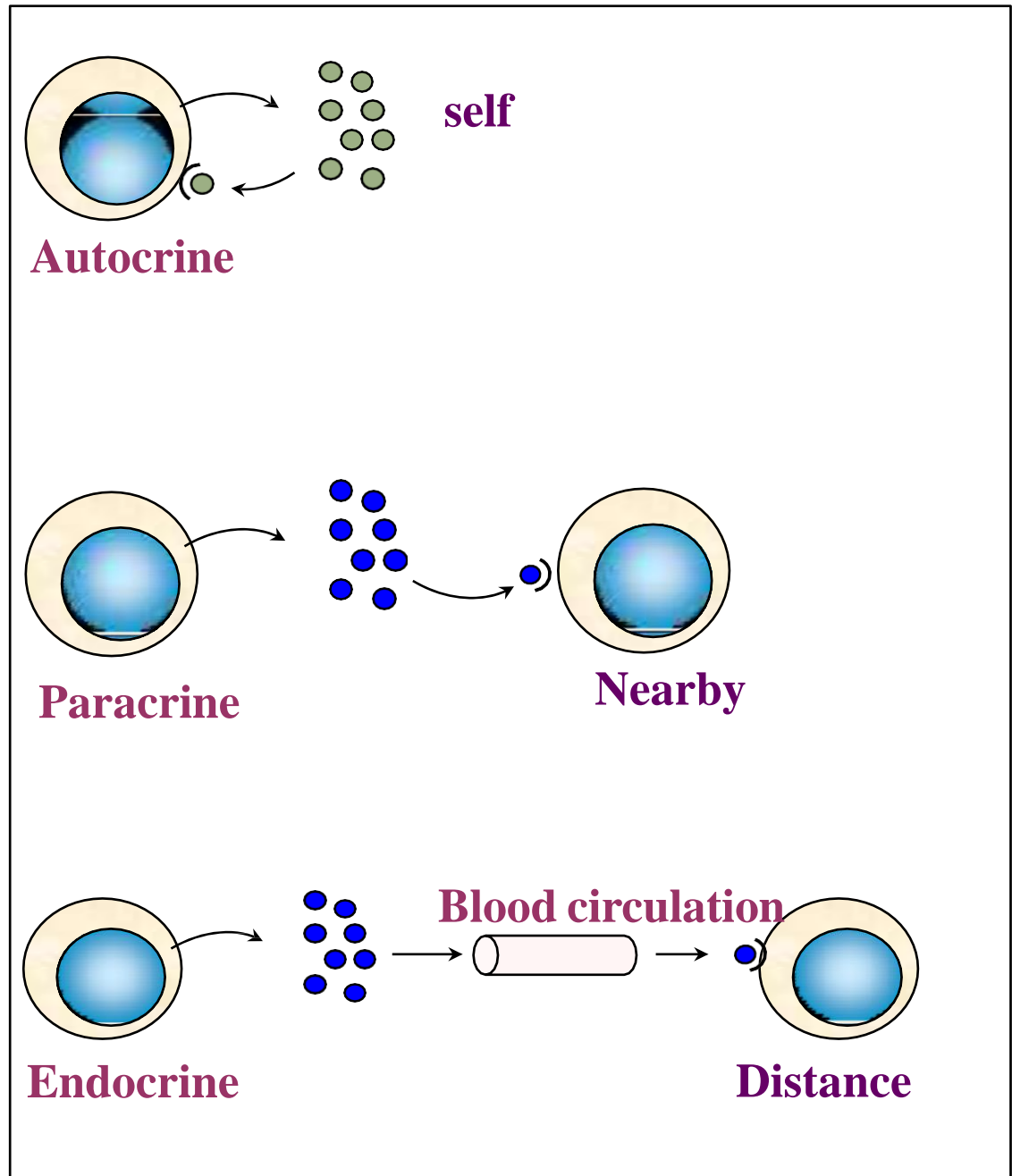
**Cytokine binds to receptors on near by cells.**

- **Endocrine**

**Cytokine binds cells in distant parts of the body.**

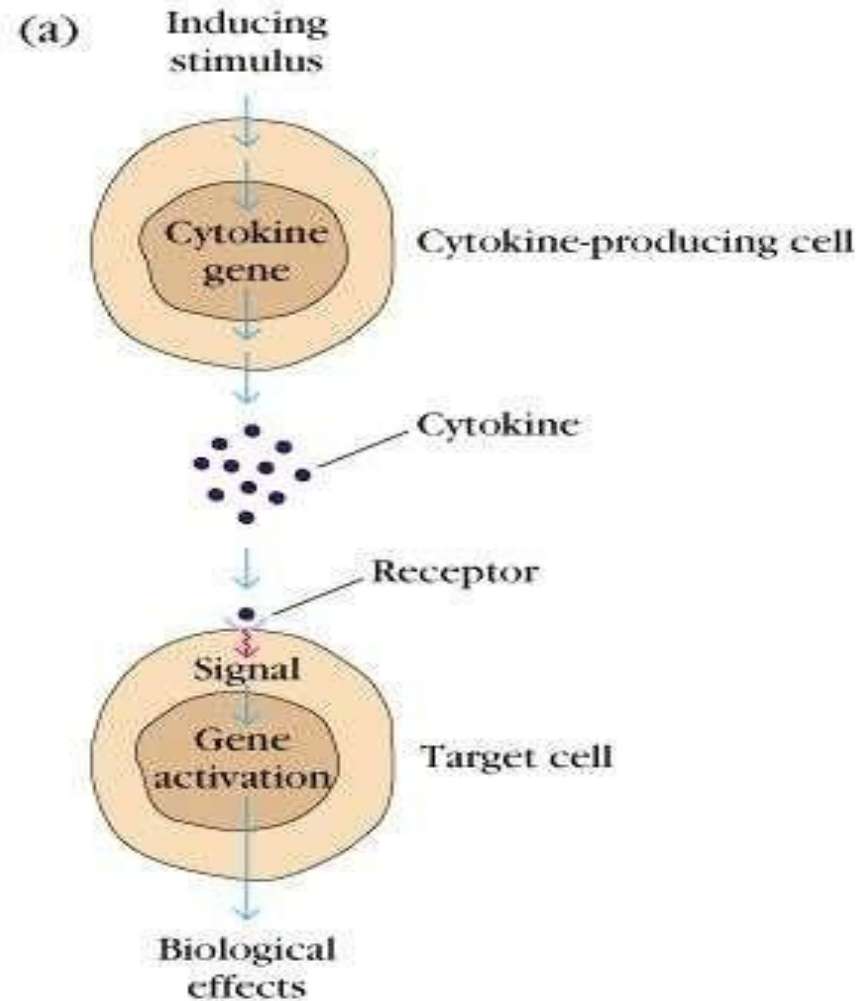


Cytokines take effect in three ways



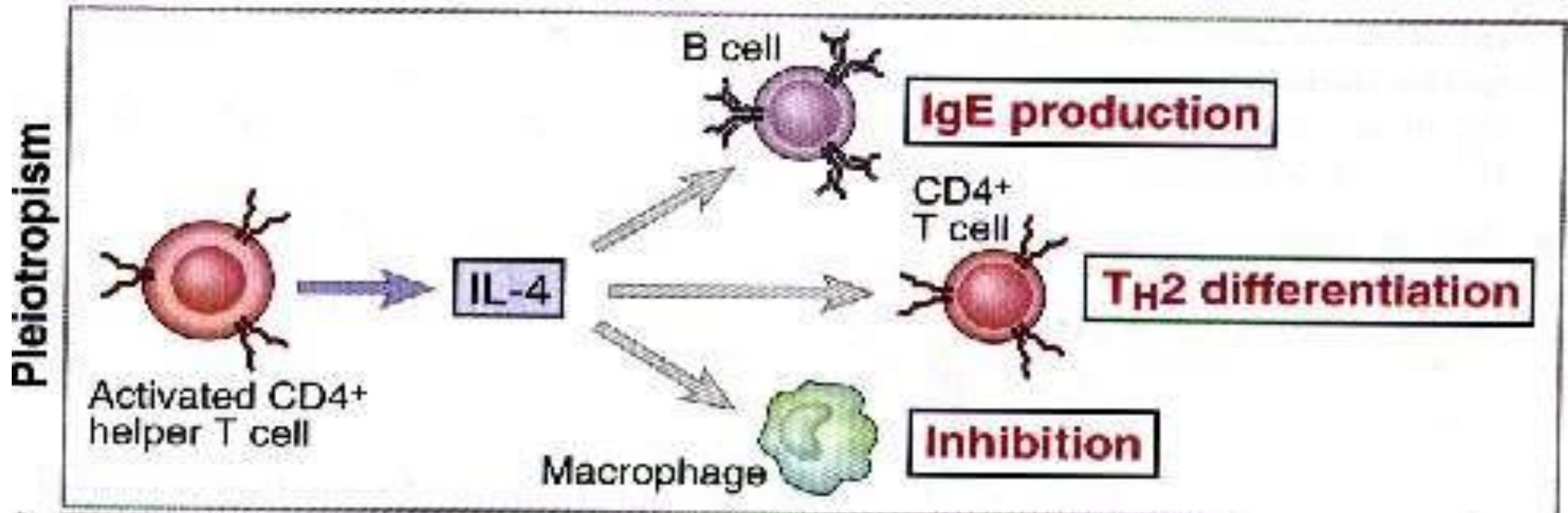
# 5. Cytokines initiate their actions by binding to specific membrane receptors on target cells.

- Receptors for cytokines often bind their ligands with high affinities.

