Cytokines (CKs)

Immunology Lecture 10

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Objectives

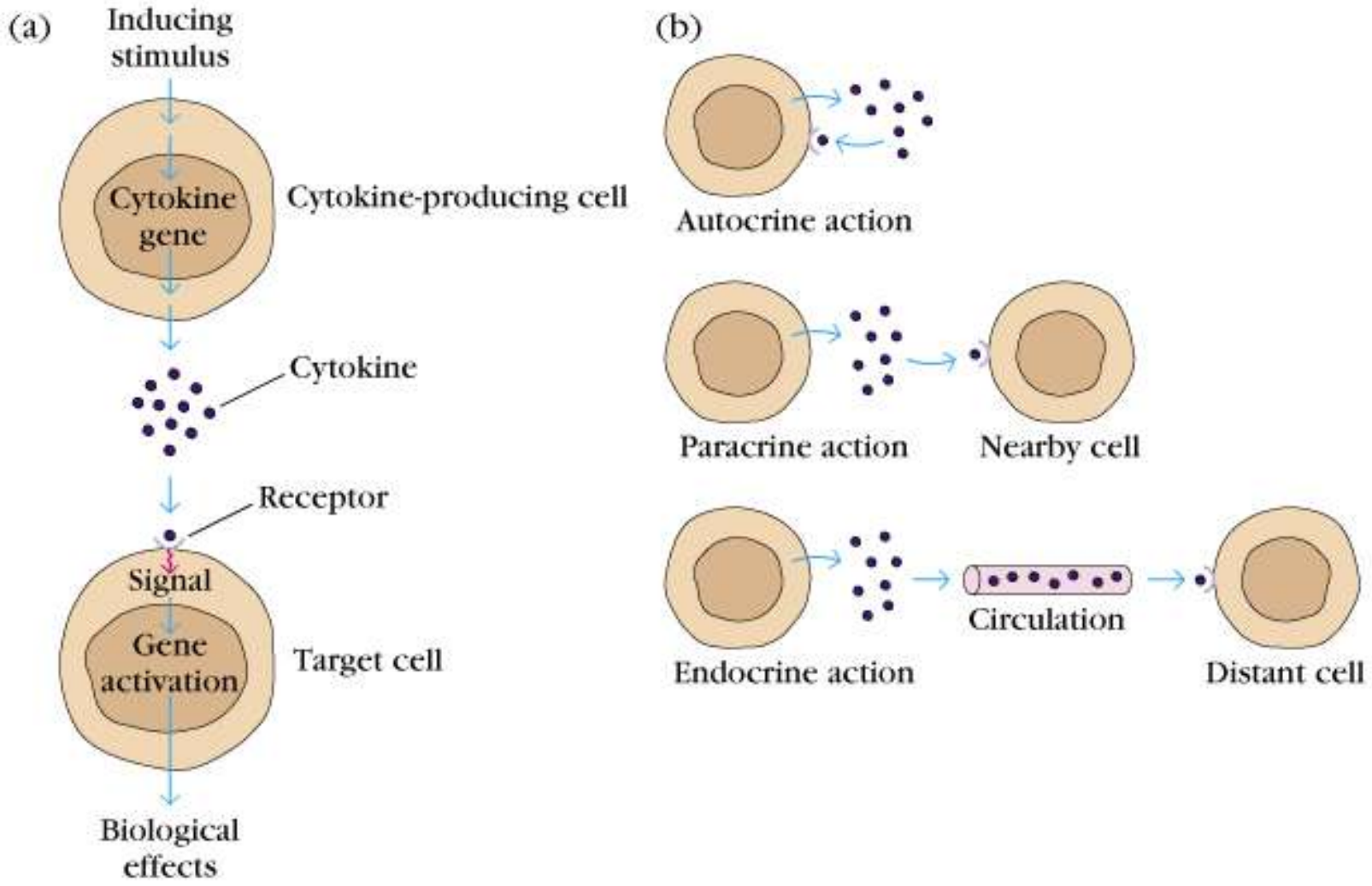
- Definition and general properties of cytokines
- Classification of cytokines
- Cytokine receptor
- Biological functions of cytokines
- Cytokine and disease

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.
- Cytokine or immunocytokine is a generic name used to describe a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to- picomolar concentrations
- Their major functions are to mediate and regulate immune response and inflammatory reactions.

General Properties

- Most cytokines are low molecular weight polypeptides or glycoprotein (8~80 KD), and most of them are monomer
- Natural cytokines are secreted by activated cells such as activated immune cells, matrix cells and tumor cells
- One kind of cytokines can be produced by different cells. One kind of cells can secrete different cytokines
- Cytokines initiate their actions by binding to specific membrane receptors on target cells.
- Cytokines can act on the cells that produce them (autocrine), on other cells in the immediate vicinity (paracrine), or on cells at a distance (endocrine) after being carried in blood or tissue fluids.

