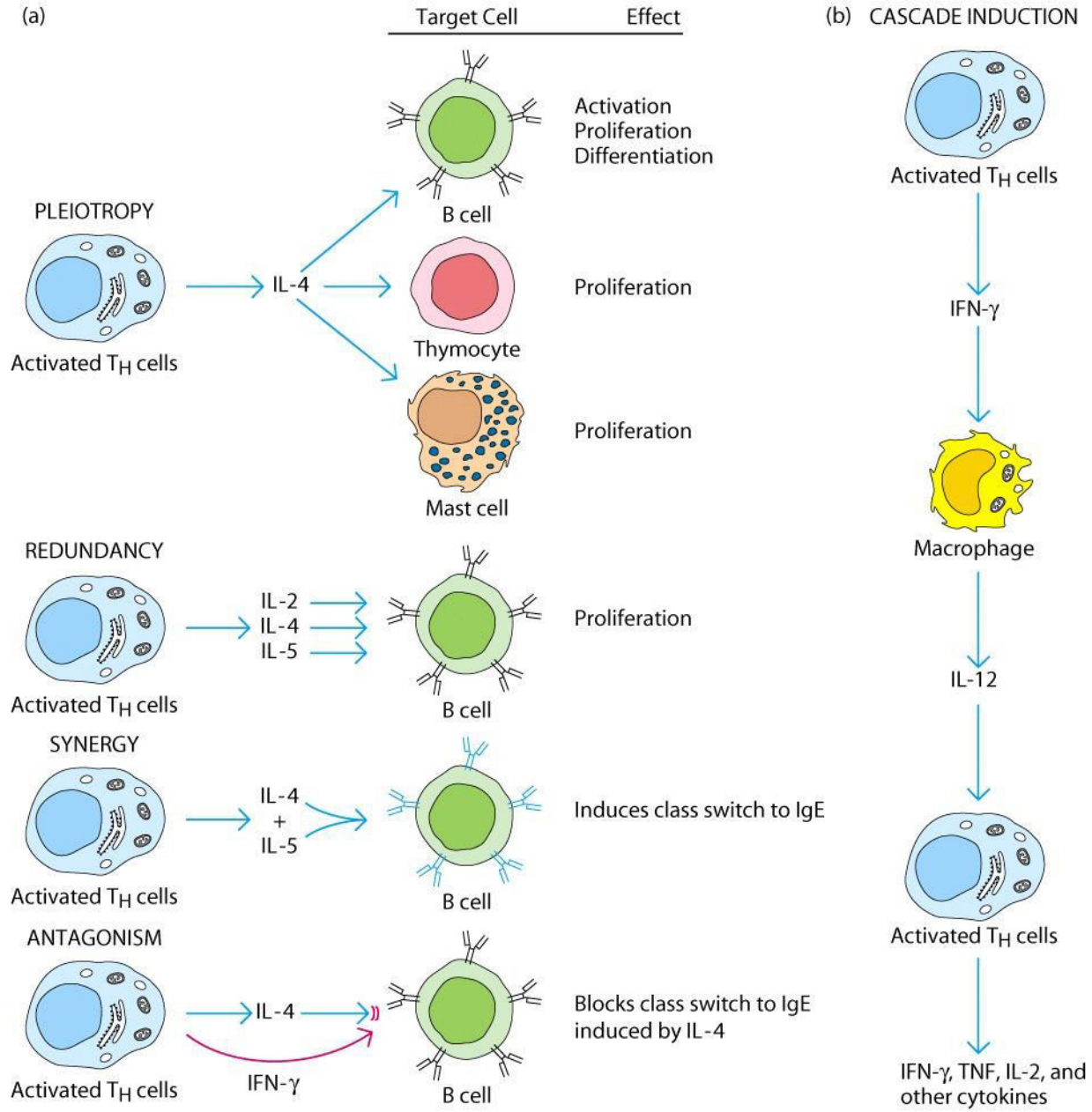
CYTOKINES AND RECEPTORS

What Is A Cytokine?

- Low molecular weight proteins (30 KDa)
- Bind receptors, alter gene expression
- Can bind the secreting cell (autocrine)
- Can bind another cell close by (paracrine)
- Few cases bind another cell far away (endocrine)
- Very low K_d receptors (10^{-10}-10^{-12} M)
- Cytokines regulate immune responses

Cytokines

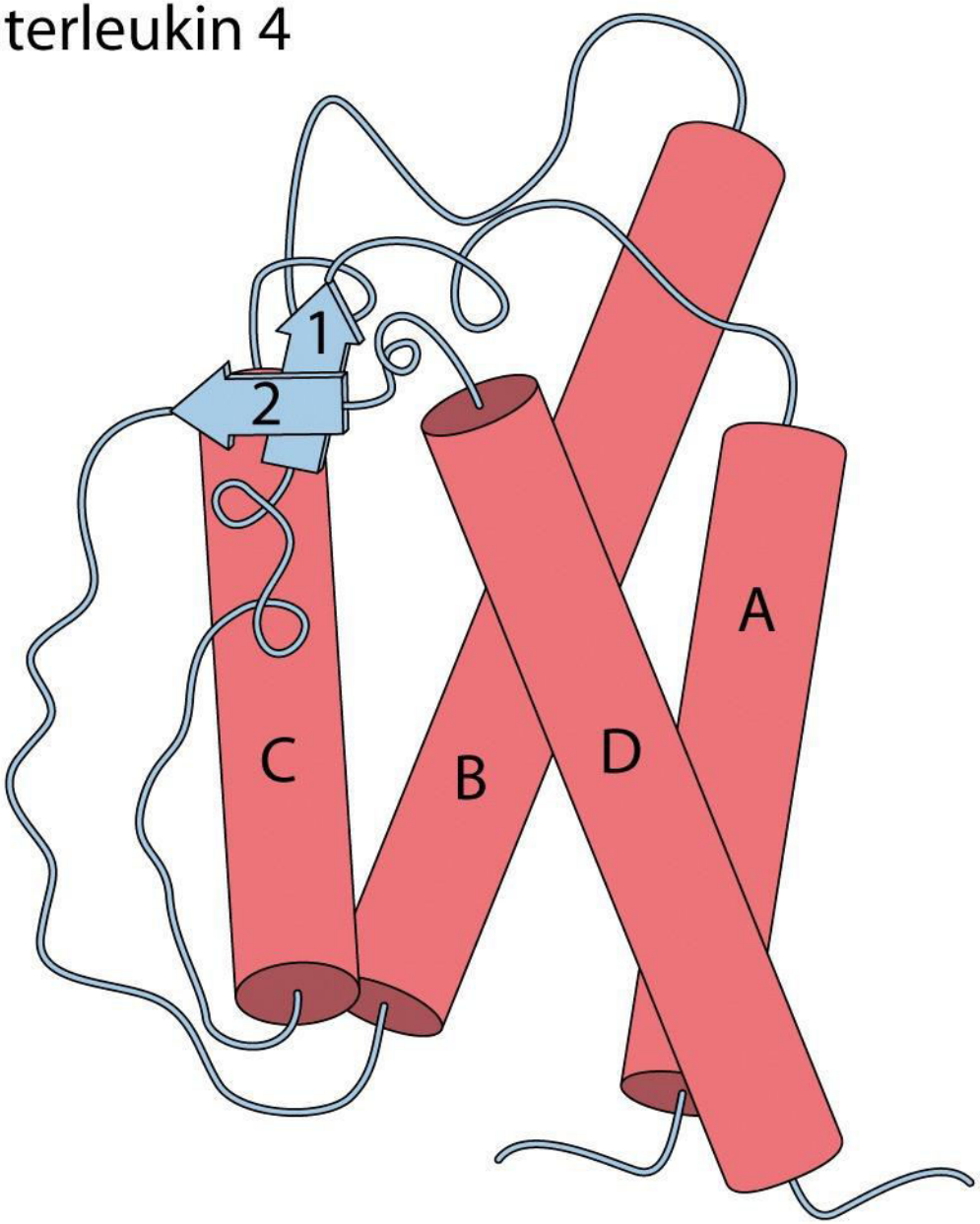
- Cytokines can activate many cells
- Ex. Cytokines secreted by T_H can affect B-cells, CTLs, MΦ, NK
- A cytokine can be pleiotropic (different effect on different cells)
- Synergism, redundancy, antagonism
- Interleukins, monokines, lymphokines, chemokines, term CYTOKINE includes all of them