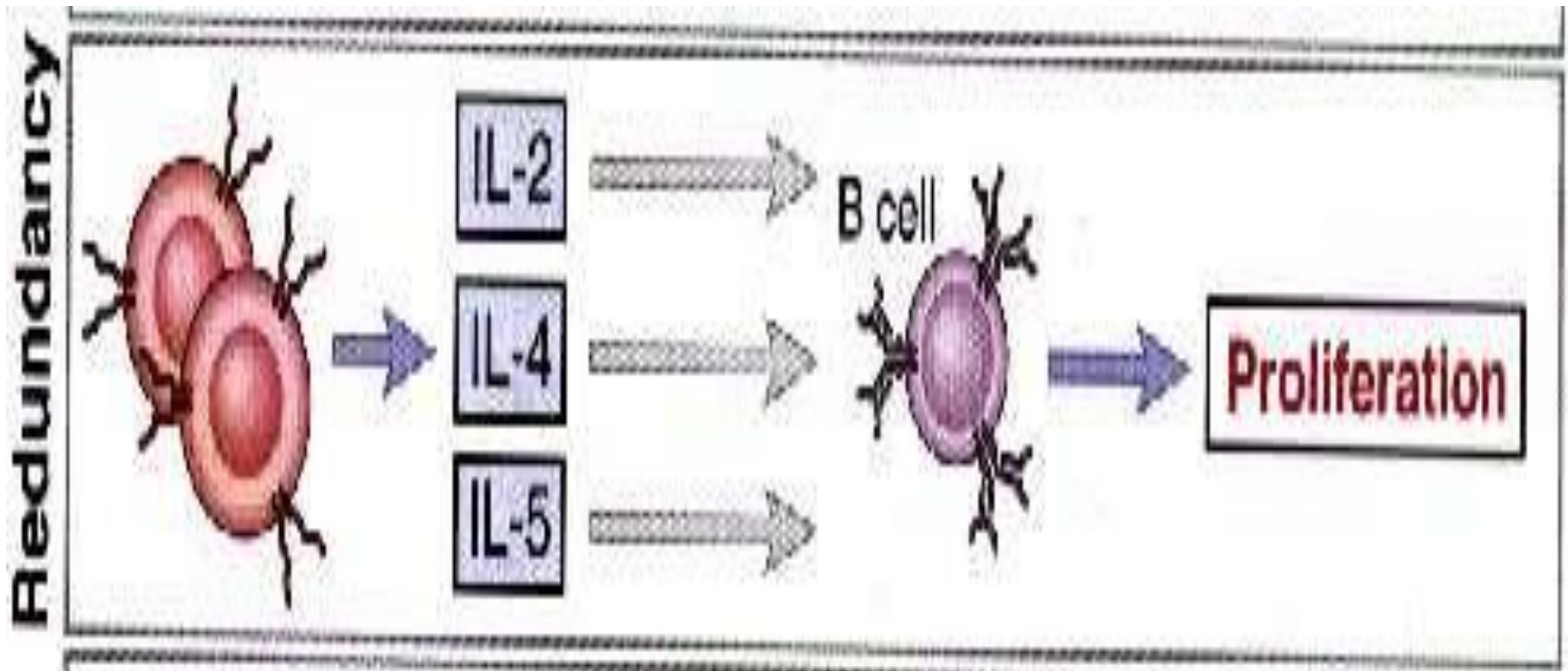


6. The effects of cytokines are often pleiotropism, redundant, synergy, antagonism, that form a cytokine network.

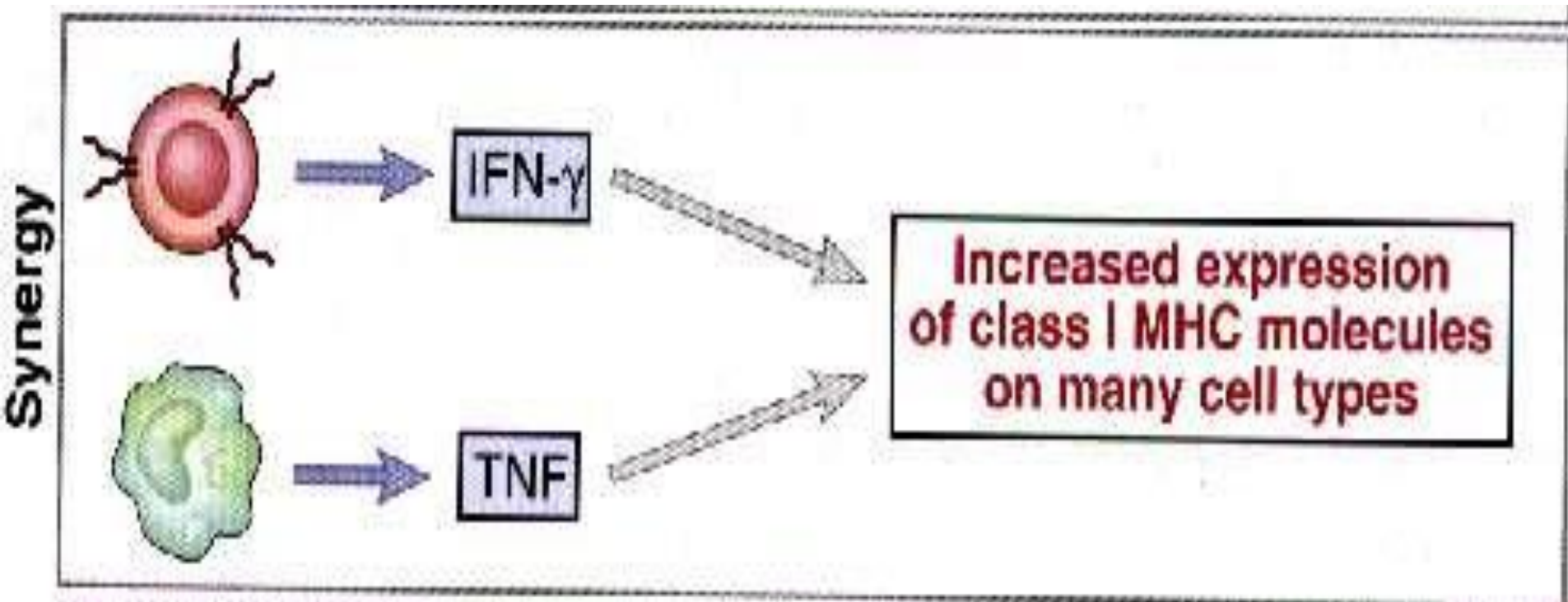
**Pleiotropism** refers to the ability of one cytokine having multiple effects on diverse cell types.



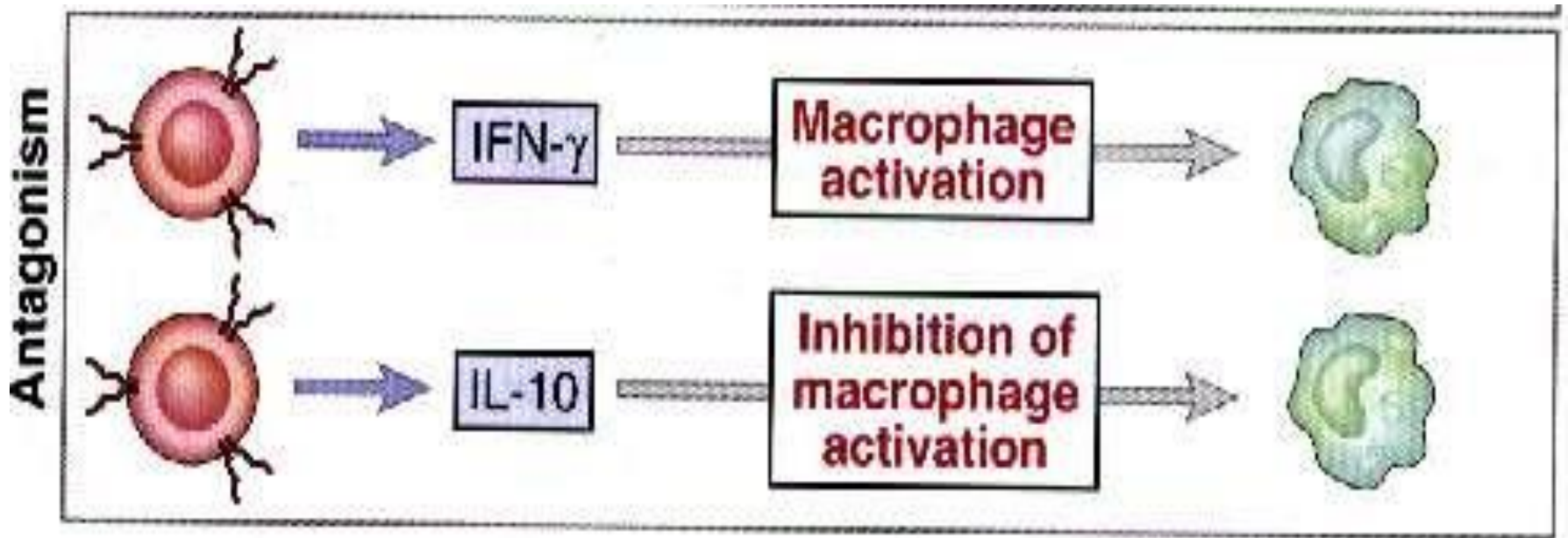
**Redundancy** refers to the property of multiple cytokines having the same or overlapping functional effects.



**Synergy** refers to the property of two or more cytokines having greater than additive effects.



- **Antagonism** refers to the ability of one cytokine inhibiting the action of another.