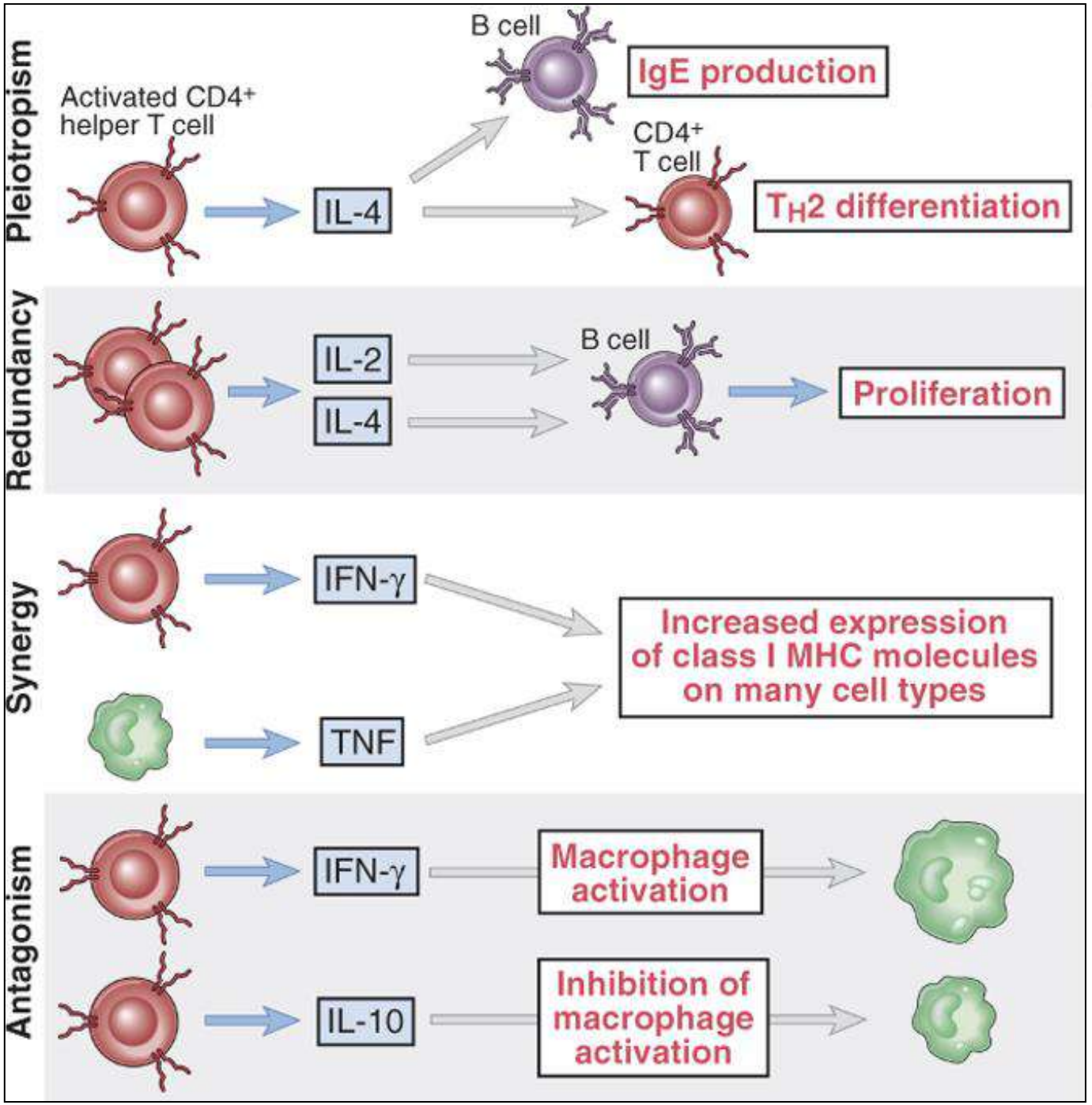

(a)
Inducing stimulus
Cytokine gene
Cytokine-producing cell
Cytokine
Receptor
Signal
Gene activation
Target cell
Biological effects
(b)
Autocrine action
Paracrine action
Nearby cell
Endocrine action
Circulation
Distant cell

Cytokine Names

- Interleukins - produced exclusively by leukocytes
- Lymphokines - produced by lymphocytes
- Monokines - produced exclusively by monocytes
- Interferons - involved in antiviral responses
- Colony Stimulating Factors - support the growth of cells in semisolid medias
- Chemokines - promote chemotaxis

Effects of Cytokines

- 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.


Pleiotropism
Activated CD4+ helper T cell
IL-4
B cell
IgE production
CD4+ T cell
TH2 differentiation
Redundancy
IL-2
IL-4
B cell
Proliferation
Synergy
IFN-γ
TNF
Increased expression of class I MHC molecules on many cell types
Antagonism
IFN-γ
Macrophage activation
IL-10
Inhibition of macrophage activation

Cytokine General Actions

- Development of cellular and humoral immune responses
- Induction of inflammation
- Regulation of hematopoiesis
- Control of cellular proliferation and differentiation
- Induction of wound healing
- Chemotaxis

Classification of cytokines

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

1. Interleukin 1 (IL-1) Family

i. Typically secreted very early in the immune response by dendritic cells and monocytes or macrophages.

ii. IL-1 secretion is stimulated by recognition of viral, parasitic, or bacterial antigens **by innate immune receptors**.

iii. IL-1 family members are generally pro-inflammatory, (what does that mean)?

- they induce an increase in the capillary permeability at the site of cytokine secretion,
- amplification of the level of leukocyte migration into the infected tissues**.**
- IL-1 has systemic (whole body) effects and signals the liver to produce acute phase (CRP) and IL-6
- These proteins further induce multiple protective effects, including the destruction of viral RNA
- generation of a systemic fever response (which helps to eliminate many temperature-sensitive bacterial strains).
- IL-18 stimulate production of the macrophage-activating cytokine IFN-γ by NK cells and T cells.

innate immune response

- IL-1 also activates both T and B cells at the induction of **the adaptive immune response.**
- **E.X. IL-1α and IL-1β ,IL-18**