(a)
Target Cell
Effect
PLEIOTROPY
Activated T_H cells
IL-4
B cell
Activation
Proliferation
Differentiation
Thymocyte
Proliferation
Mast cell
Proliferation
REDUNDANCY
Activated T_H cells
IL-2
IL-4
IL-5
B cell
Proliferation
SYNERGY
Activated T_H cells
IL-4
+
IL-5
B cell
Induces class switch to IgE
ANTAGONISM
Activated T_H cells
IL-4
IFN-γ
B cell
Blocks class switch to IgE induced by IL-4
(b) CASCADE INDUCTION
Activated T_H cells
IFN-γ
Macrophage
IL-12
Activated T_H cells
IFN-γ, TNF, IL-2, and other cytokines

Cytokine Categories

- 4 Categories
  - TNF family
  - Chemokine family
  - Interferon family
  - Hematopoietin family
- Hematopoietin family
  - α-helical structure prevalence
  - Little or no β-sheet
  - Ex. IL-2 and IL-4
  - Amino acid sequences vary considerably

(b) Interleukin 4



Cells That Make Cytokines And Their Function

- A Variety Of Cells Are Capable Of Making Cytokines
- However The Biggest Producers: T_H
- Cytokines Are Involved In
  - Hematopoiesis
  - Adaptive Immunity
  - Innate Immunity
  - Inflammation

Functional Categories of Cytokines

Functional Categories of Cytokines

- **Mediators and regulators of innate immunity**
  Tumor necrosis factor (TNF), IL-1, IL-6, IL-12, Type I IFNs, IL-15, IL-18, chemokines
- **Mediators and regulators of adptive immunity**
  IL-2, IL-4, IL-5, IFN-g, TGF-β, LT(TNF- β), IL-13, etc
- **Stimulators of hematopoiesis**
  granulocyte-CSF, G-CSF
  macrophage-CSF, M—CSF
  granulocyte-macrophage-CSF, GM-CSF)
  erythropoietin, EPO
  TPO
  stem cell factor, SCF

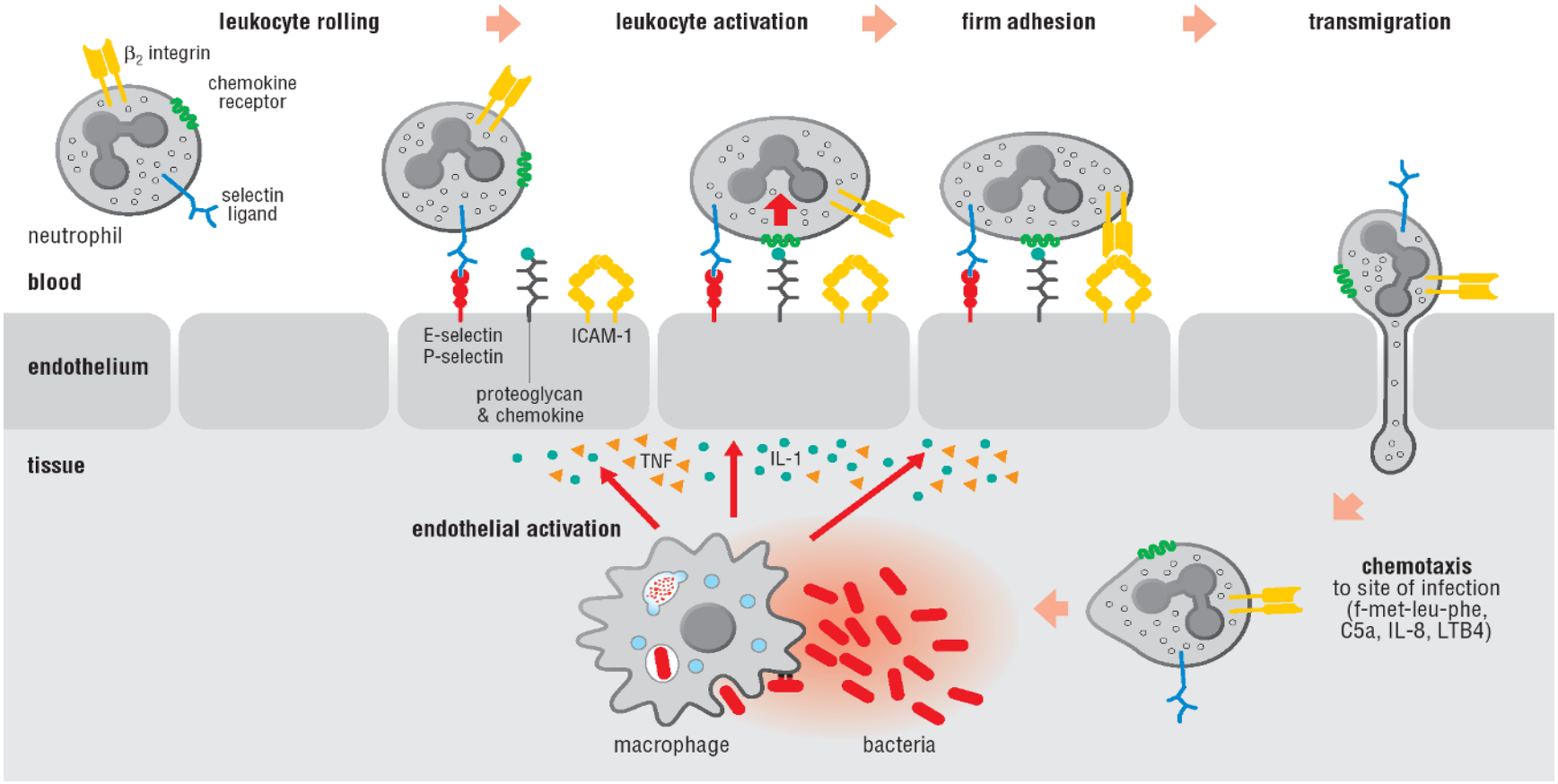
Cytokines
That Mediate and Regulate Innate Immunity

- Tumor necrosis factor (TNF)
- IL-1
- IL-6

→ Proinflammatory cytokines

- chemokines
- Type I IFNs
- IL-12
- IL-15
- IL-18

*Mononuclear phagocytes are the principal source of cytokines of innate immunity



Active recruitment of the cells to the sites of infection→
recognition of microbes →phagocytosis →destruction

TNF

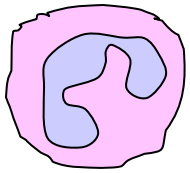
Low quantities (plasma conc.<10^{-9}M)

Moderate quantities

High quantities (plasma conc.≥10^{-7}M)

Local inflammation

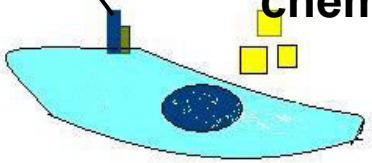
Leukocyte



Activation

Adhesion molecule

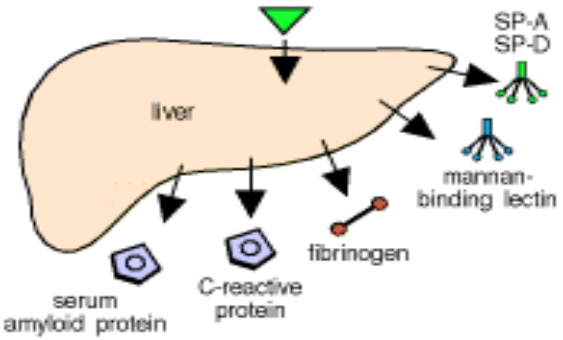
IL-1, chemokines

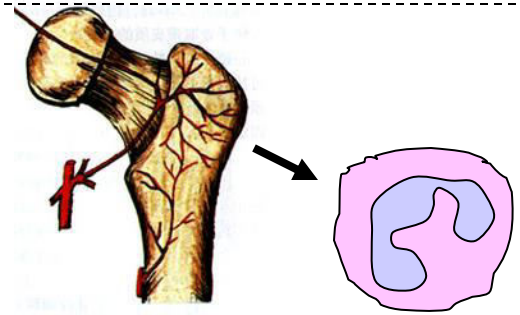


Endothelial cell

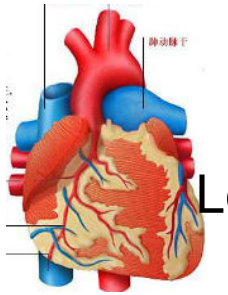
Systemic effects

Fever

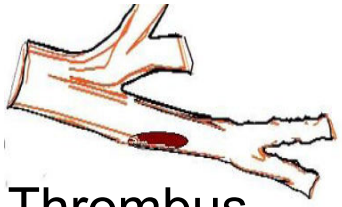




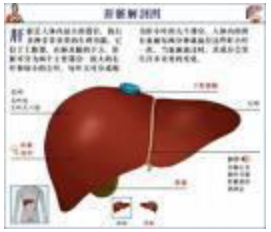
Septic shock



Low output



Thrombus



Hypoglycemia

Type I IFNs

- **Major cellular sources**
  IFN-α: mononuclear phagocytes
  IFN-β: fibroblasts