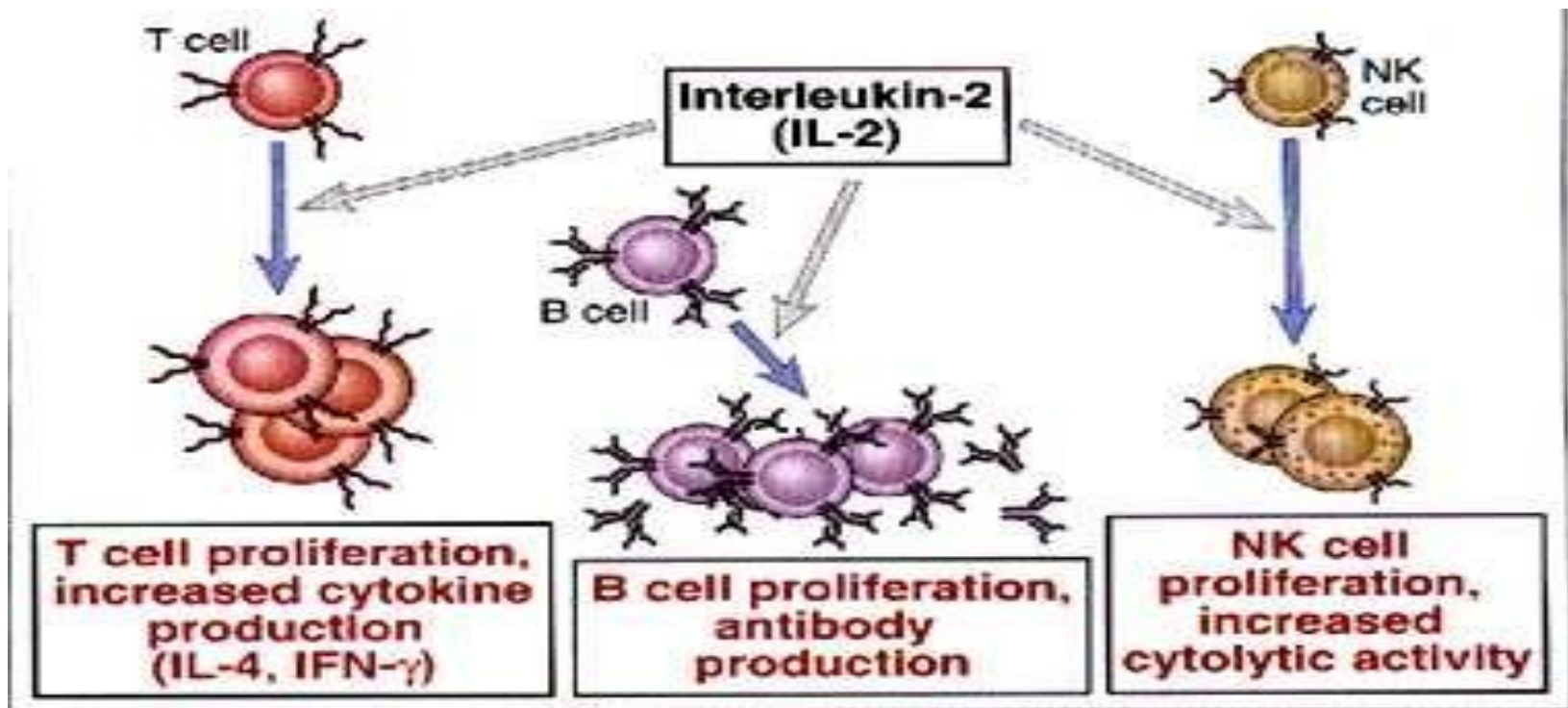


# Part II Classification of cytokines

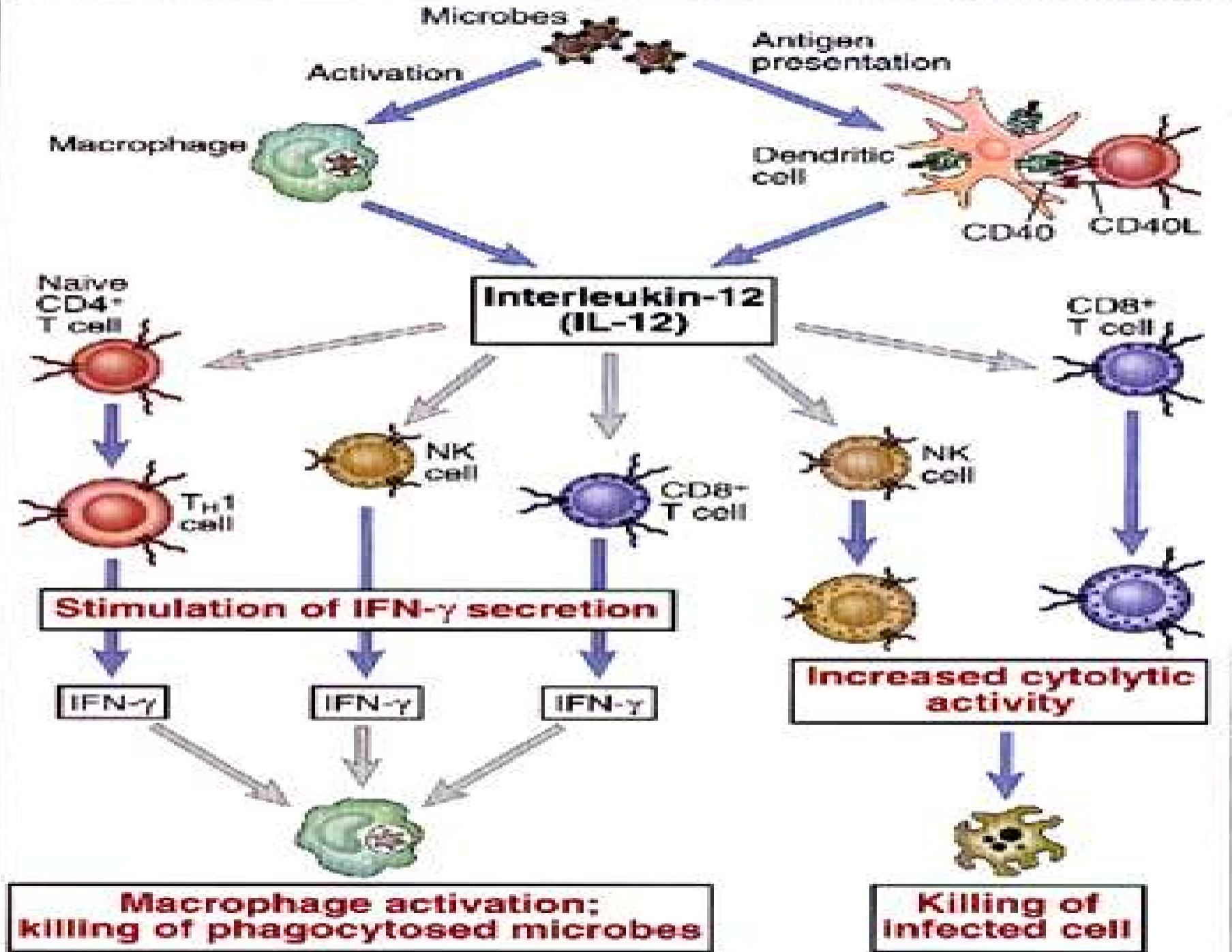
- **Interleukin, IL**
- **Interferon , IFN**
- **Tumor necrosis factor, TNF**
- **Colony stimulating factor**
- **Transforming growth factor**

# I . Interleukin (IL)

- **Cytokines secreted by leukocytes that have the ability to act as signal molecules between different population of leukocytes.**