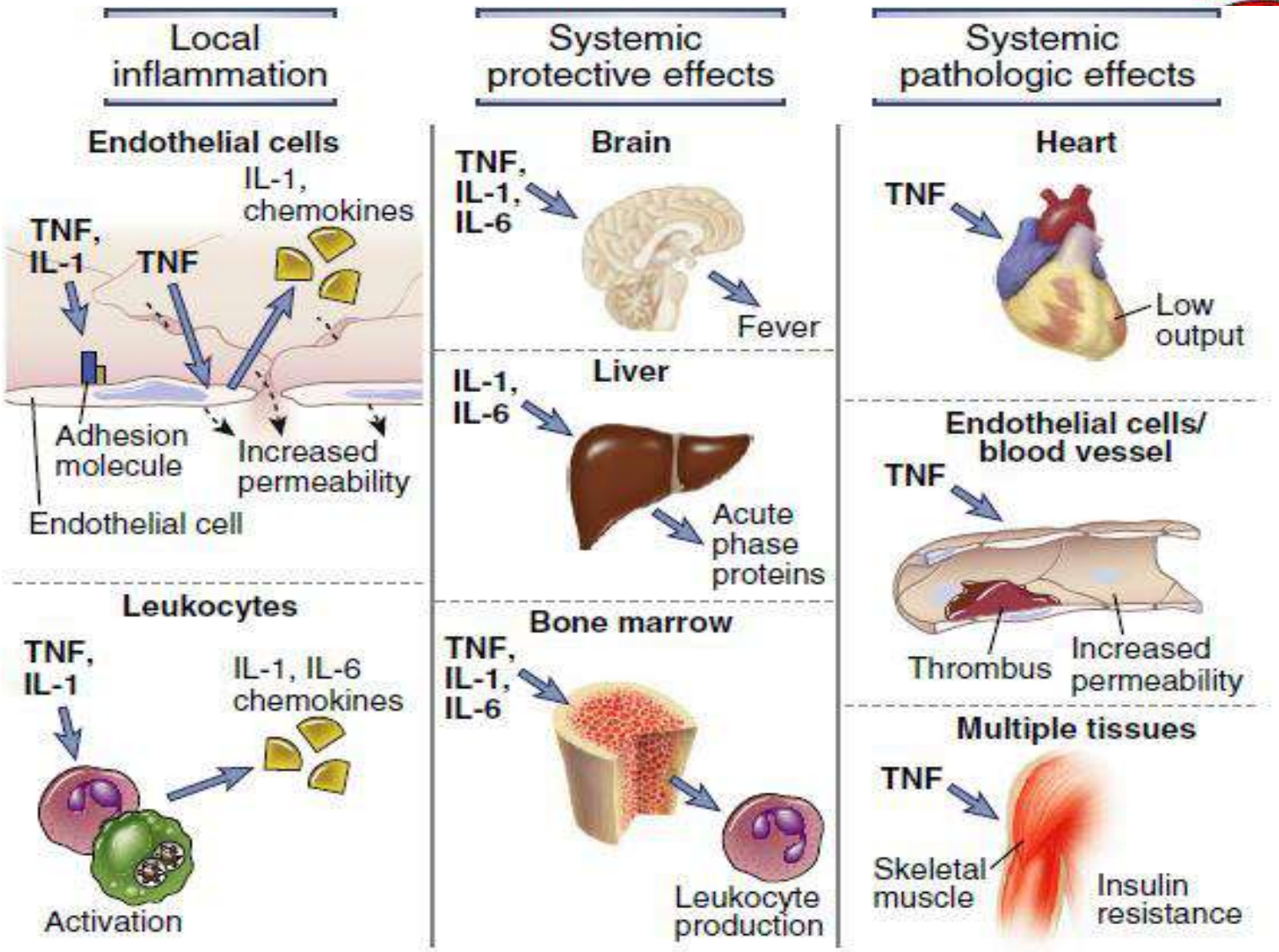


FIGURE 4-15 Local and systemic actions of cytokines in inflammation. TNF, IL-1, and IL-6 have multiple local and systemic inflammatory effects. TNF and IL-1 act on leukocytes and endothelium to induce acute inflammation, and both cytokines induce the expression of IL-6 from leukocytes and other cell types. TNF, IL-1, and IL-6 mediate protective systemic effects of inflammation, including induction of fever, acute-phase protein synthesis by the liver, and increased production of leukocytes by the bone marrow. Systemic TNF can cause the pathologic abnormalities that lead to septic shock, including decreased cardiac function, thrombosis, capillary leak, and metabolic abnormalities due to insulin resistance.

- Hematopoietin (Class I) Family
  - Called Class I because earliest to be structurally characterized (not first to be discovered)
  - Large family of small cytokine molecules with functional diversity
  - Not all involved in hematopoietic functions

Their cellular origins and target cells are as diverse as their ultimate functions, which range from;

- signaling the onset of T- and B-cell proliferation (e.g., IL-2),
- Signaling the onset of B-cell differentiation to plasma cells and antibody secretion (e.g., IL-6),
- Signaling the differentiation of a T helper cell along one particular differentiation pathway versus another (e.g., IL-4 vs. IL-12)
- Finally, Initiating the differentiation of particular leukocyte lineages (e.g., granulocyte monocyte-colony stimulating factors GM-CSF, G-CSF).
- **E.X. IL-2, IL-4, IL-5, IL-7, IL-9,IL-12, IL-15, IL-21 and GM-CSF**

- **IL-17 Family (**most recently described cytokines ,proinflammatory cytokine cluster**)**

- **interleukins 17A, 17B, 17C, 17D, and 17F**. Signaling through most members of this family culminates in the **generation of inflammation**.
- **IL-17 released** by activated T cells and stimulates the production of factors that signal a proinflammatory state, including IL-6, chemokines CXCL8, and (G-CSF).

2. Interferon (Class II)

First cytokines to be discovered

- **Type I -** Secreted by not only macrophages and dendritic cells but also by virus infected cells: (1) **Interferons α**, and (2) **interferon-β**,
- **Type II** – produced by activate T and NK cells **, known as interferon-γ & cytokines include IL-10**

	Types	Produced cells	Main functions
IFN-α	Type I	leukocyte	anti-virus, immune regulation
IFN-β	Type I	fibroblast	anti-tumor
IFN-γ	Type II	Th1, NK	weaker anti-virus effect, stronger immune regulation effect, anti-tumor

- Interferon-γ is used medically to bias the adaptive immune system toward a cytotoxic response in diseases such as leprosy and toxoplasmosis (intracellular pathogens), **in which antibody responses are less effective. BY**
  - and inducing the activation of macrophages, with subsequent destruction of any intracellular pathogens
  - and the differentiation of cytotoxic T cells.
- All three INFs

(increase the expression of MHC complex proteins on the surface of cells, thus enhancing their **antigen-presentation capabilities.)**