- **Potent stimulus**
  viral infection

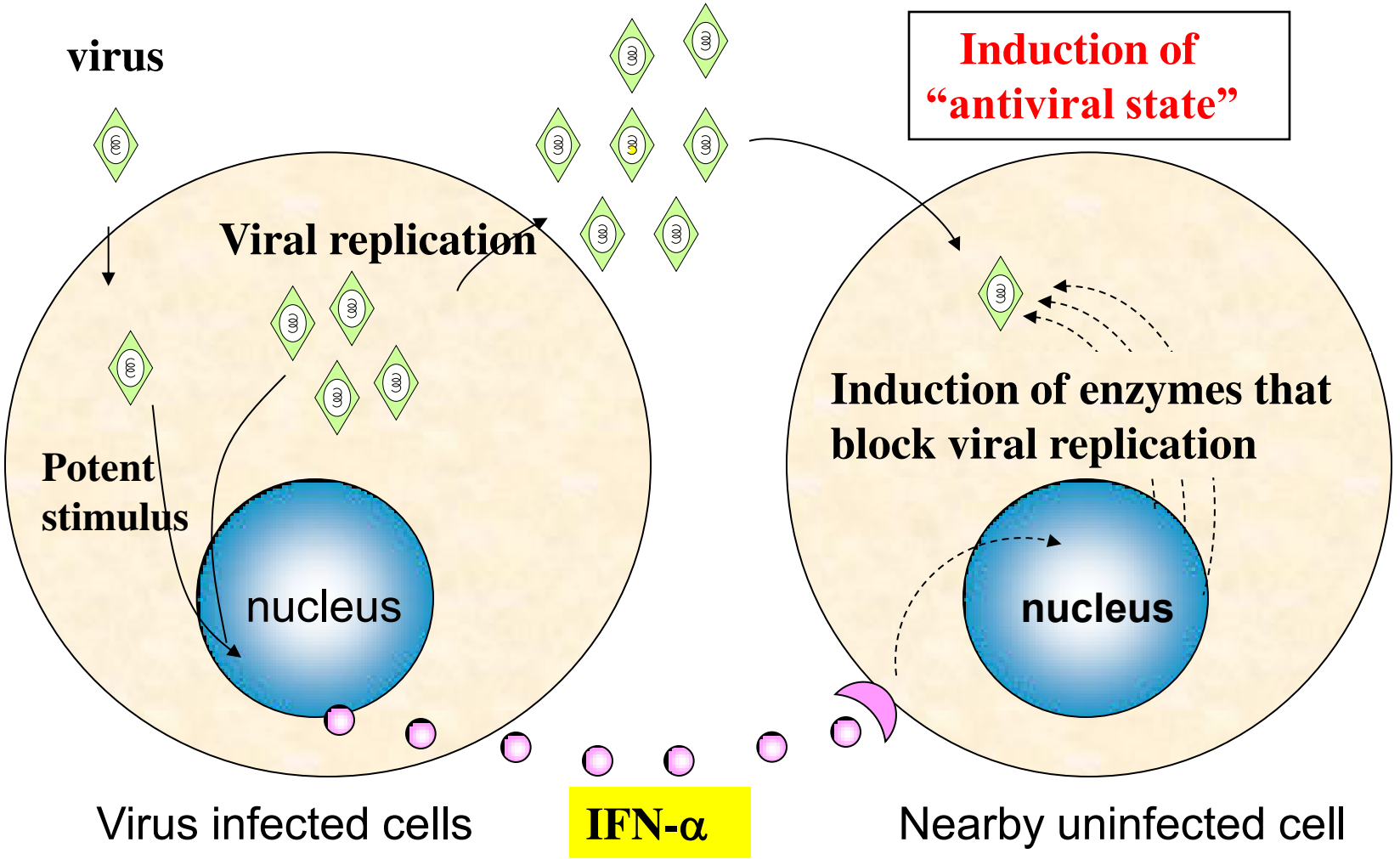
- **Function**
  mediate the early innate immune response to viral infections

Inhibits viral replication

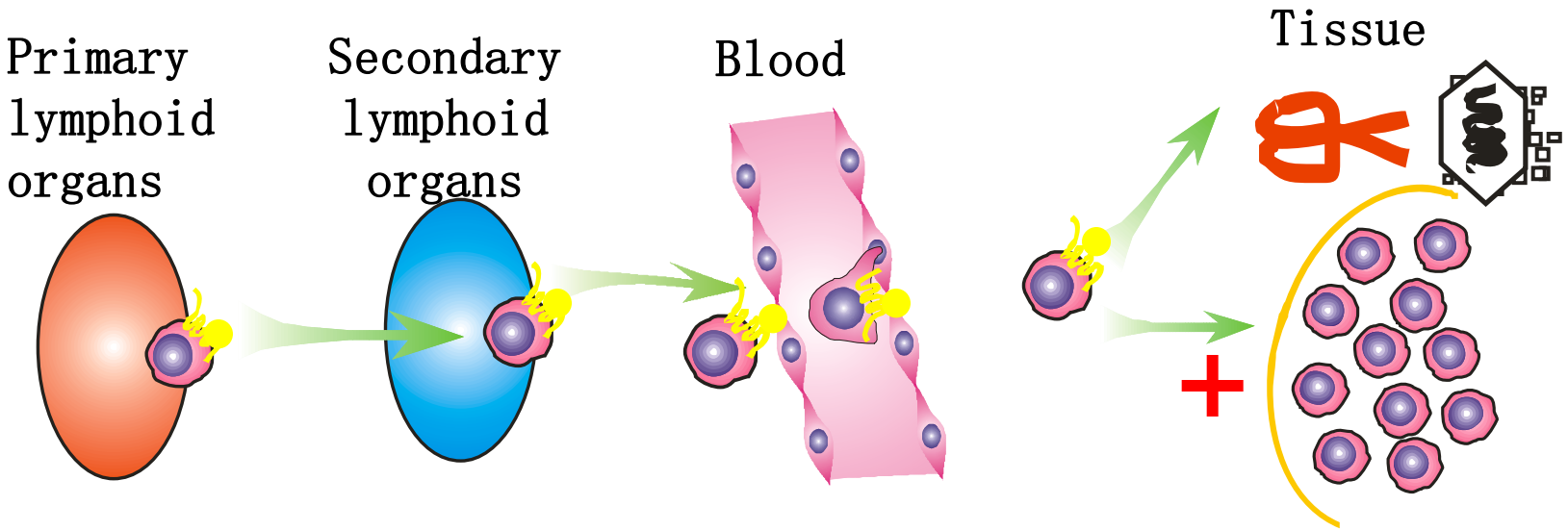
Increase expression of class I MHC molecules