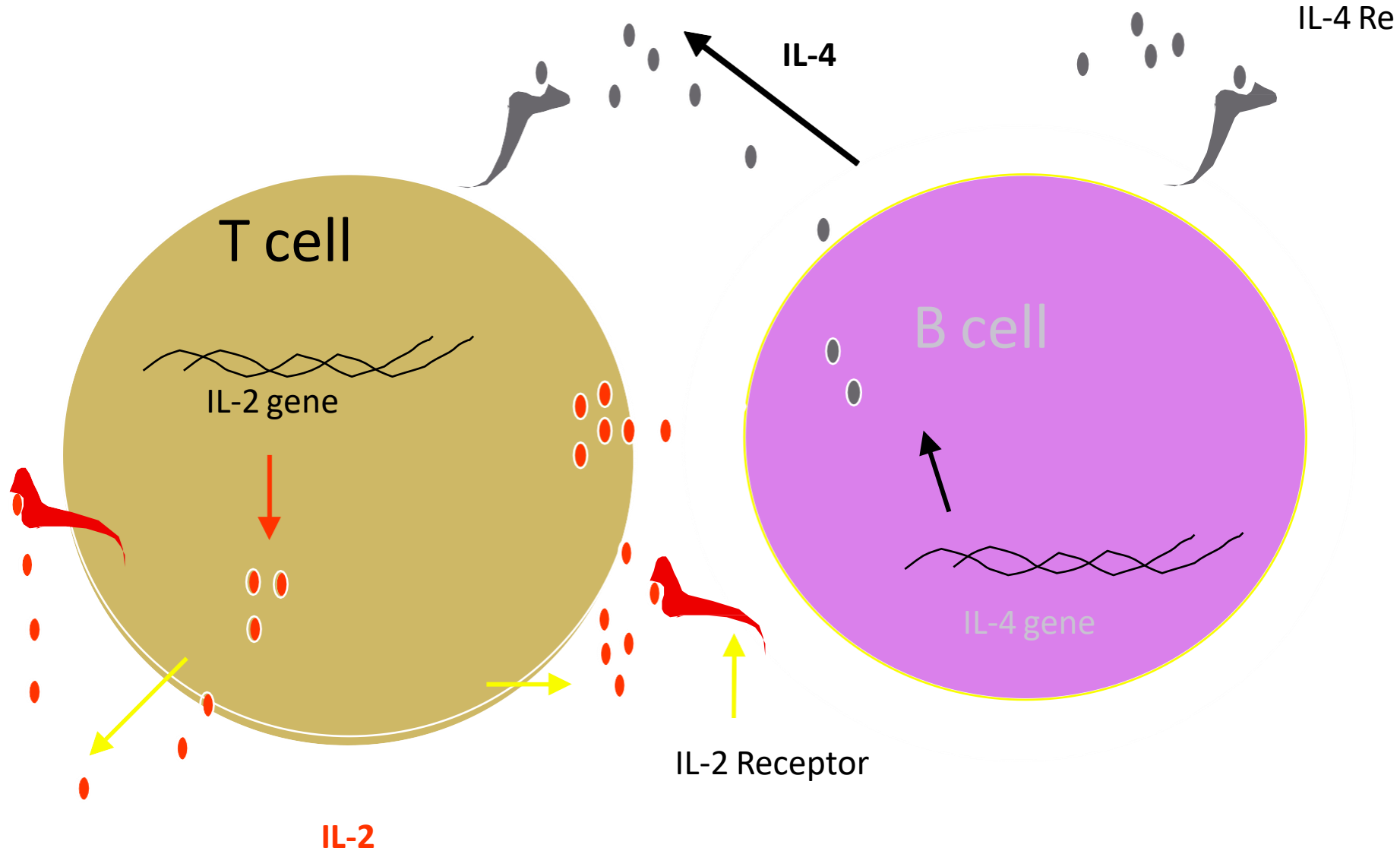






# Cytokine Network on a Local Level

---



## II. Interferon (IFN)

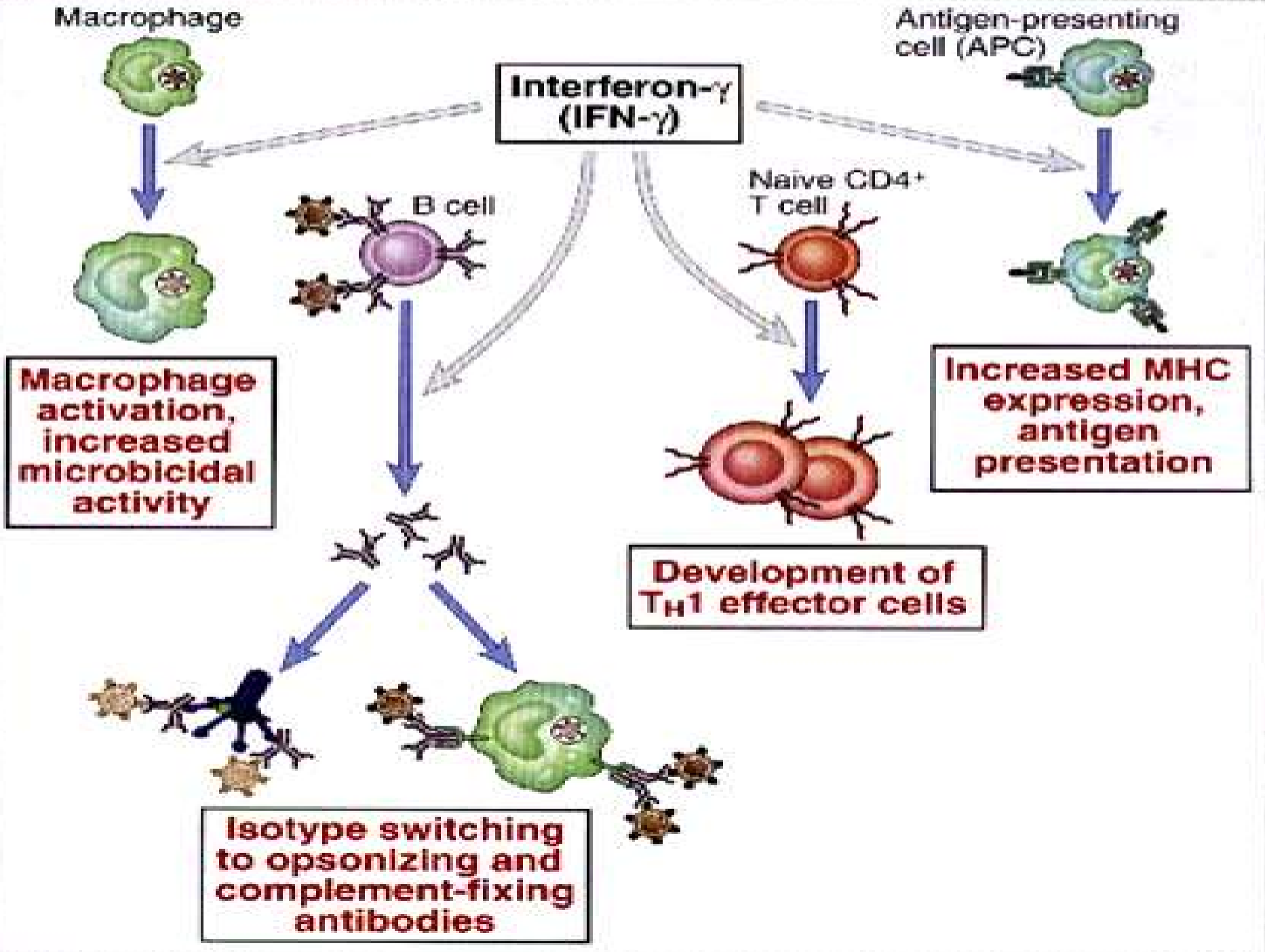
A group of glycoproteins that produced by human or animal cells following the infection of virus and exposure to various inducing agents

# Comparison of IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$

---

<b>Types</b>	<b>Produced cells</b>	<b>Main functions</b>
<b>IFN-<math>\alpha</math></b>	<b>leukocyte</b>	<b>anti-virus, immune regulation</b>
<b>IFN-<math>\beta</math></b>	<b>fibroblast</b>	<b>anti-tumor</b>
<b>IFN-<math>\gamma</math></b>	<b>Th1, NK</b>	<b>weaker anti-virus effect</b> <b>stronger immune regulation effect</b> <b>anti-tumor</b>

---

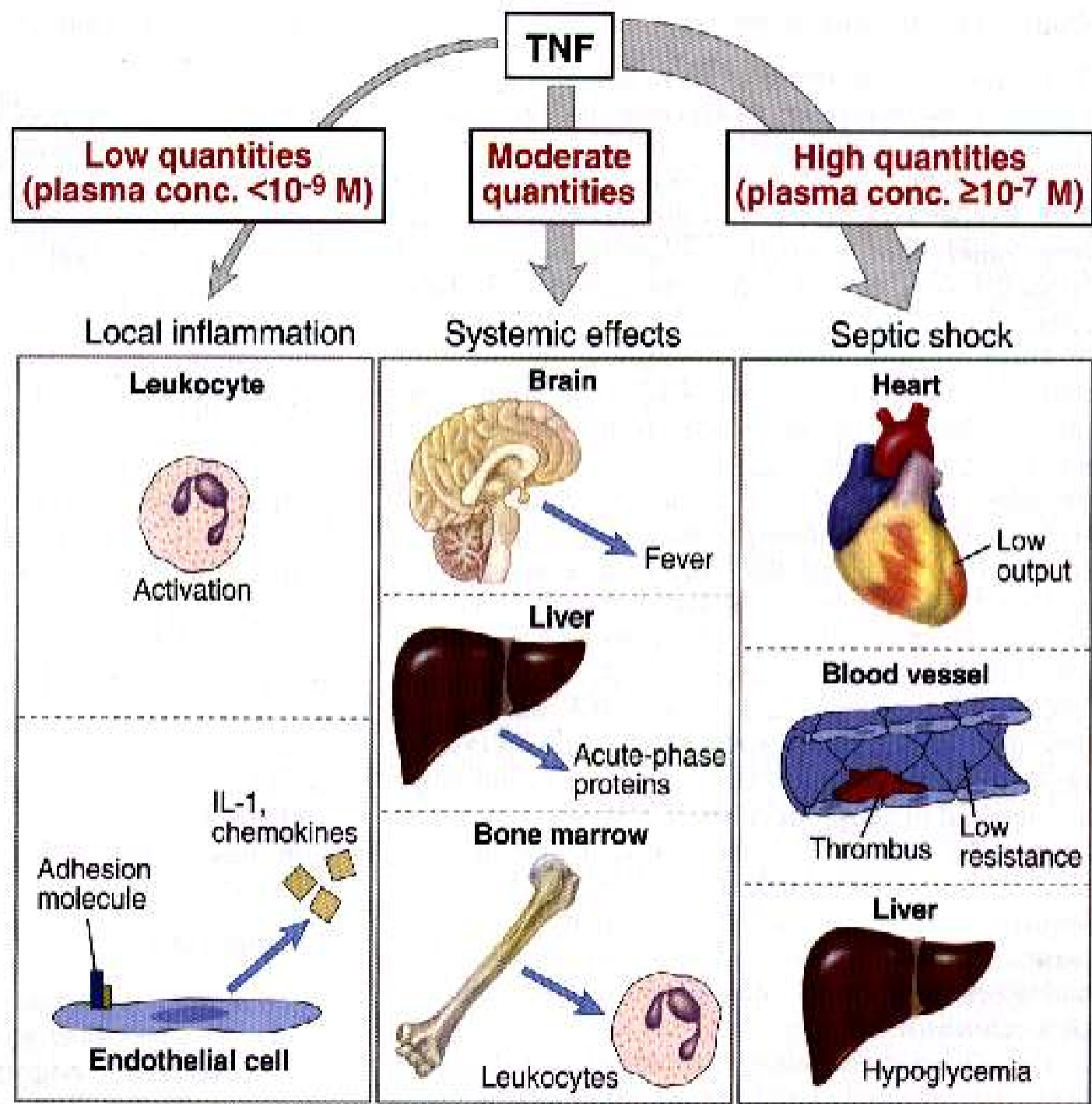


# III. Tumor necrosis factor (TNF)

- **TNFs were originally thought of as selective antitumour agents, but are now known to have a multiplicity of actions.**
- **TNF- $\alpha$  is produced mainly by activated monocytes and macrophages.**
- **TNF- $\beta$ (lymphotoxin, LT) is produced mainly by activated Th0 and Th1.**