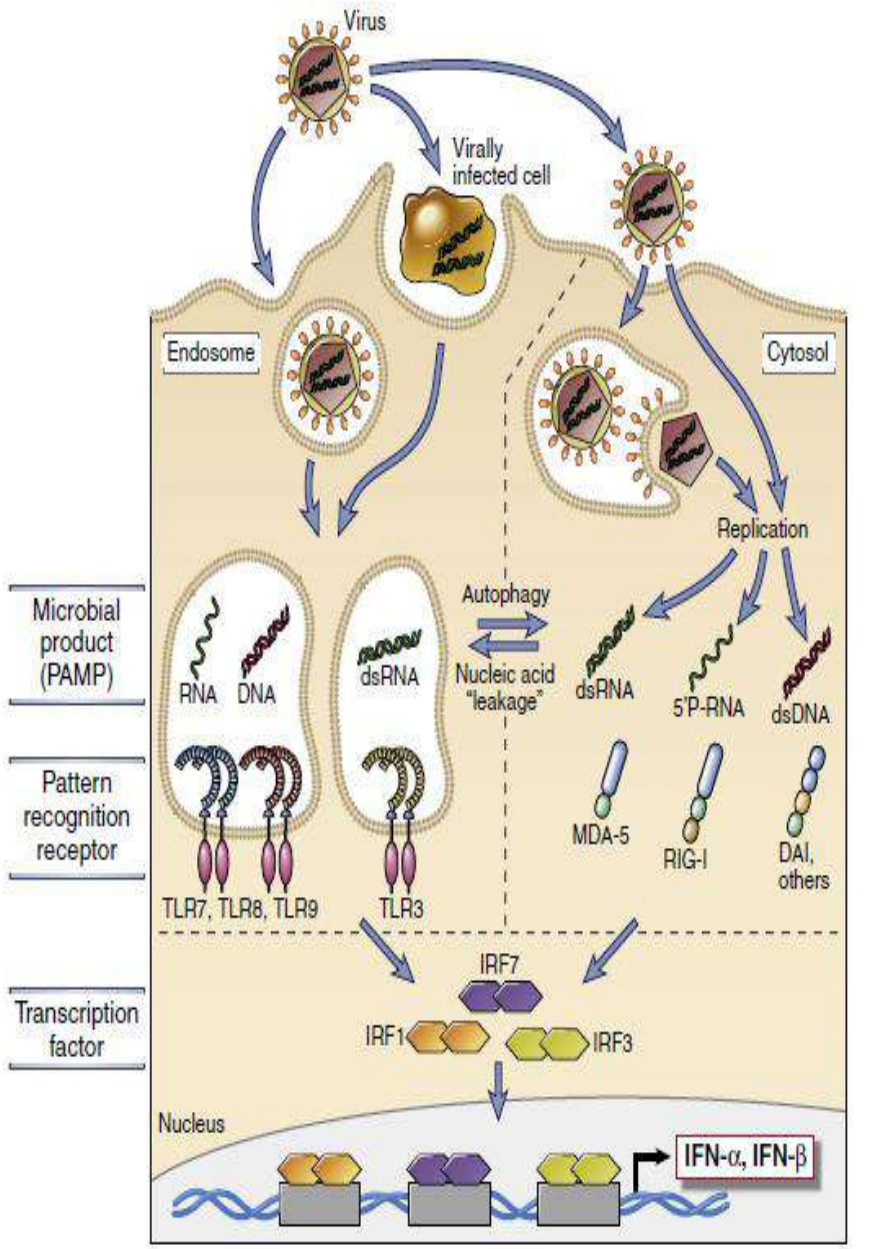


FIGURE 4-16 Mechanisms of induction of type I interferons by viruses. Viral nucleic acids and proteins are recognized by several cellular receptor families (TLRs, the family of cytosolic RIG-like receptors, or RLRs, which include MDA-5, RIG-I, DAI and others, and cytosolic DNA sensors), which activate transcription factors (the IRF proteins) that stimulate the production of

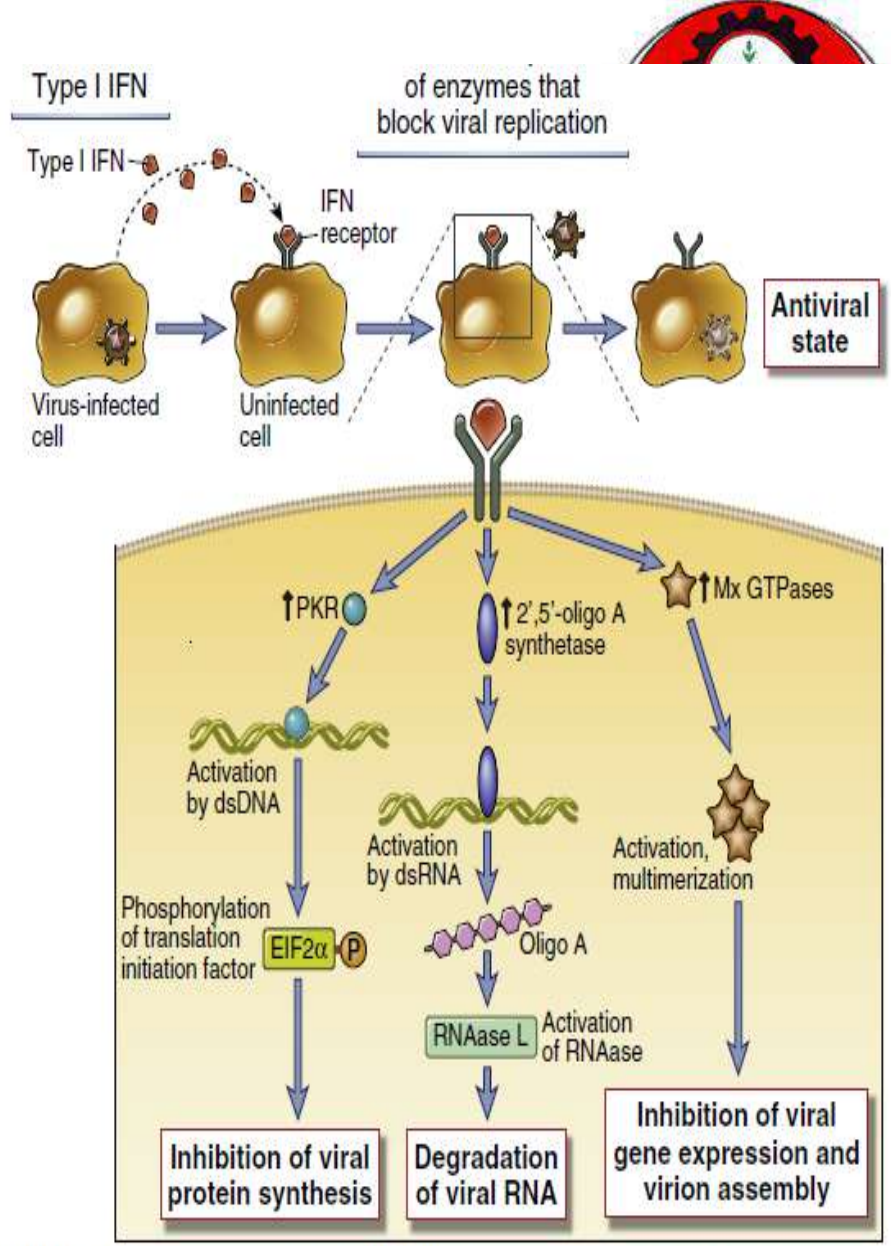


FIGURE 4-17 Biologic actions of type I interferons. Type I interferons (IFN-α, IFN-β) are produced by virus-infected cells in response to intracellular TLR signaling and other sensors of viral RNA. Type I interferons bind to receptors on neighboring uninfected cells and activate JAK-STAT signaling pathways, which induce expression of genes whose products interfere with viral replication. Type I interferons also bind to receptors on infected cells and induce expression of genes whose products enhance the cell's susceptibility to CTL-mediated killing. *PKR*, double stranded RNA-activated protein kinase.

3. Tumor Necrosis Family (TNF)

- Can signal development, activation, or death of certain cells (homeostasis)
- Which induce apoptosis**, or programmed cell death,** <u>is a mechanism of cell death in which the cell dies from within and is fragmented into membrane-bound vesicles that can be rapidly phagocytosed by neighboring macrophages</u>.