Stimulates the development of Th1 cells in human

type I IFN inhibits viral replication



Chemokines → directing migration of leukocytes



Cellular sources

(1) inflammatory stimuli → to inflammatory sites

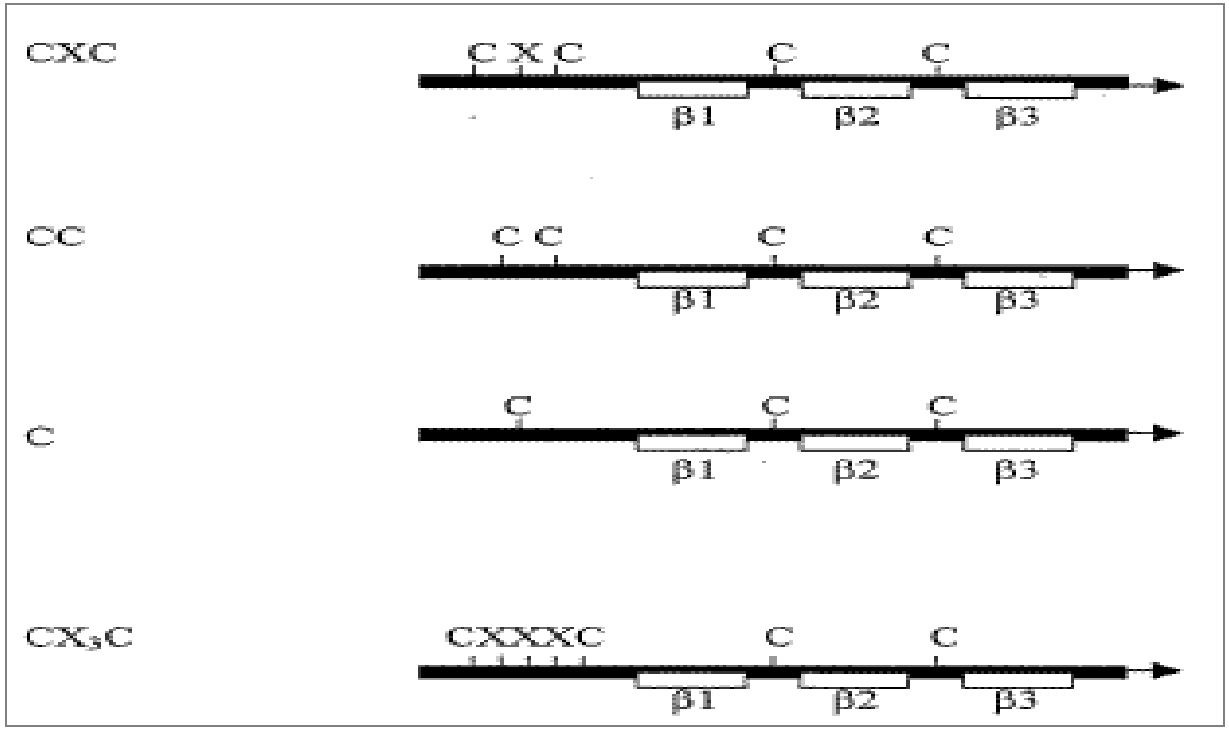
(2) Constitutively produced in lymphoid organs → Physiologic traffic of lymphocytes through the organs

Cytokines and Inflammation

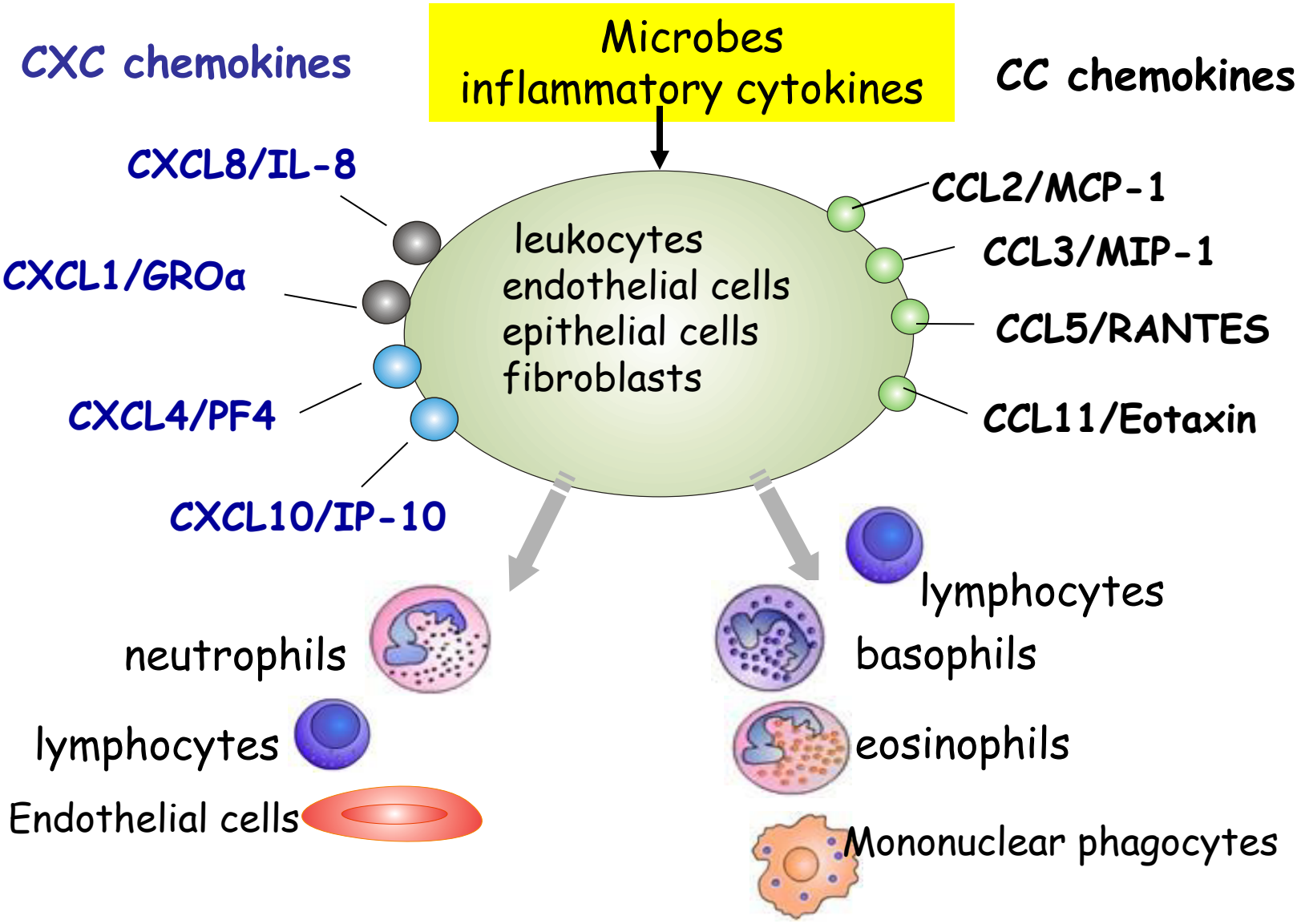
- Macrophages or DCs stimulated via microbes make pro-inflammatory cytokines, especially TNF (Tumor necrosis factor), IL-1, and IL-6
- TNF and IL-1 signal to endothelial cells to make them:
  - Leaky to fluid (influx of plasma; containing antibodies, complement components, etc.)
  - Sticky for leukocytes, leading to influx of neutrophils first, then monocytes, lymphocytes
- Chemokines induce movement of leukocytes and their migration toward chemical gradient of the cytokine