**Figure 11-5 Biologic actions of TNF.**

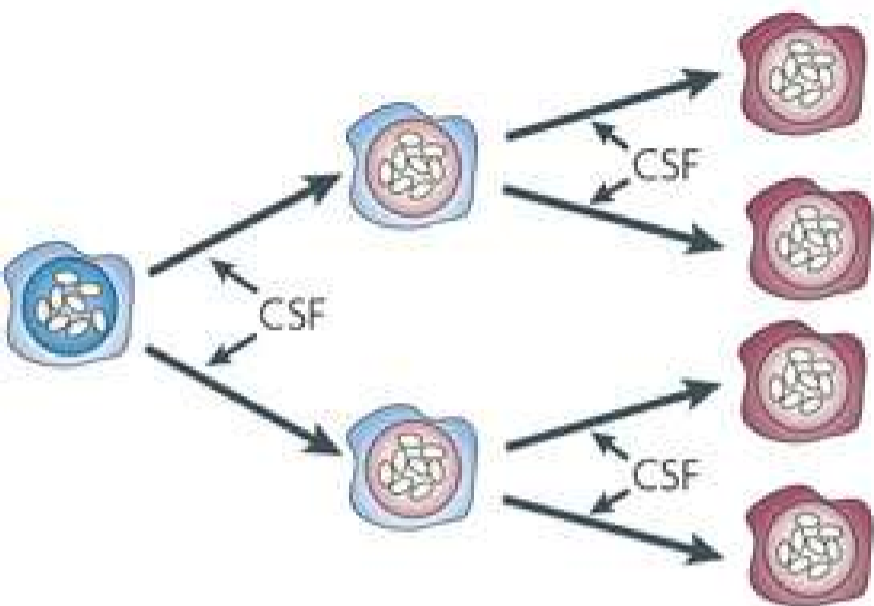
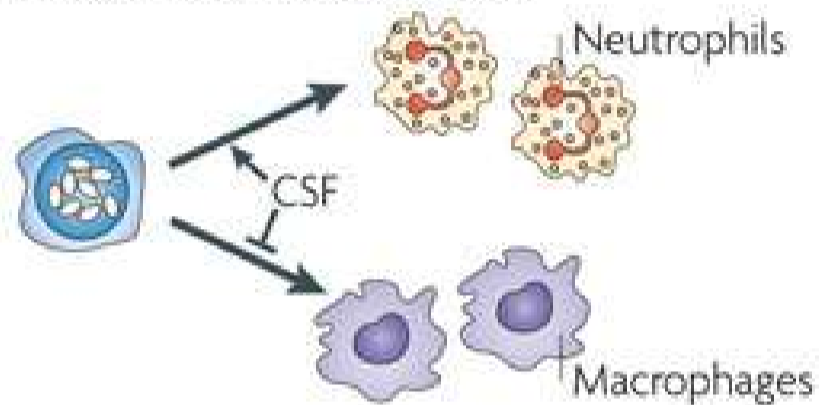
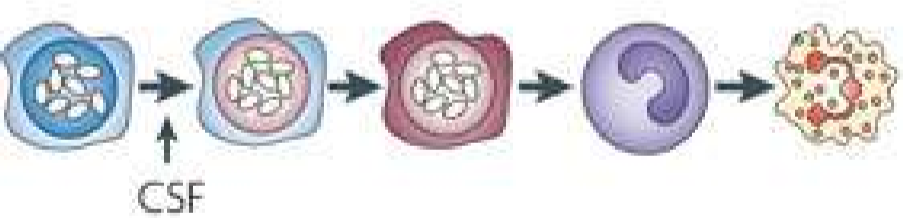
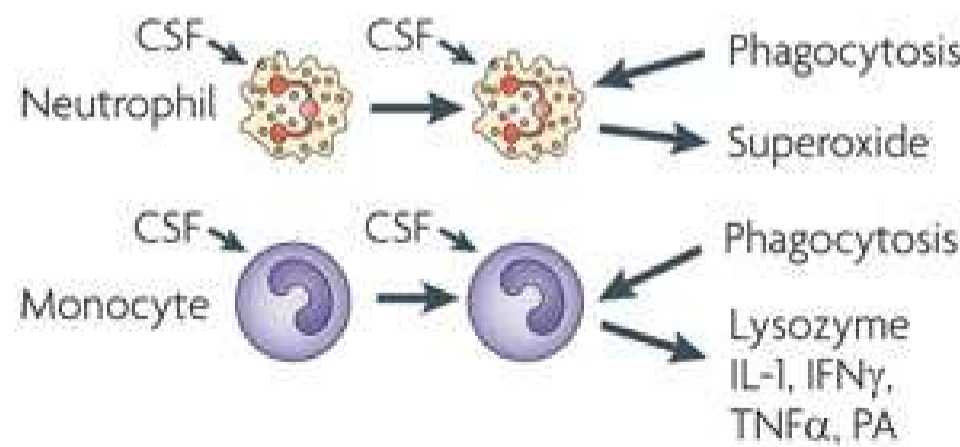
At low concentrations, TNF acts on leukocytes and endothelium to induce acute inflammation. At moderate concentrations, TNF mediates the systemic effects of inflammation. At high concentrations, TNF causes the pathologic abnormalities of septic shock.



# **IV. Colony-stimulating factors (CSF)**

- **Cytokines that stimulate proliferation and/or differentiation of pluripotent hematopoietic stem cell and different progenitors.**
- **Granulocyte macrophage-CSF(GM-CSF)**
- **Monocyte-CSF(M-CSF)**
- **Granulocyte-CSF(G-CSF)**
- **Stem cell factor(SCF)**
- **Erythropoietin(EPO)**



**a Proliferative stimulation****b Suppression of apoptosis****c Differentiation commitment****d Maturation induction****e Functional stimulation of mature cells**

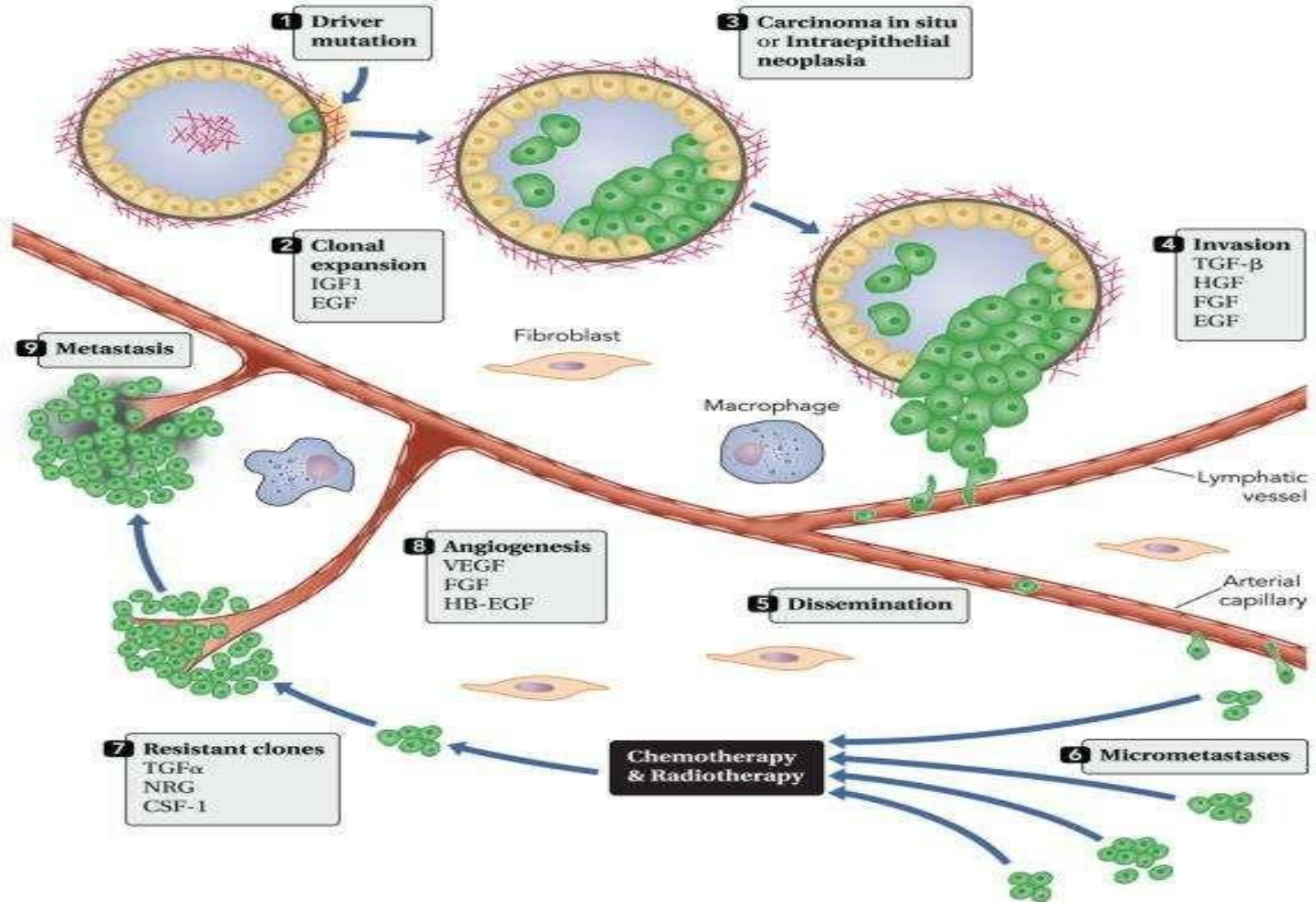
# VI. Growth factor

- **Growth-factor are cytokines which stimulate the growth of their target cells.**
- **Transforming growth factor- $\beta$ (TGF- $\beta$ )**
- **Epithelia growth factor(EGF)**
- **Vascular endothelia cell growth factor(VEGF)**
- **Fibroblastic growth factor(FGF)**

How does overexpression of growth factor receptor participate in the formation of cancers ?