Cytokines of the TNF Family

- **There are two members having the same name of the TNF family**: TNF-α and TNF-β. Both of these are secreted as soluble proteins.

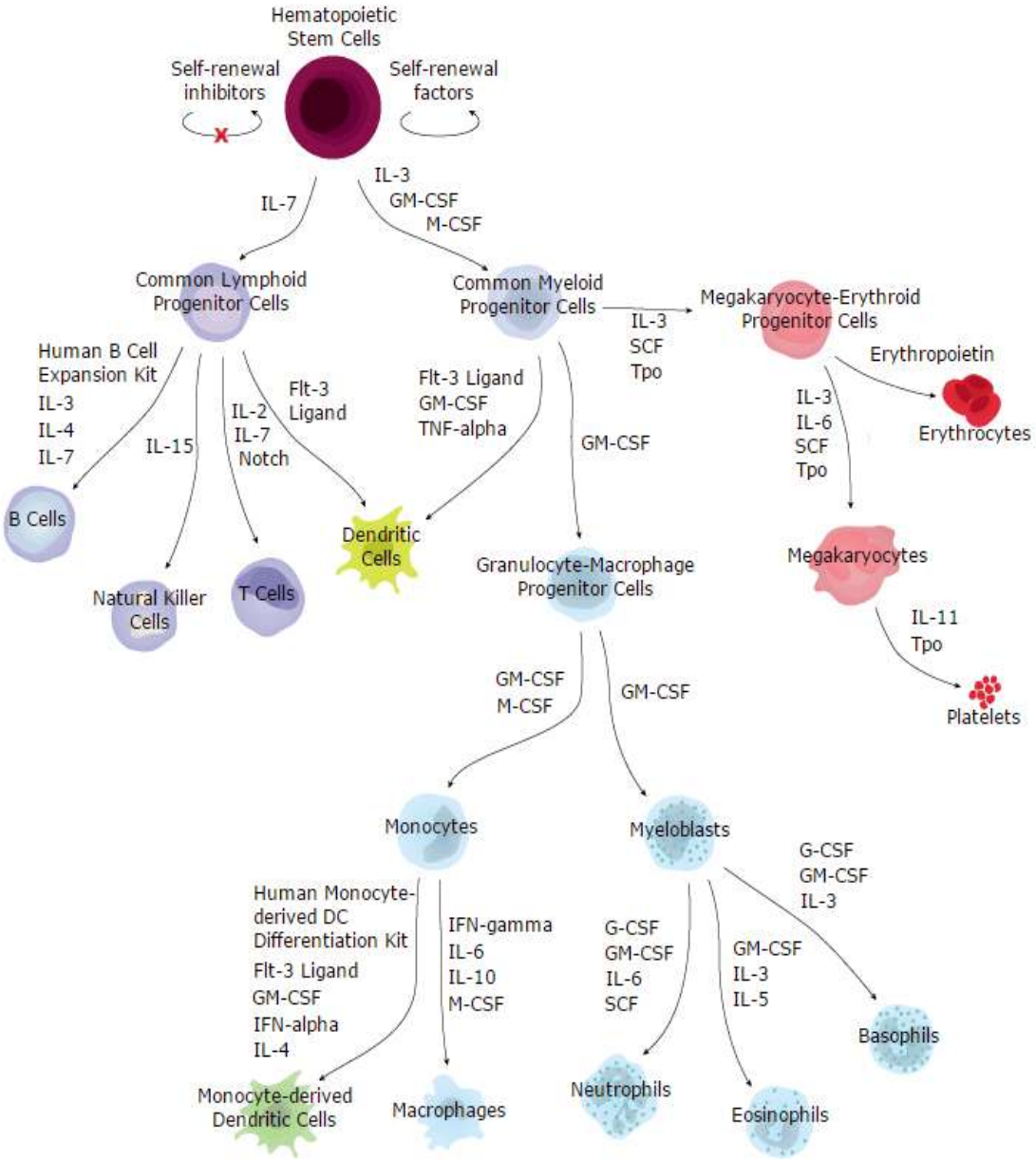
- There are two members of the TNF family: TNF-α and TNF-β
- **TNF-α** is a proinflammatory cytokine, **produced** primarily by activated macrophages, and lymphocytes, in response to infection, or inflammation.
- **TNF-β** is **produced** by activated lymphocytes and can deliver a variety of signals. On binding to neutrophils, endothelial cells lead to increased expression of MHC and of adhesion molecules.
- **Fas ligand (FasL)**, induces apoptosis.

regulate immune system and progression of cancer.

4. Colony-Stimulating Factors (CSF)

- Cytokines that stimulate proliferation or differentiation of pluripotent hematopoietic stem cell and different progenitors.
  - Multi-CSF (IL-3)
  - Granulocyte macrophage-CSF (GM-CSF)
  - Monocyte-CSF (M-CSF)
  - Granulocyte-CSF (G-CSF)
  - Stem cell factor (SCF)
  - Erythropoietin (EPO) secreted by kidney in response to cellular hypoxia

Hematopoietic Stem Cell Differentiation Pathways & Lineage-specific Markers



5. Chemokines

- Direct the Migration of Leukocytes through the Body
- Are structurally related family of small cytokines that bind to cell-surface receptors and **induce the movement** of leukocytes up toward the chemokine source.
- This soluble factor-directed cell movement is known as chemotaxis, and molecules that can elicit such movement are referred to as chemoattractants
- located on the surfaces of endothelial cells, enables them to bind to the inner surfaces of blood vessels and directing leukocyte movement.

•CXCLgroup: attract neutrophils
•CCL group: attract monocytes and macrophages (although not neutrophils) to the site of infection.