Chemokine family and structure

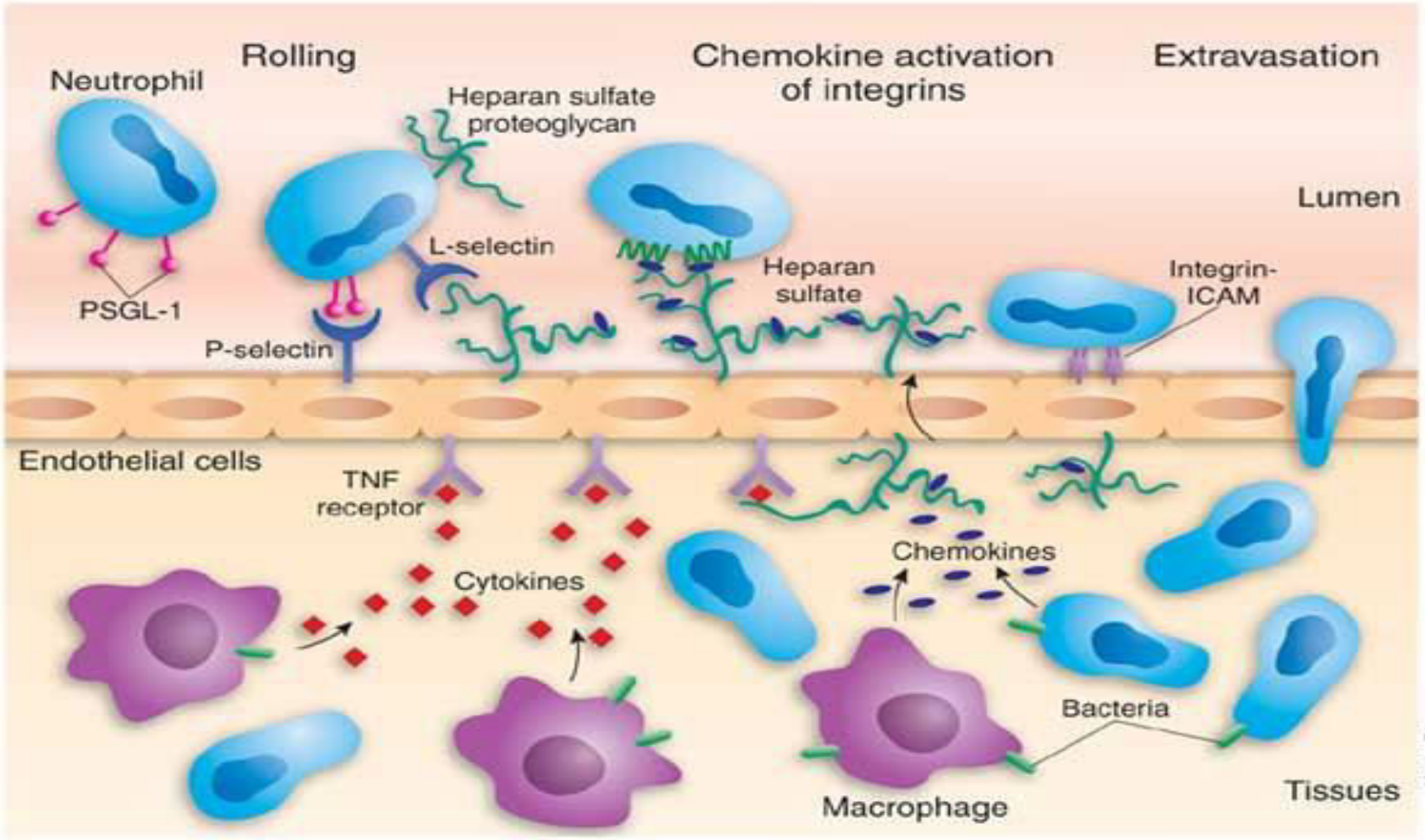
Family **Structure**

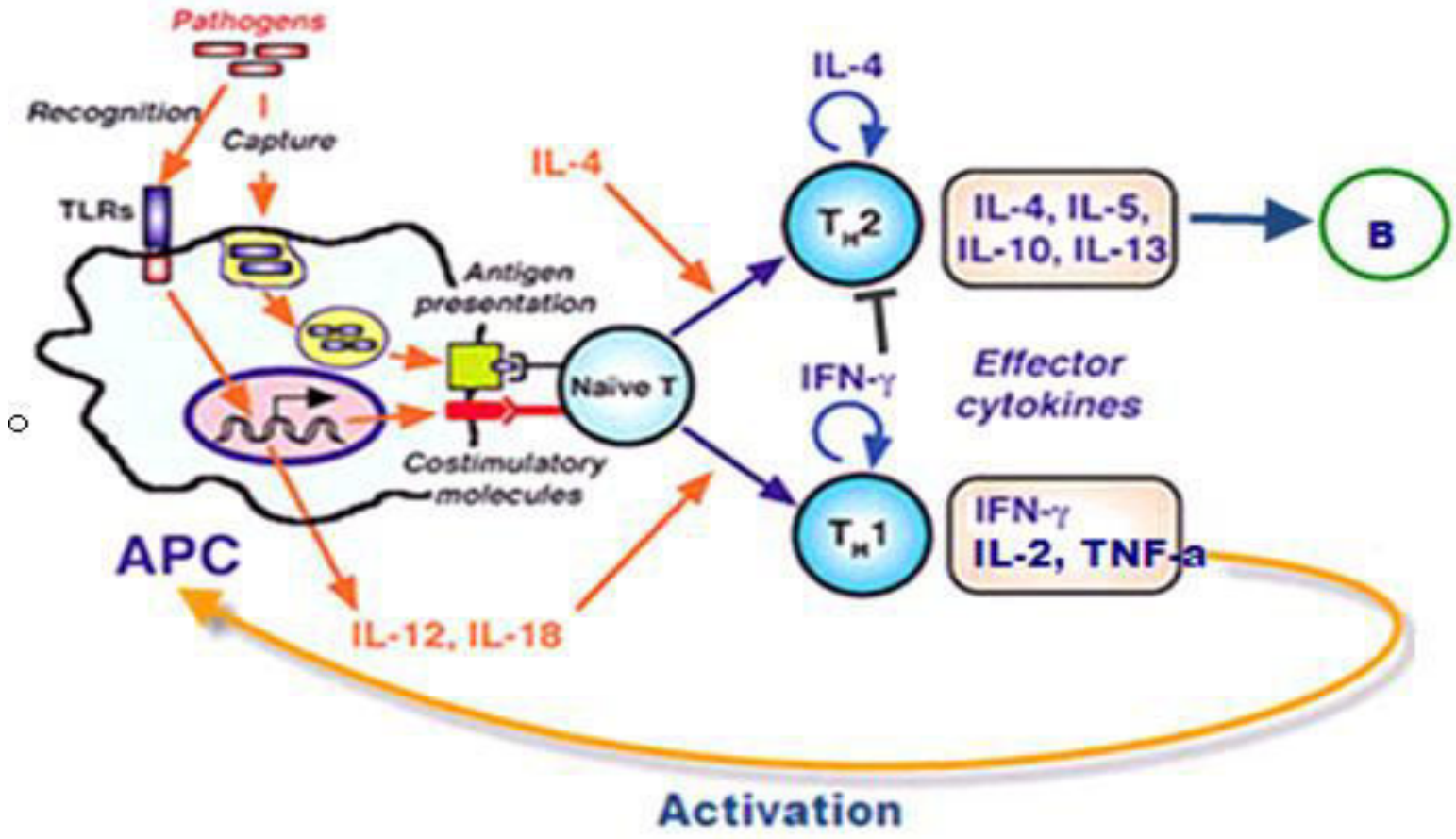


The chemokines are classified into families based on the number and location of N-terminal of cyctein residues **CXC、CC、C、CX3C**


CXC chemokines
Microbes
inflammatory cytokines
CC chemokines
CXCL8/IL-8
CXCL1/GROα
CXCL4/PF4
CXCL10/IP-10
leukocytes
endothelial cells
epithelial cells
fibroblasts
CCL2/MCP-1
CCL3/MIP-1
CCL5/RANTES
CCL11/Eotaxin
neutrophils
lymphocytes
Endothelial cells
lymphocytes
basophils
eosinophils
Mononuclear phagocytes

Chemokines recruit the cells to sites of infection





- Cytokine of adaptive immunity are produced mainly by T lymphocytes in response to specific recognition of protein Ags.
- The function of T helper cells is mediated by cytokines

Function of T cell derived Cytokines

- In the activation phase of T cell-dependant immune response:
  Regulate the growth and differentiation of various lymphocyte population

- In the effector phase of adaptive immune response:
  Recruit, activate, and regulate specialized effector cells, such as mononuclear phagocytes, neutrophils, and eosinophils, to eliminate antigens