- 1. When the receptor molecules are overexpressed, their high numbers cause them to collide *frequently*, and these encounters, like the dimerization events triggered by ligand binding, can result in trans-phosphorylation, receptor activation, and signal emission.**
- 2. Alternatively, excessive receptor expression may make some cancer cells hyper-responsive to the low levels of growth factors that may be present in their surroundings.**

# The stepwise progression of cancer and roles for growth factors



# Cytokine Receptors

## 1. Membrane Binding Cytokine Receptors

- Ig- superfamily receptor
- Class 1- hematopoietin receptor
- Class 2- Interferon receptor

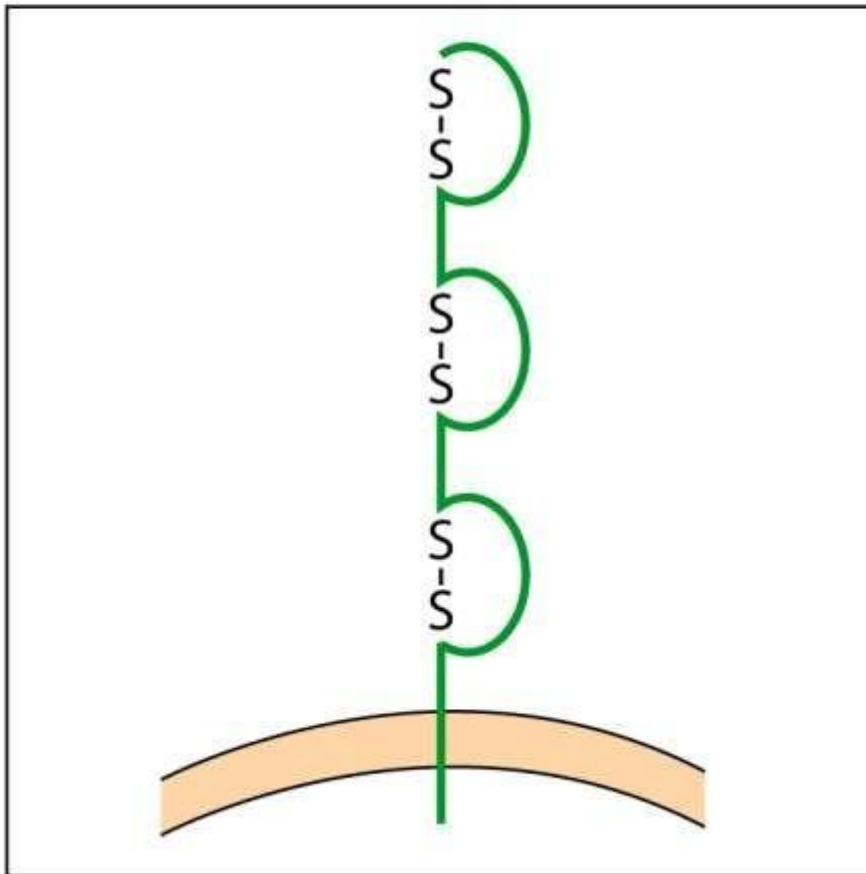
## 2. TNF receptor

## 3. Chemokine receptor

## RECEPTOR FAMILY

## LIGANDS

(a) Immunoglobulin superfamily receptors

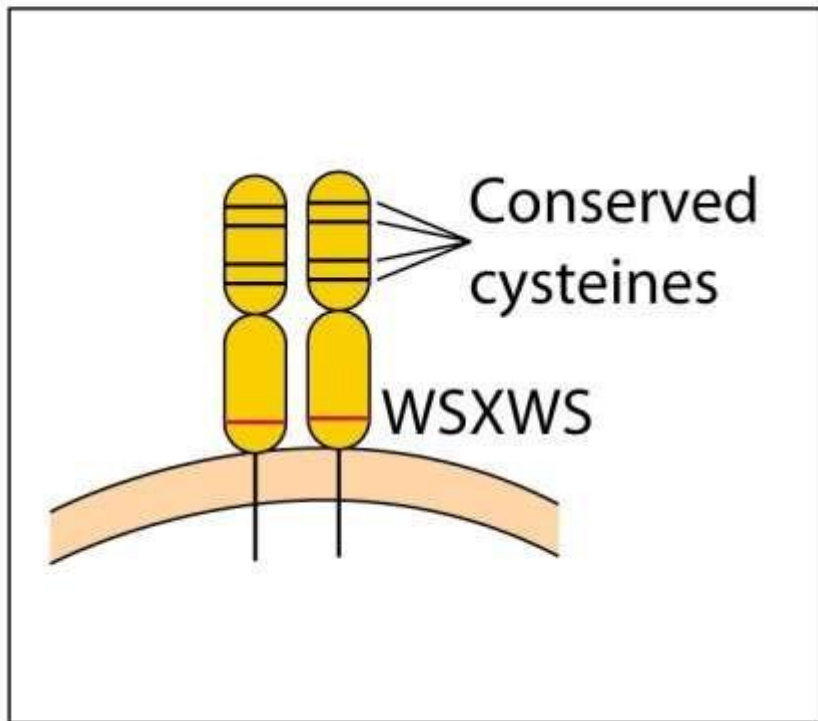


IL-1

M-CSF

C-Kit

(b) Class I cytokine receptors  
(hematopoietin)

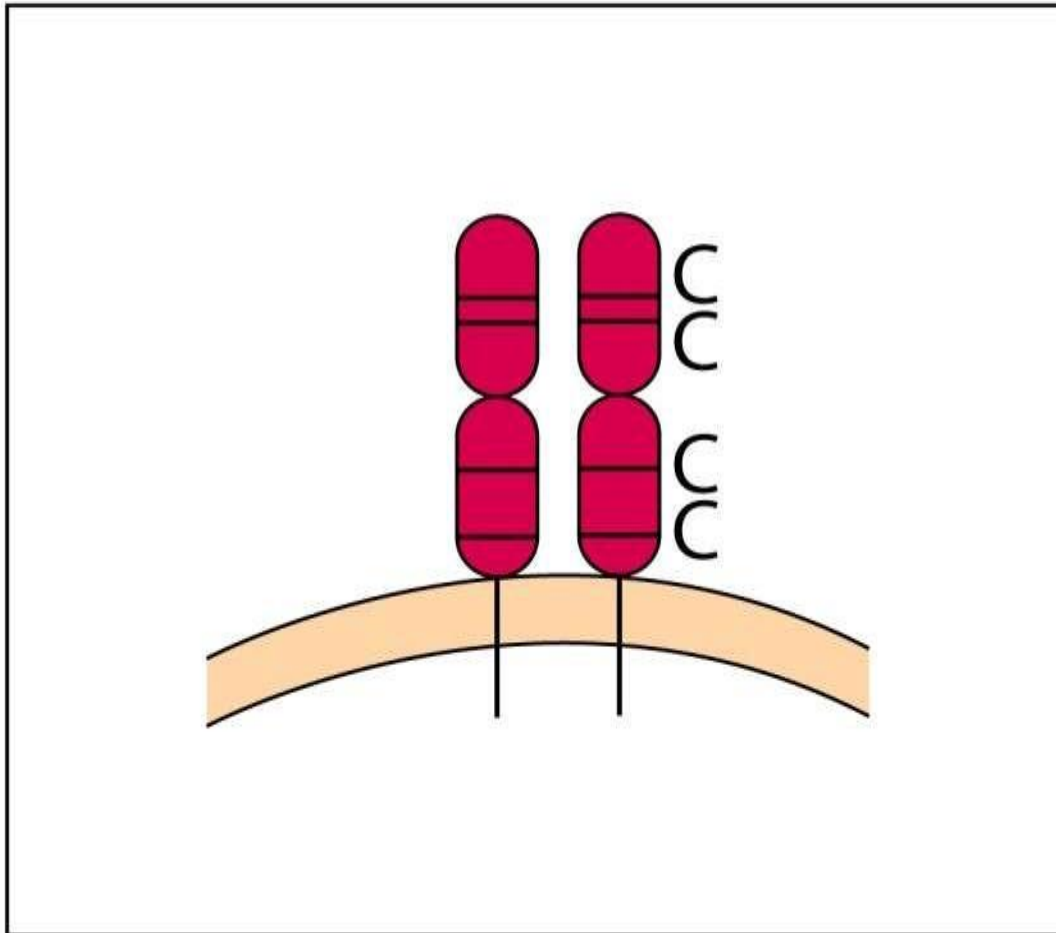


LIGANDS

IL-2	IL-13
IL-3	IL-15
IL-4	GM-CSF
IL-5	G-CSF
IL-6	OSM
IL-7	LIF
IL-9	CNTF
IL-11	Growth hormone
IL-12	Prolactin

(c) Class II cytokine receptors  
(interferon)