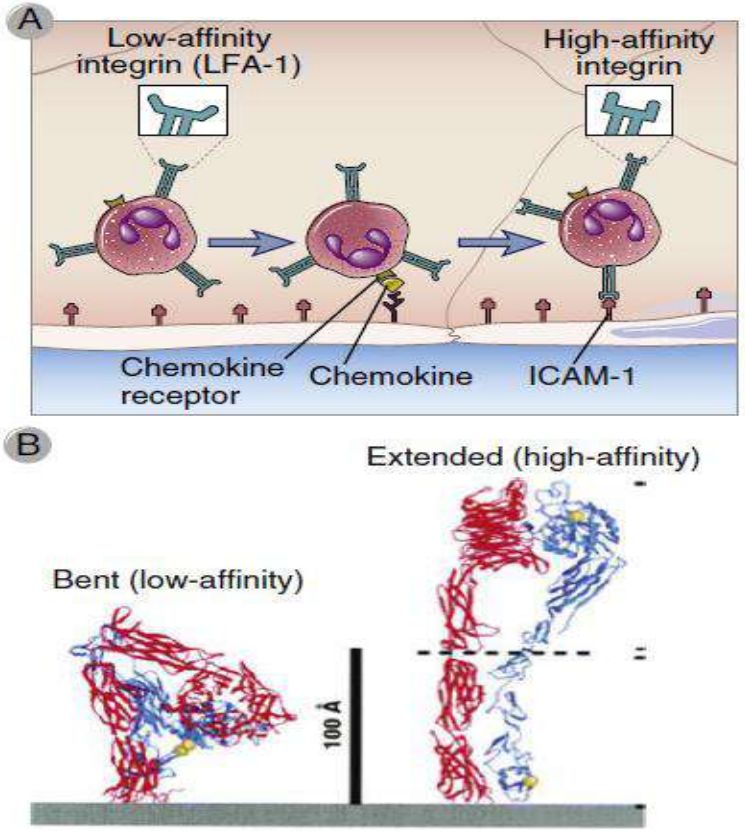


FIGURE 3-2 Integrin activation. A, The integrins on blood leukocytes

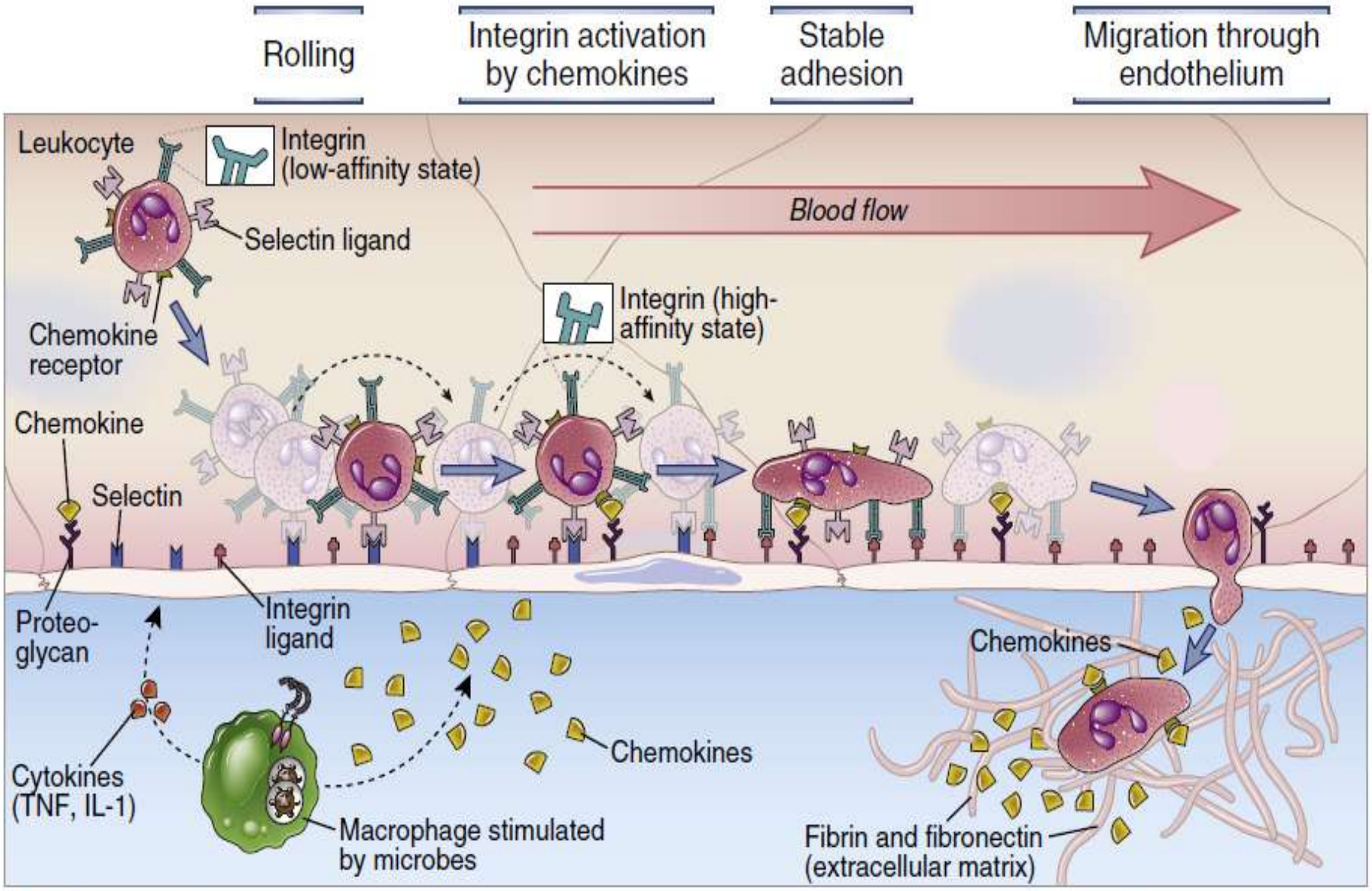


FIGURE 3-3 Multistep leukocyte-endothelial interactions mediating leukocyte recruitment into tissues. At sites of infection, macrophages that have encountered microbes produce cytokines (such as TNF and IL-1) that activate the endothelial cells of nearby venules to produce selectins, ligands for integrins, and chemokines. Selectins mediate weak tethering of blood leukocytes on the endothelium, and the shear force of blood flow causes the leukocytes to roll along the endothelial surface. Chemokines produced in the surrounding infected tissues or by the endothelial cells are displayed on

6. Transforming Growth Factor

- Growth-factor are cytokines which stimulate the growth of their target cells.