Cytokines that Stimulate Hematopoiesis

Colony stimulating factor, CSF

- **Cellular sources:**

  Bone marrow stromal cells, leukocytes

- **Function:**

  stimulate the growth and differentiation of immature leukocytes

- **Members:**

  granulocyte-CSF, G-CSF

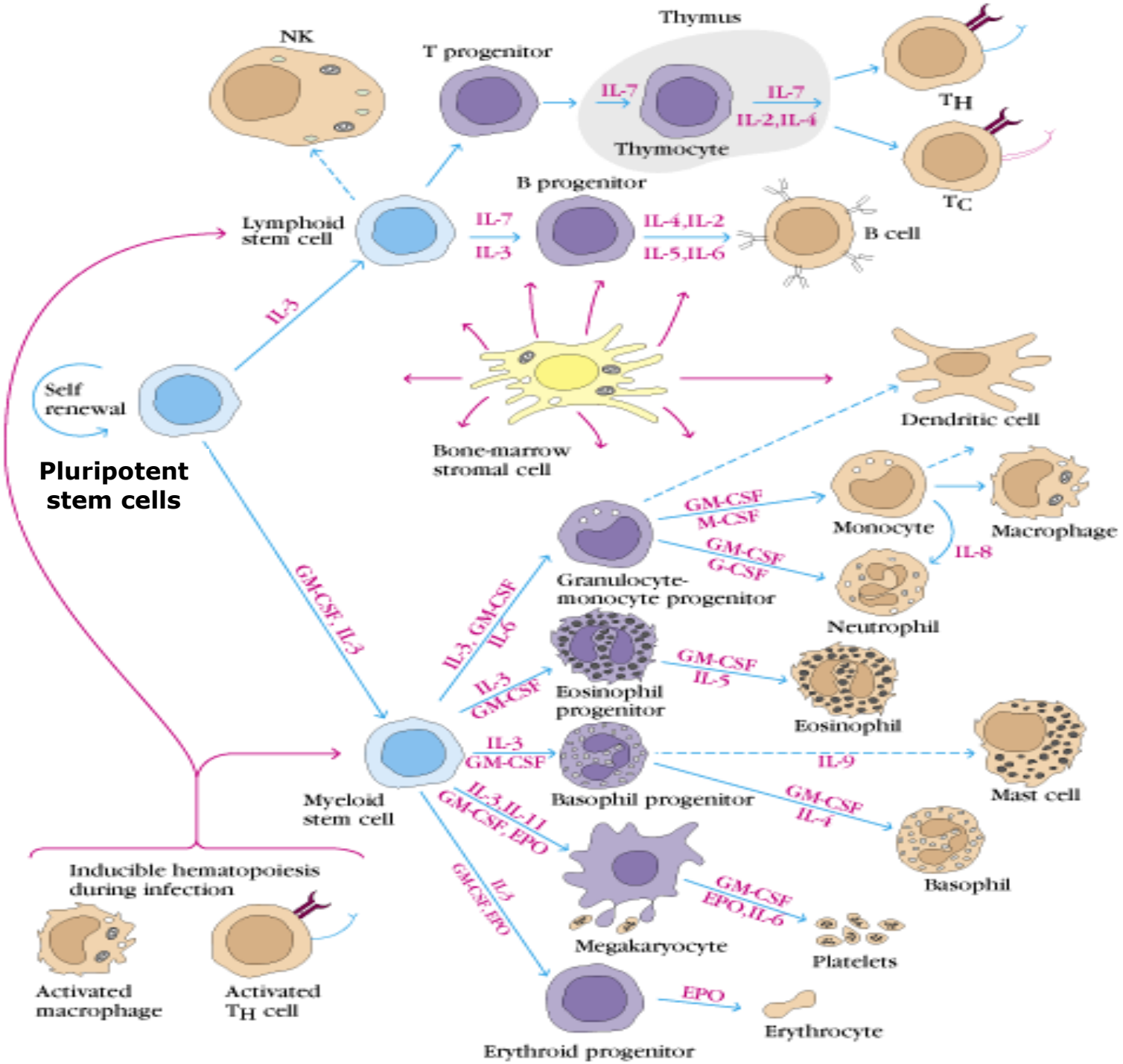
  macrophage-CSF, M—CSF

  granulocyte-macrophage-CSF, GM-CSF)

  erythropoietin, EPO

  TPO

  stem cell factor, SCF


NK
T progenitor
Thymus
IL-7
Thymocyte
IL-7
IL-2,IL-4
TH
TC
B progenitor
Lymphoid stem cell
IL-7
IL-3
IL-4,IL-2
IL-5,IL-6
B cell
IL-3
Self renewal
Pluripotent stem cells
Bone-marrow stromal cell
Dendritic cell
GM-CSF, IL-3
IL-3, GM-CSF IL-6
Granulocyte-monocyte progenitor
GM-CSF M-CSF
GM-CSF G-CSF
Monocyte
Macrophage
IL-8
Neutrophil
IL-3 GM-CSF
Eosinophil progenitor
GM-CSF IL-5
Eosinophil
IL-3 GM-CSF
Basophil progenitor
IL-9
Mast cell
GM-CSF IL-4
Basophil
Myeloid stem cell
IL-3,IL-11 GM-CSF, EPO
Megakaryocyte
GM-CSF EPO,IL-6
Platelets
IL-3 GM-CSF, EPO
Erythroid progenitor
EPO
Erythrocyte
Inducible hematopoiesis during infection
Activated macrophage
Activated TH cell

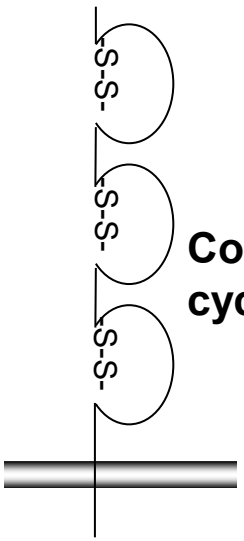
Cytokine Receptors

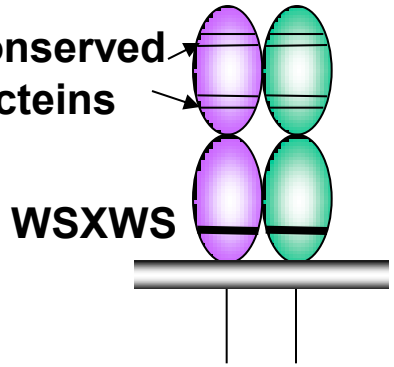
- Type I cytokine receptors (Hematopoietin)
- Type II cytokine receptors
- Ig superfamily
- TNF receptors
- Seven-transmembrane α-helical receptors

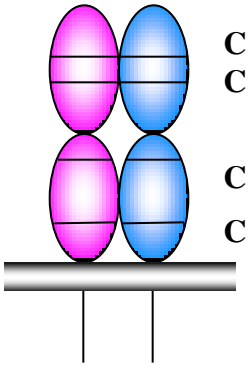
*Classification of cytokine receptors based on structural homologies among the extracellular cytokine-binding domain.

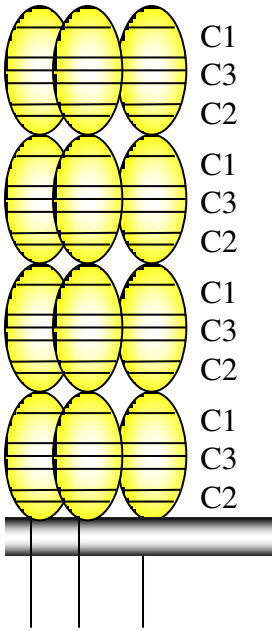
Cytokine receptor families and ligands

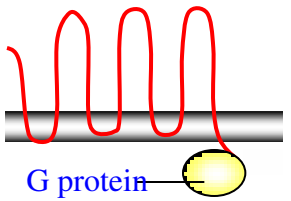
Ig superfamily	Type I cytokine-R	Type II cytokine-R	TNF-R	Chemokine-R