LIGANDS



IFN- $\alpha$

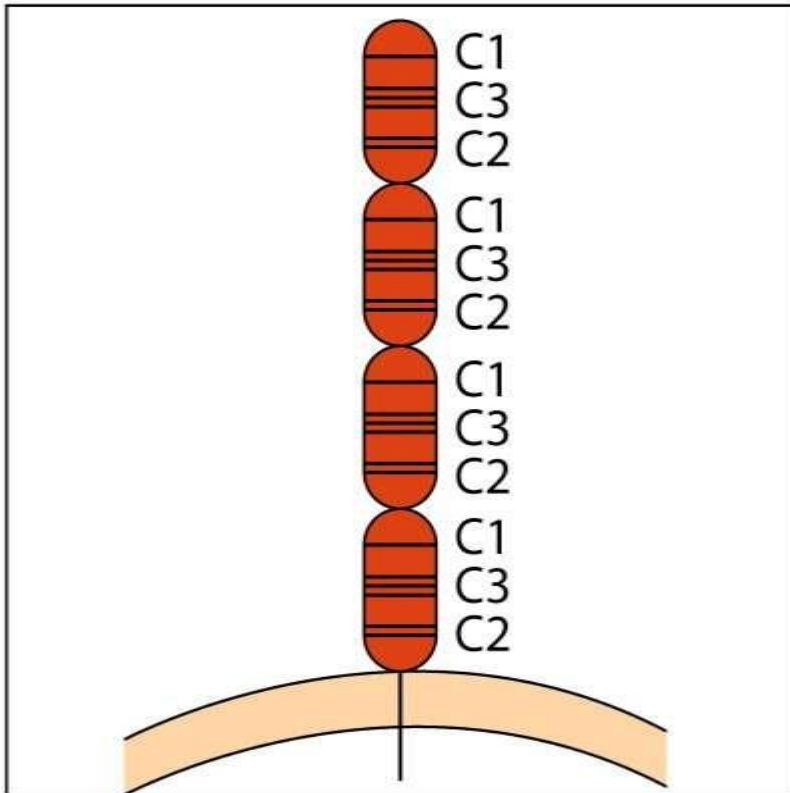
IFN- $\beta$

IFN- $\gamma$

IL-10



(d) TNF receptors



LIGANDS

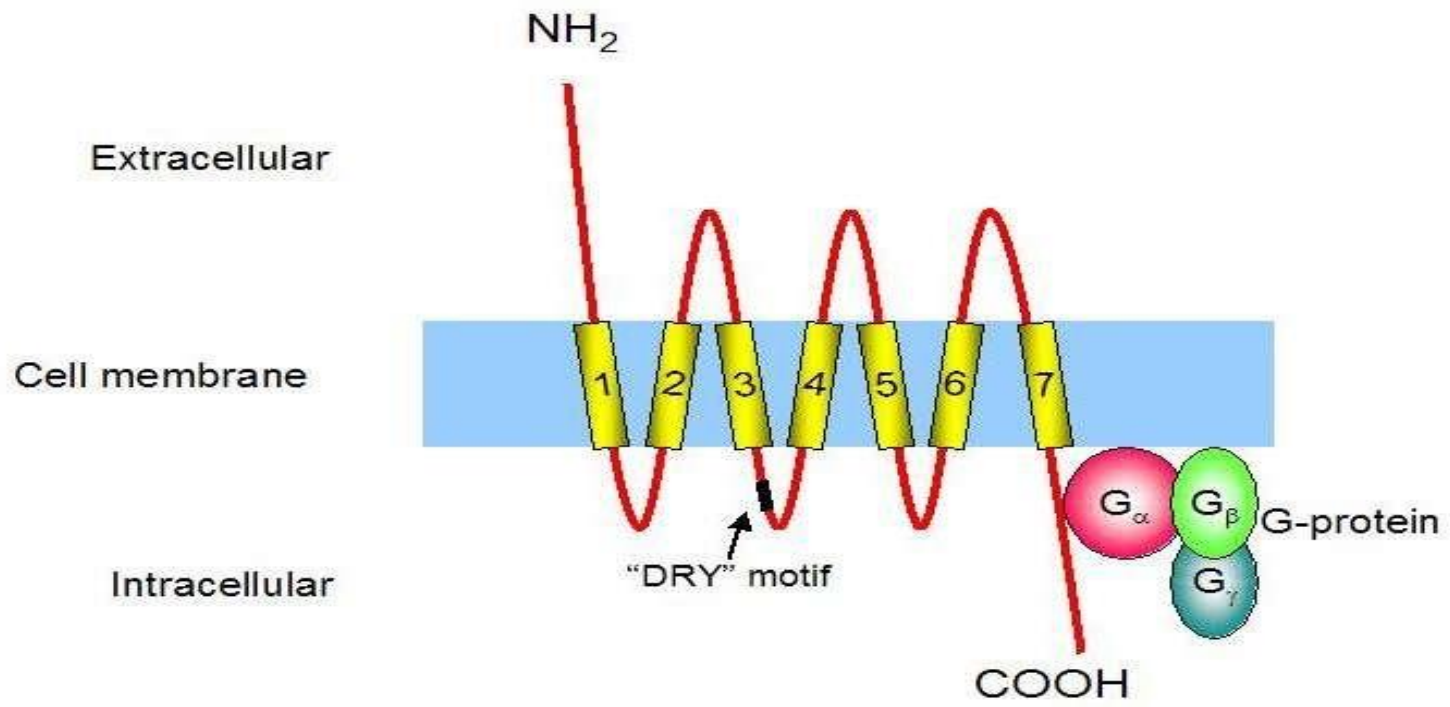
TNF- $\alpha$

TNF- $\beta$

CD40

Nerve growth factor (NGF)

FAS



# Cytokines

Cytokines	Receptor	Agonist	Antagonist	Pharmacology Action
<p>1) Interleukin</p> <p>a) IL-1 IL-1 alpha IL-1 beta</p> <p>b) IL-2</p> <p>c) IL-4</p>	<p>IL-1RI IL-1R2</p> <p>IL-2R alpha IL-2R beta IL-2R gamma</p>	<p>Recombinant</p> <p>-</p> <p>IL-1NK<sup>beta</sup></p>	<p>Corticosteroid FR-167653</p> <p>Cyclosporine Tacrolimus</p>	<p>1) Inflammation and fever 2) Phagocyte activation 3) Hematopoiesis</p> <p>1) Proliferation of activated T cell 2) Promote NK and Tc cell functions 3) Promote B cell proliferation</p> <p>1) Promote B cell &amp; T cell proliferation</p>

<p>d) IL-7</p> <p>e) IL-9</p> <p>2) Tumour necrosis factor (TNF)</p> <p>a) TNF alpha</p> <p>b) TNF beta</p> <p>3) Interferon (INF )</p> <p>a) INF alpha</p> <p>b) INF beta</p> <p>4) TGF beta</p>	<p>TNFR1</p> <p>TNFR2</p> <p>TNFR-Rp</p> <p>INFR-1</p> <p>TGF beta-1,2,3,4 &amp; 5</p>		<p>Infliximab</p> <p>RO-452081</p> <p>CC1069</p> <p>CC1104</p> <p>CC1115</p>	<p>1) T &amp; B cell lymphopoiesis</p> <p>1) T &amp; B cell lymphopoiesis</p> <p>1) Cytotoxicity</p> <p>2) Apoptosis</p> <p>3) Septic shock</p> <p>1) Inhibit viral replication</p> <p>2) Anti viral activity</p> <p>1) Anti-inflammatory</p> <p>2) Promote B cell expression</p> <p>3) Promote fibroblast proliferation</p>
---	--	--	--	--

# Cytokine signaling mechanisms

- **Cytokines represent a diverse number of molecules.**
- **The super family of cytokine receptors more specifically refers to those cytokines that signal via the Jak-STAT pathway.**
- **These include Interleukins 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, & 15, and G-CSF, TNF and the interferons.**
- **Many growth factor signal pathways cross-communicate with the STAT pathway.**

# Signal Transduction

- Initiated by cytokine binding Activates JAK

(Janus kinase)