➢ Transforming growth factor-β (TGF- β)

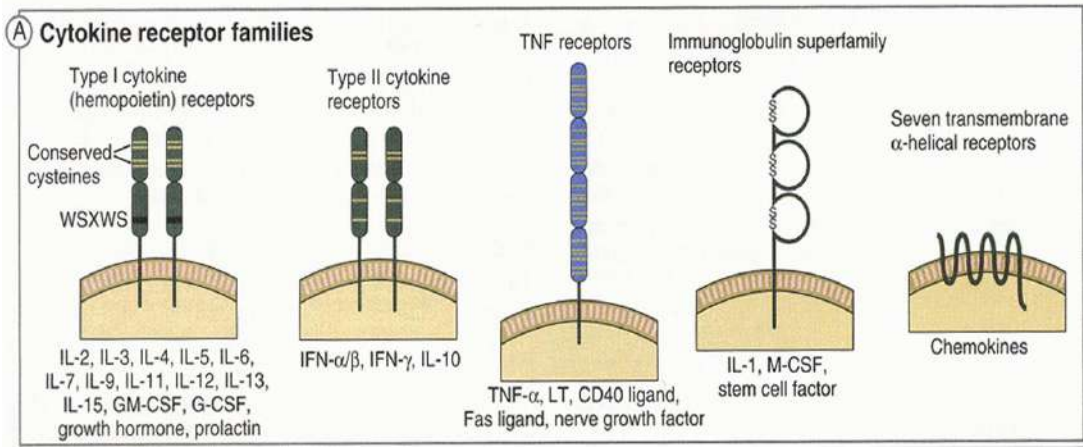
➢ Epithelia growth factor (EGF)

➢ Vascular endothelia cell growth factor (VEGF)

➢ Fibroblastic growth factor (FGF)

CK receptor

- Membrane-binding cytokine receptors:
- The receptor consists of extra-cellular region, trans-membrane region and cytoplasmic region.
- CK receptors can be grouped into five families according to structure and function:
  - Ig receptor superfamily
  - Type I CK receptor superfamily
  - Type II CK receptor superfamily
  - Type III CK receptor superfamily
  - G-protein linked receptor superfamily



Functional Categories

- Mediate/regulate innate immunity
  - TNF, IL-1, IL-12, IFN type1, IL-10
- Mediate/regulate adaptive immunity
  - IL-2, IL-4, IFN-γ, TGF-β
- Stimulates hematopoiesis
  - IL-3, IL-7

Pro-Inflammatory

Innate and Acute Phase Responses

Cytokine	Source	Major Target	Function
IFN-α/β	Virally infected nucleated cells	Cells surrounding virally infected cells	Induce antiviral state, activate NK cells, enhance Cell Mediated Immunity
IL-1β	Macrophages, DCs, Fibroblasts, Epi/Endothelium	T cells/B cells/ PMNs/ CNS/ Liver	Promote inflammatory/ acute phase response/ promote fever
TNFα		Macrophages/ T cells/ NK cells	Acute phase response/ inflammation/ fever/ Wasting (Cachexia)
IL-6	DCs, Macrophages/ T and B cells/ Fibroblasts/ Epi/Endothelium	T and B cells/ hepatocytes	Acute phase reactants/ fever/ T and B cell growth

Inflammatory Innate to Adaptive Responses

Cytokine	Source	Major Target	Function
IFN-γ	CD4 Th1 cells, NK cells	Macrophages, DCs, T cells, B Cells	Activate Macrophage/ promote IgG class switch/ Promote Th1/Inhibit Th2
IL-17	CD4 Th17 Cells	Epi/Endothelium/ Neutrophils/ Fibroblasts	Recruit Neutrophils/ Promote inflammation
TNFβ aka Lymphotoxin	CD4 Th1 cells	PMNs, Tumor Cells	Kill tumors/ activate PMNs/ Activate Endothelium allowing trafficking
IL-2	CD4 T cells (Th1, Th0)	Lymphoctes	Lymphocyte proliferation
IL-12/IL-23	DCs, Macrophages	Nk Cells, CD4 Th1/TH17	Activate T cell IFNγ or IL-17 Production

Allergy and Helminth Infections

Th2 (Less inflammatory than Th1/Th17)

Cytokine	Source	Major Target	Function
IL-4	CD4 T cells (Th0, Th2, Tfh, ILCs)	B and T cells	T and B cell growth and differentiation/ IgG, IgA, IgE production/ Th2 response/ Allergic responses
IL-5	CD4 Th2	B Cells and Eosinophils (for Helminth infections)	
IL-10	CD4 Th2 and Treg	B cells, CD4 Th1/Th17 cells	B cell growth / inhibit Th1 and Th17 responses

Immunosuppressive/Anti-inflammatory

T regulatory (Tregs)

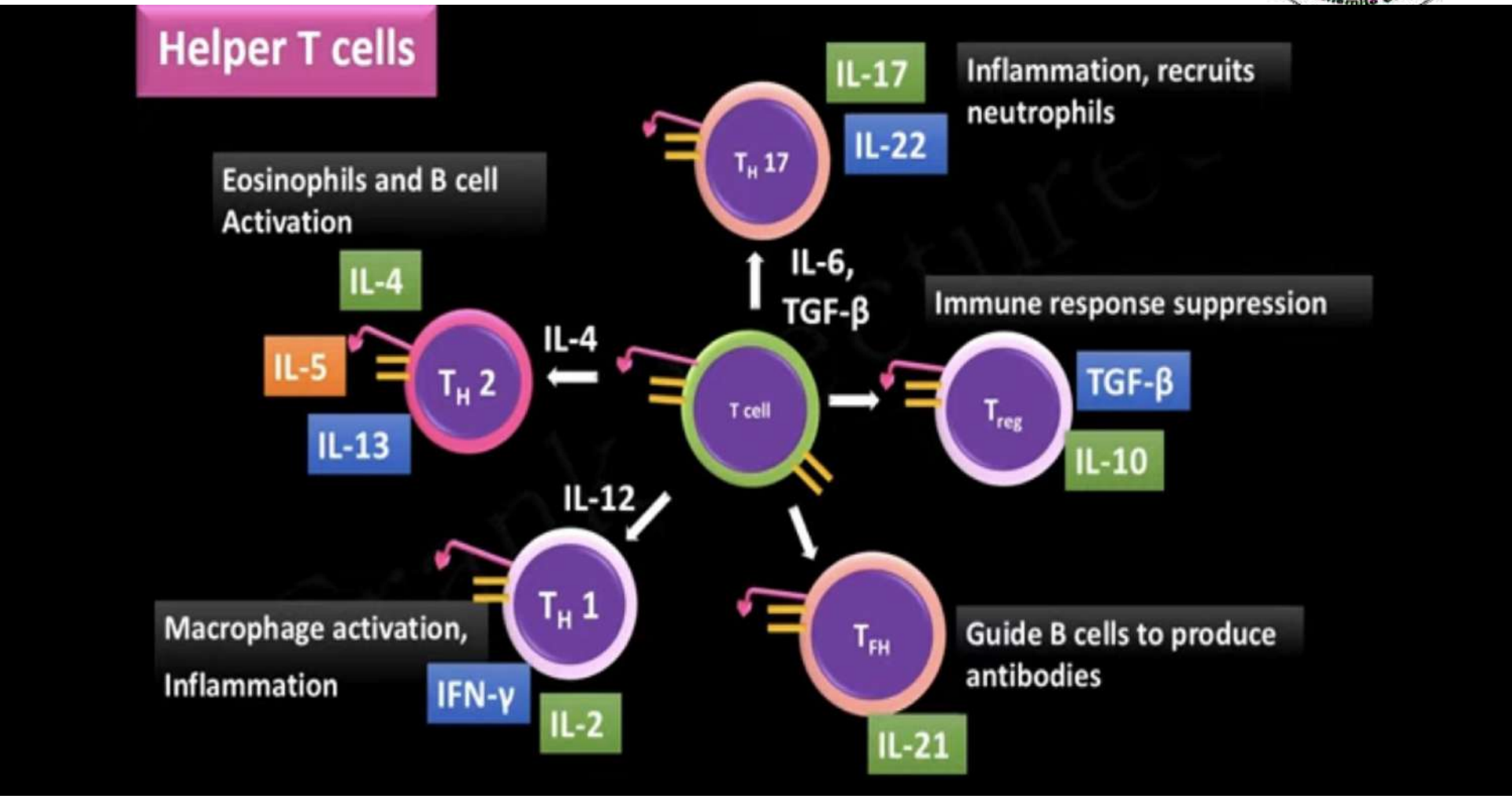
Cytokine	Source	Major Target	Function
IL-10	Treg cells/ Th2	B cells, CD4 Th1/Th17 cells	B cell growth / inhibit Th1 and Th17 responses
TGF-β	CD4 Tregs	B cells, T cells, Macrophages, DCs	Immunosuppression of all immune responses/ promote oral tolerance/ wound healing