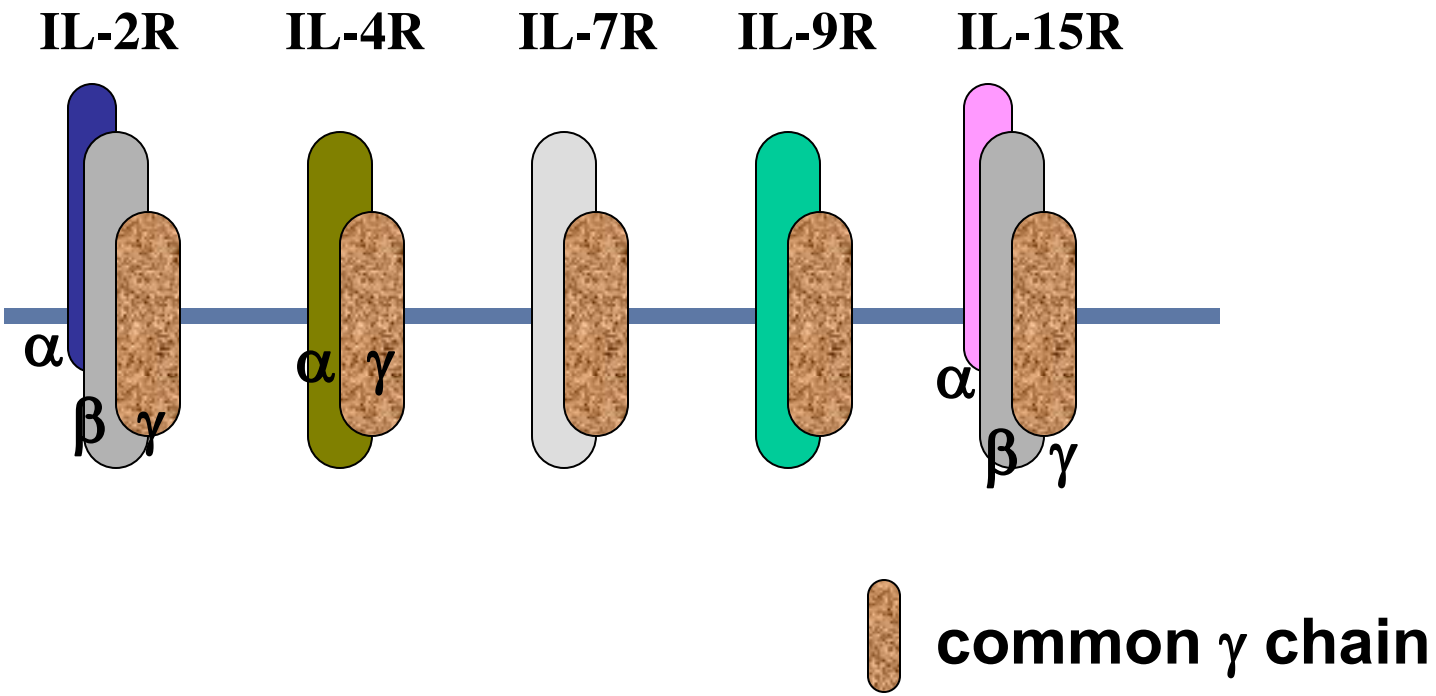






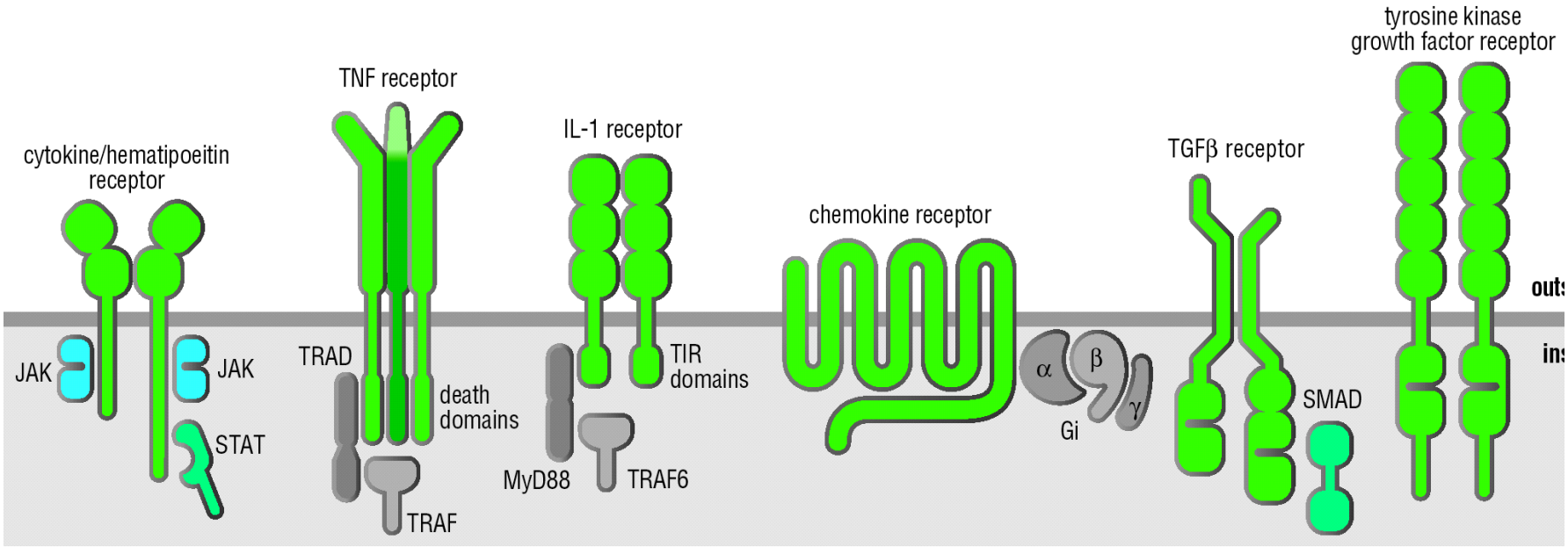
IL-1 M-CSF C-kit	IL-2 IL-3 IL-4 IL-5 IL-6 IL-7 IL-9 IL-11 IL-12 IL-13 IL-15 OSM GM-CSF G-CSF EPO	IFN-α IFN-β IFN-γ IL-10	TNF-α TNF-β CD40L NGF FASL	IL-8 RANTES MIP-1 PF4

γ –chain shared by IL-2 receptor family



Cytokine receptors consist of unique ligand-binding chains and one or more signal-transducing chains,which are often shared by receptors for different cytokines

Cytokine receptors and signaling



Different cytokines binding to cytokine receptors activated distinct signal transduction pathways resulting in gene activation.