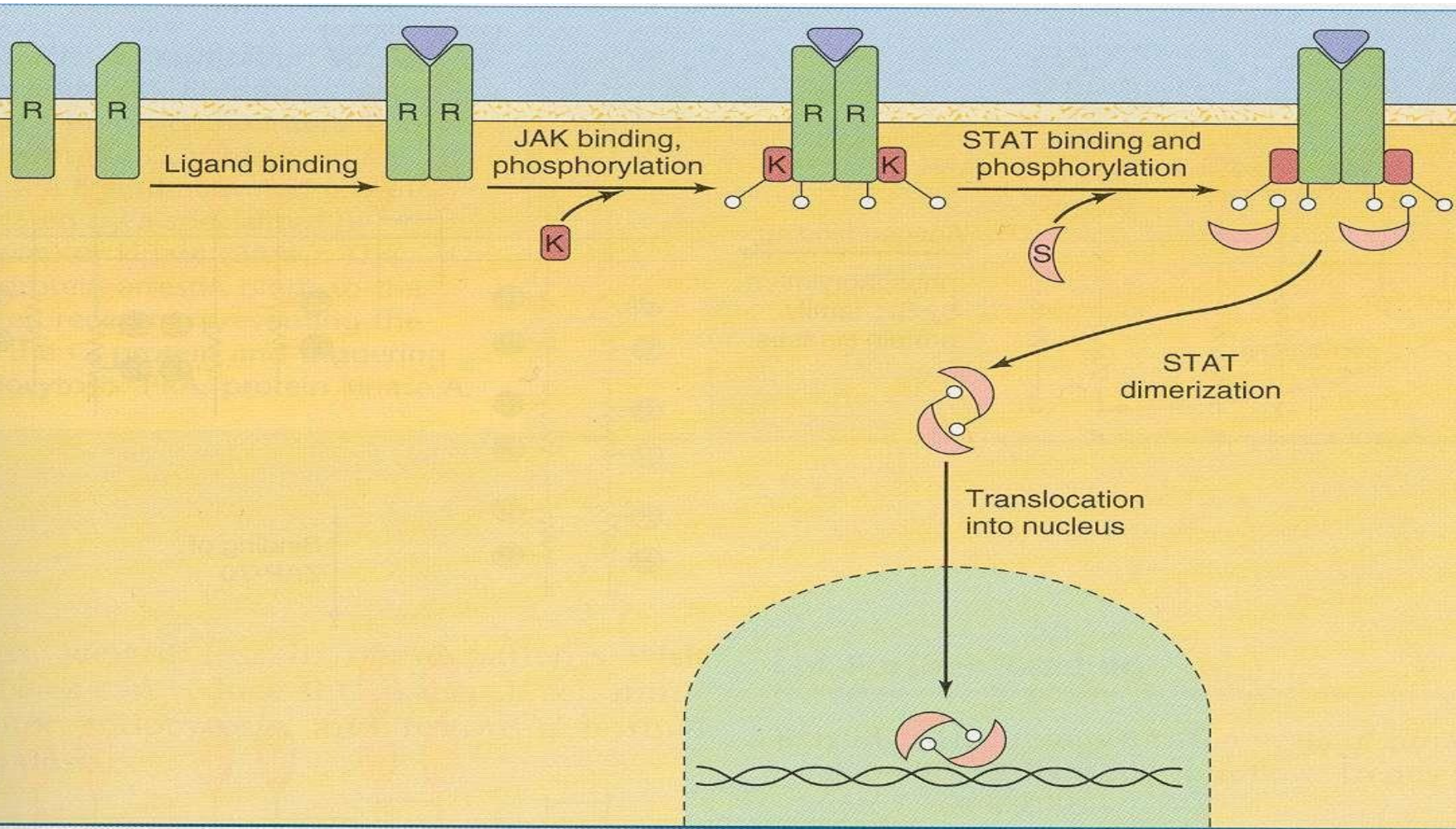
- Phosphorylation of tyrosine

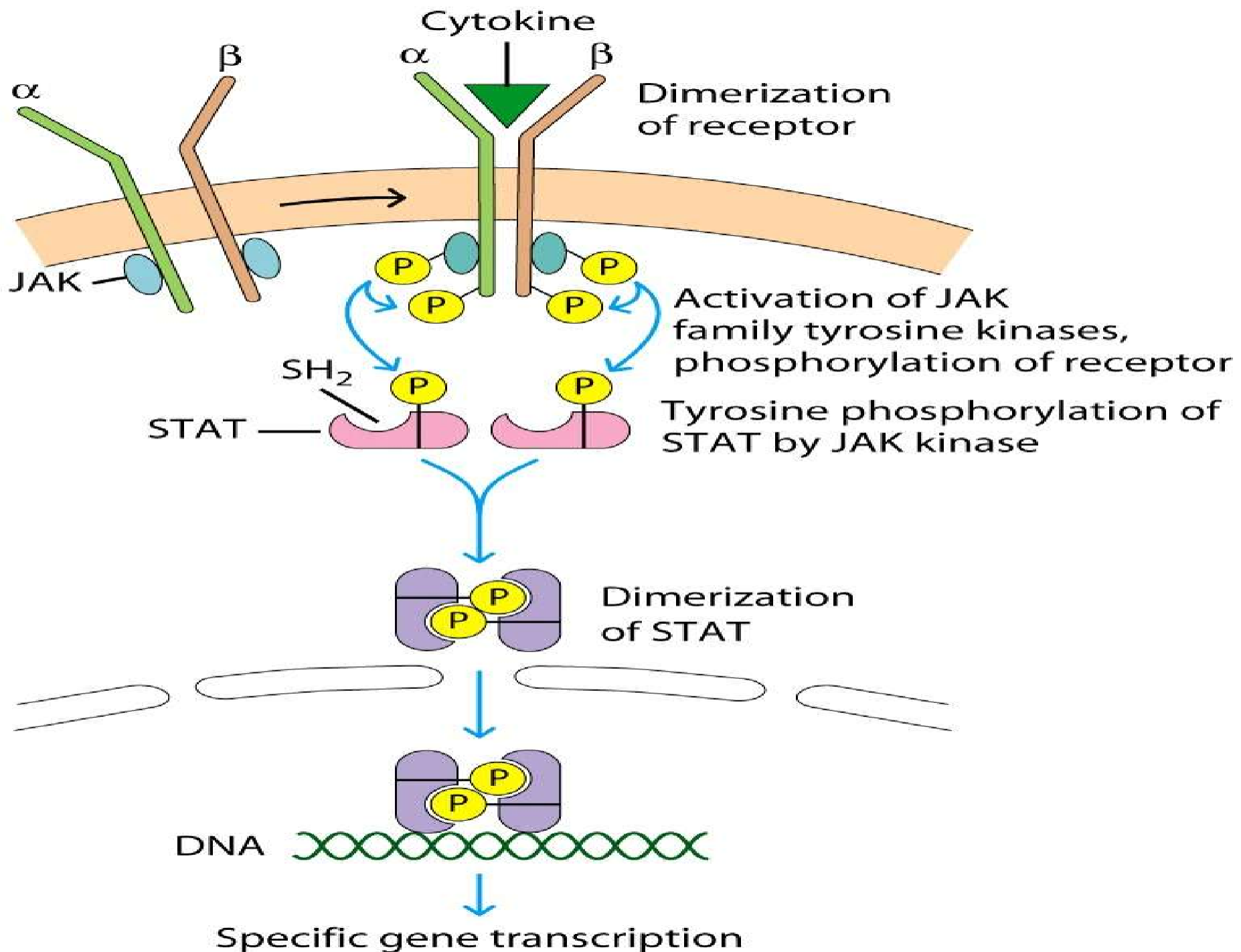
- Binding of STAT(Signal transducers and activators of transcription)

- Translocation of STAT to cell's DNA

- Transcription of specific target genes

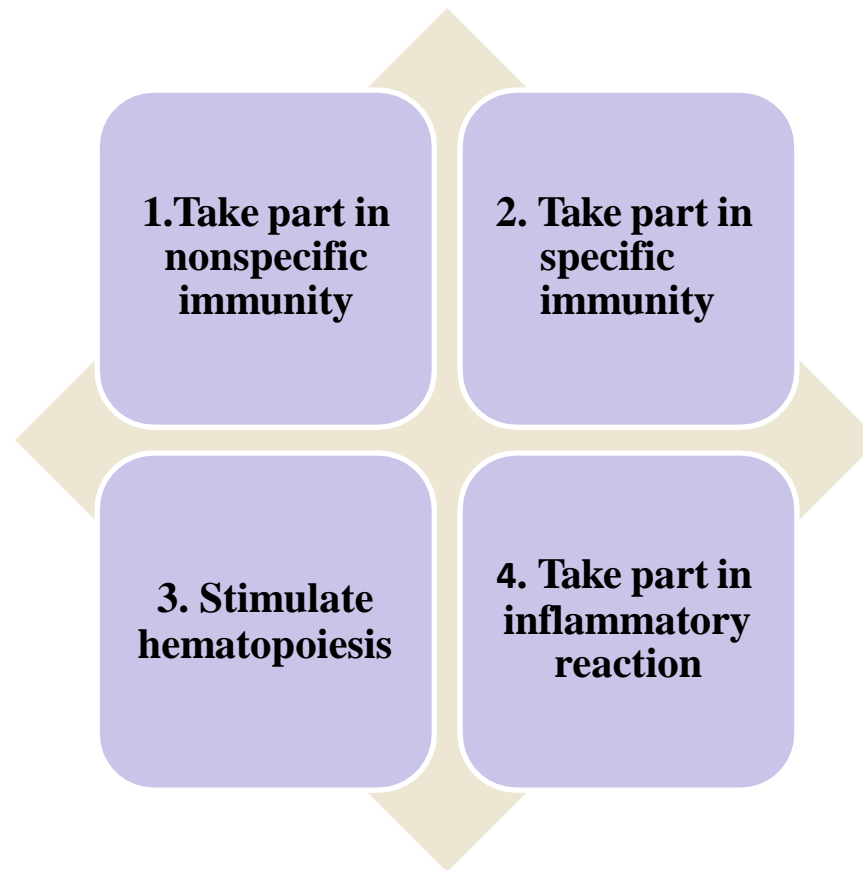
# Signaling through cytokine receptor







# Biological functions of cytokines



# *Role Of Cytokines In various Diseases*

## **1) Neuroinflammatory**

a) Neurodegenerative disease - AD, PD, Multiple sclerosis

## **2) Respiratory**

a) Asthma, COPD (Chronic Obstructive Pulmonary Disease)

## **3) CVS**

a) Hypertrophy

b) Ischemia reperfusion Injury

## **4) GIT**

a) IBD, IBS, ulcerative colitis

## **5) Renal**

a) Glomerulonephritis

b) Diabetic nephropathy

## **6) Liver**

a) Viral hepatitis

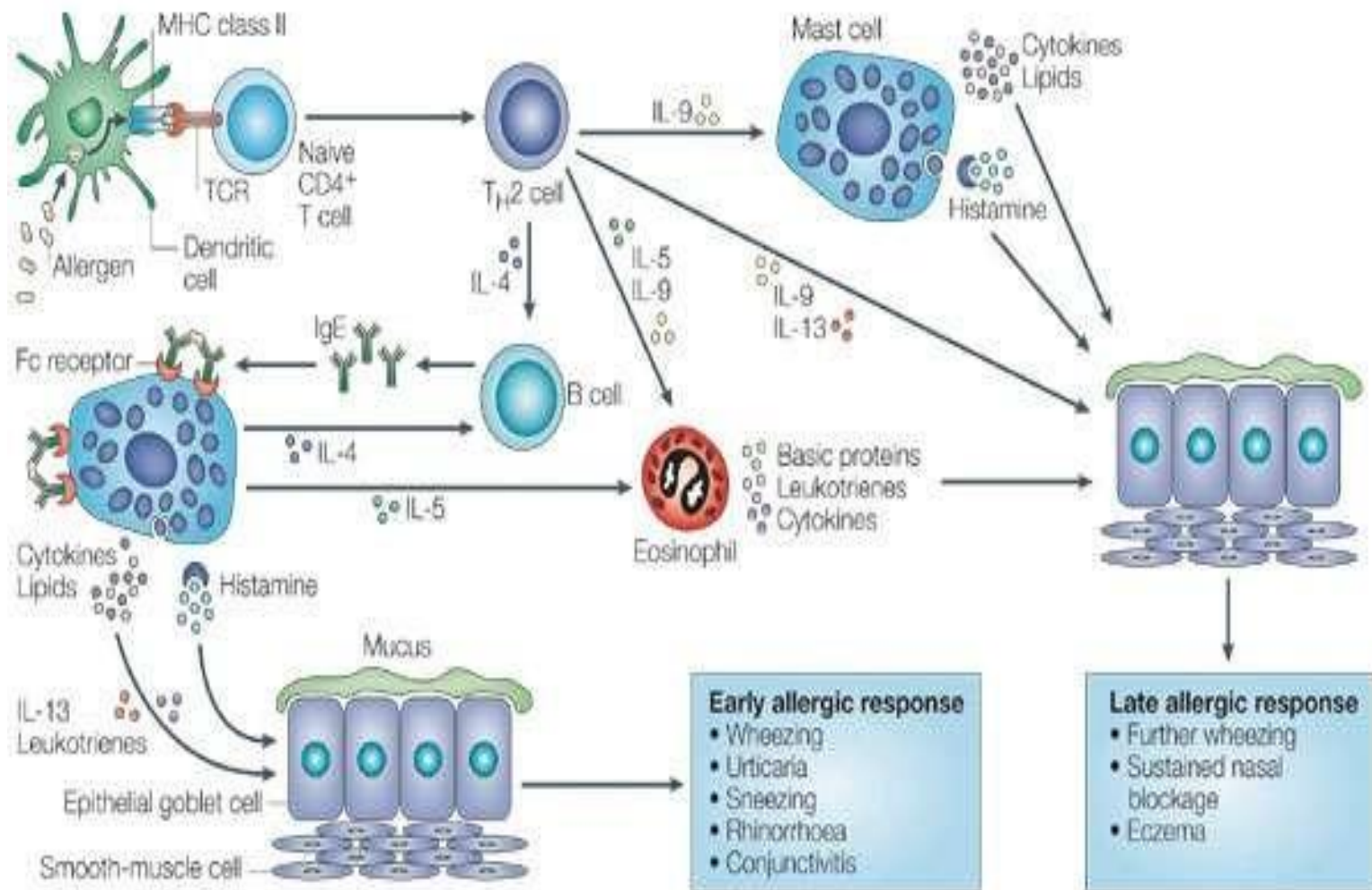
b) Alcohol hepatitis

## **7) Fever**

IL-1B ; TNF

## **8) Rheumatoid arthritis**

# Role in asthma and allergy



# 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.**