Growth and Differentiation

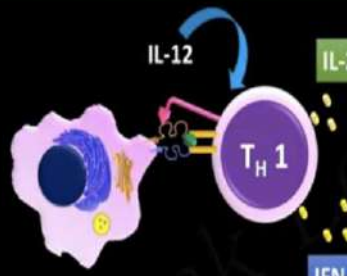
Cytokine	Source	Major Target	Function
GM-CSF & M-CSF	Stromal cells/ T cells	Bone Marrow progenitor cells/ Stem cells/ Pre-cursor cells	Hematopoiesis/ directed growth and differentiation of Monocytes and Granulocytes
IL-3	CD4 T cells/ keritonocytes		
IL-7	Bone marrow, stroma		Growth of Pre-B cells, T cells, and NK cells
*IL-2	CD4 T cells	Lymphocytes	Proliferation

Chemotactic Agents

Chemotactic Agent	Source	Major Target	Function
IL-8/CXCL8	Fibroblasts/ Neutrophils/ Macrophages	Phagocytes	Recruit these cells to the site of inflammation
C5a	Complement Cascade		
IL-17	CD4+ Th17		
Over 30 others!	Many cells	Neutrophils, B cells, T cells, Macrophages, DCs, NK cells, Mast Cells etc.	

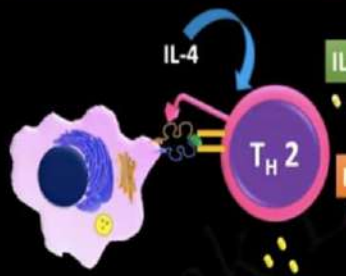

Helper T cells
IL-17
IL-22
Inflammation, recruits neutrophils
T_H 17
IL-6, TGF-β
Eosinophils and B cell Activation
IL-4
IL-5
IL-13
T_H 2
IL-4
T cell
Immune response suppression
T_{reg}
TGF-β
IL-10
IL-12
T_H 1
IFN-γ
IL-2
Macrophage activation, Inflammation
T_{FH}
Guide B cells to produce antibodies
IL-21

When there is an intracellular infection



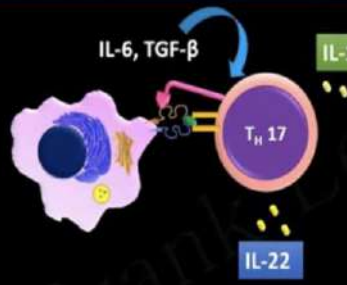
- IL-2 • Promotes growth and differentiation of other T cells
- IFN-γ • Activates the macrophages
- Also stimulates production of antibodies

When there is a infection by parasites



- IL-4 • Stimulates B cells to produce IgE antibodies
- IL-5 • Activates mast cells and eosinophils
- IL-13 • Induces production of mucus in the intestines

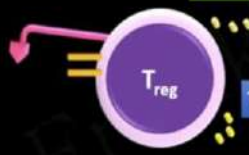
When there is a infection by fungi or extracellular bacteria



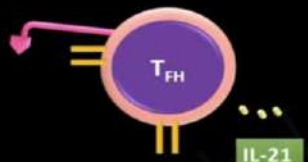
- IL-17 • Recruit neutrophils to the site of infection
- IL-22 • Stimulate epithelial cells to produce antimicrobial peptides

Once a pathogen is eradicated

- Suppress T cell responses and limit immune response
- Prevent Autoimmunity



- IL-10 • Potent suppressor of macrophage funtions
- TGF-β • Induces generation of more T_{reg} cells



- IL-21 • Guide B cells to make appropriate antibodies to clear particular infection

Specific Interleukins Functions

- **IL1:** Play role in inflammation
- **IL2:** Growth factor for B and T cells (clonal expansion)
- **IL3:** Haematopoetic growth factor which stimulates colony formation of blood cells
- **IL4:** Stimulates development of Th2 cells from naïve Th cell. Stimulates Ig class switch from IgG1 to IgE (allergy)
- **IL5:** Produced by Th2 cells and aids in the growth and differentiation of eosinophils
- **IL6:** acute phase response
- **IL10:** Suppresses inflammatory responses and Inhibits production of IFN-γ, IL-2, IL-3, TNFα, GM-CSF
- **IL-12:** is involved in the differentiation of naive T cells into Th1 cells

Cytokines and Clinical Applications

- Cytokines and cytokines inhibitors can be used in many clinical applications and treatments.
  - Advantages: Known ligands, receptors and mechanisms of action
  - Problems with cytokine therapies: Effective dose levels, short half-life, can cause unpredictable side effects
- **Colony stimulating factors (CSFs):** hematological disorders associated with cancer therapy
- **Erythropoietin (EPO):** anemia associated with kidney disease
- **Interferon α:** antiviral therapy (chronic Hepatatis B and C)
- **IFN-β:** multiple sclerosis
- **IFN-γ:** chronic granulomatous disease (CGD)
- **IL-2:** kidney cancer, melanoma
- **IL-11:** thrombocytopenia in cancer patients