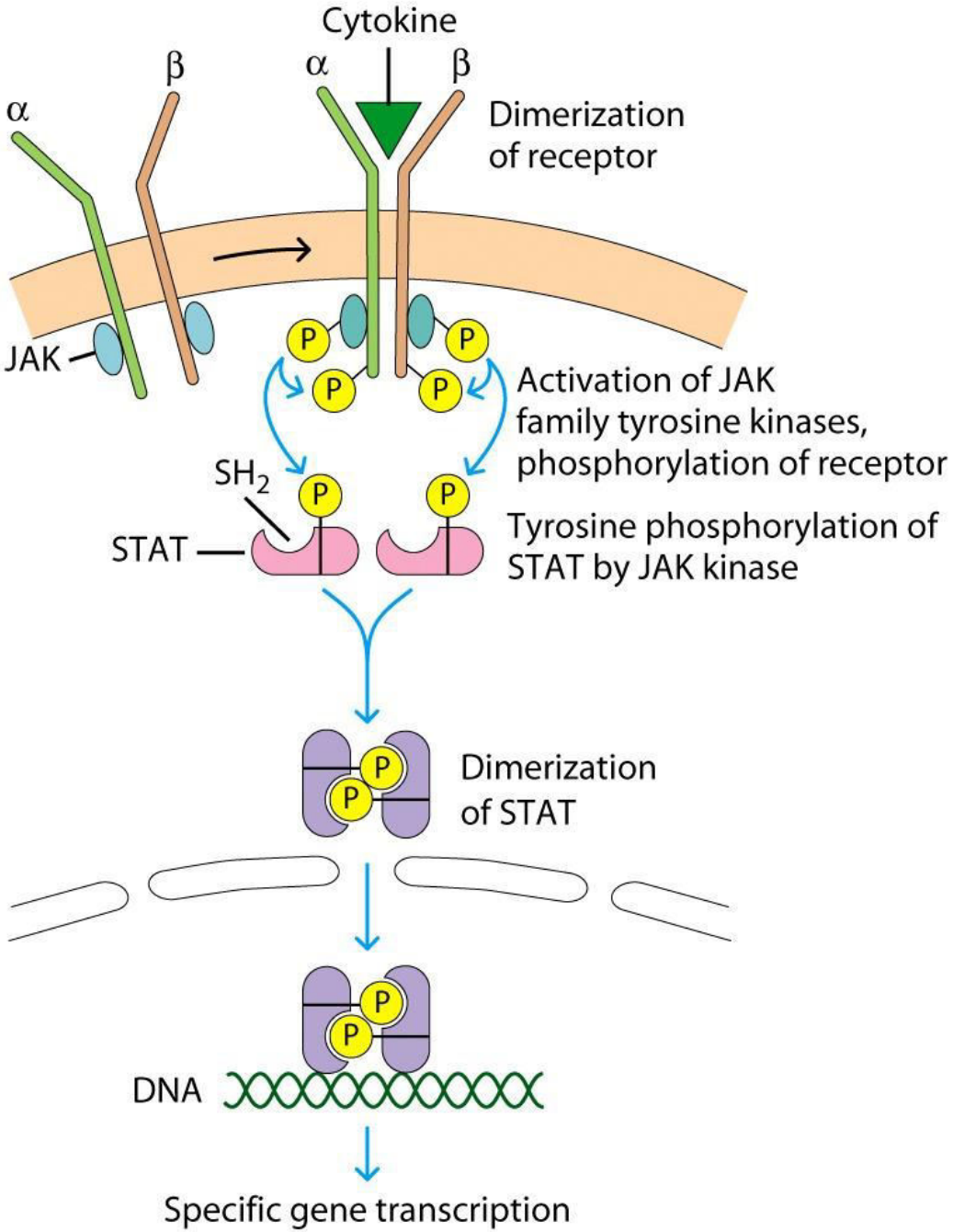

Cytokine
α
β
α
β
Dimerization
of receptor
JAK
P
P
P
P
Activation of JAK
family tyrosine kinases,
phosphorylation of receptor
SH2
STAT
P
P
Tyrosine phosphorylation of
STAT by JAK kinase
P
P
Dimerization
of STAT
P
P
DNA
Specific gene transcription

TABLE 12-2 STAT and JAK interaction with selected cytokine receptors during signal transduction

Cytokine receptor	JAK	STAT
IFN-γ	JAK1 and JAK2	Stat1
IFN-α/β	JAK1 and Tyk-2	Stat2
IL-2	JAK1 and JAK3	Stat5
IL-3	JAK2	Stat5
IL-4	JAK1 and JAK3	Stat6
IL-6	JAK1 (and sometimes others)	Stat3
IL-10	JAK1 and Tyk-2*	Stat3
IL-12	JAK2 and Tyk-2*	Stat4

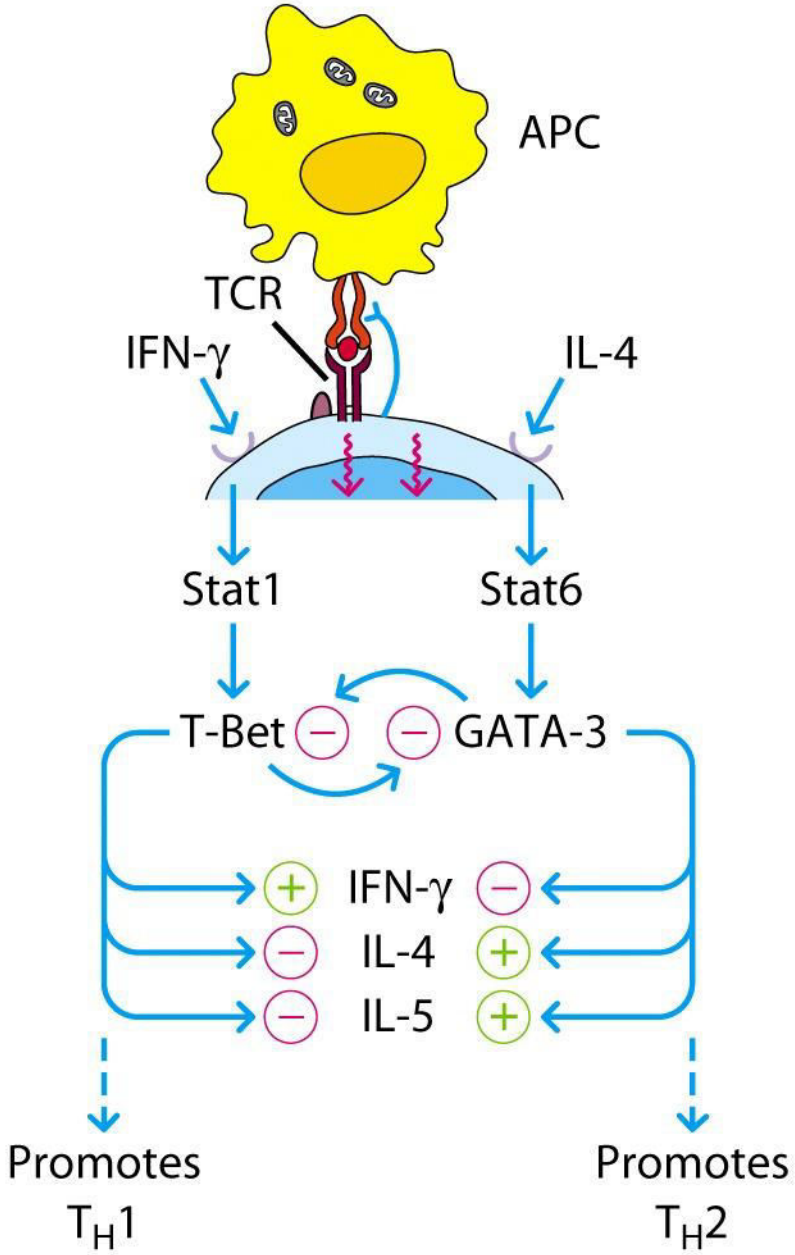
*Despite its name, Tyk-2 is also a Janus kinase.

SOURCE: Adapted from E. A. Bach, M. Aguet, and R. D. Schreiber, 1997, *Annu. Rev. Immun.* **15:**563.

TABLE 12-4 Cytokine secretion and principal functions of mouse T_H1 and T_H2 subsets

Cytokine/function	T_H1	T_H2
CYTOKINE SECRETION		
IL-2	+	–
IFN-γ	++	–
TNF-β	++	–
GM-CSF	++	+
IL-3	++	++
IL-4	–	++
IL-5	–	++
IL-10	–	++
IL-13	–	++
FUNCTIONS		
Help for total antibody production	+	++
Help for IgE production	–	++
Help for IgG2a production	++	+
Eosinophil and mast-cell production	–	++
Macrophage activation	++	–
Delayed-type hypersensitivity	++	–
T_C-cell activation	++	–

SOURCE: Adapted from F. Powrie and R. L. Coffman, 1993, *Immunol. Today* **14:**270.


APC
TCR
IFN-γ
IL-4
Stat1
Stat6
T-Bet
GATA-3
IFN-γ
IL-4
IL-5
Promotes
T_H1
Promotes
T_H2

Cytokines and Diseases

1. Toxic shock Syndrome

- It is Initiated by release of Super antigens from microorganisms like *Staphylococcus and Streptococcus.*

- The toxins causes a burst of cytokine production by T cells.

Super antigen activated T cells produce excessive productions of cytokines and cause dysregulation of cytokine network.

- *IL-1 and TNF-alpha.*

2. Bacterial septic shock:
E.Coli ,Klebsiella pneumonis, Enterobacter aerogens , Pseudomonas etc.

- Bacterial Septic Shock
  - Certain Gram- bacteria
  - Symptoms: drop in blood pressure, fever, diarrhoea, blood clotting
  - Endotoxins bind TLRs on dendritic cells and macrophages
    - Over-produce IL-1 and TNF-α
    - Cytokine imbalance causes abnormal temp, abnormal respiration, capillary leakage, tissue injury, organ failure
    - Neutralization by monoclonal antibodies may help

Lymphoid and Myeloid Cancers :

- T cell Leukemia diseases –Overproduction of Il-2 cytokine
- High levels of IL-6 is secreted by cadiac myxoma cells, myeloma cells and plasmacytoma cells . (a benign heart tumor).
- Hodgkin's Disease : Overproduction of IL-5

Chagas Disease :

- Caused by Trypanosoma cruzi.
- Severe immune suppression.

Autoimmunity And cytokines:

- SLE (Systemic lupus erythematosus) affects multisystem of the body.

Associated with elevated levels of IL-10

Rheumatoid arthritis :

TNFα, IL-1, IL-6, GM-CSF, and chemokines such as IL-8 are abundant in all patients.

- Abnormalities in production of cytokines or receptors are associated with certain types of cancer

- Chaga's Disease
  - Caused by *Trypanosoma cruzi*
  - Severe immunosuppression
    - Evidence that soluble factor produced by *T. cruzi* leads to reduction in T cell IL-2 (CD25) receptor