CYTOKINES

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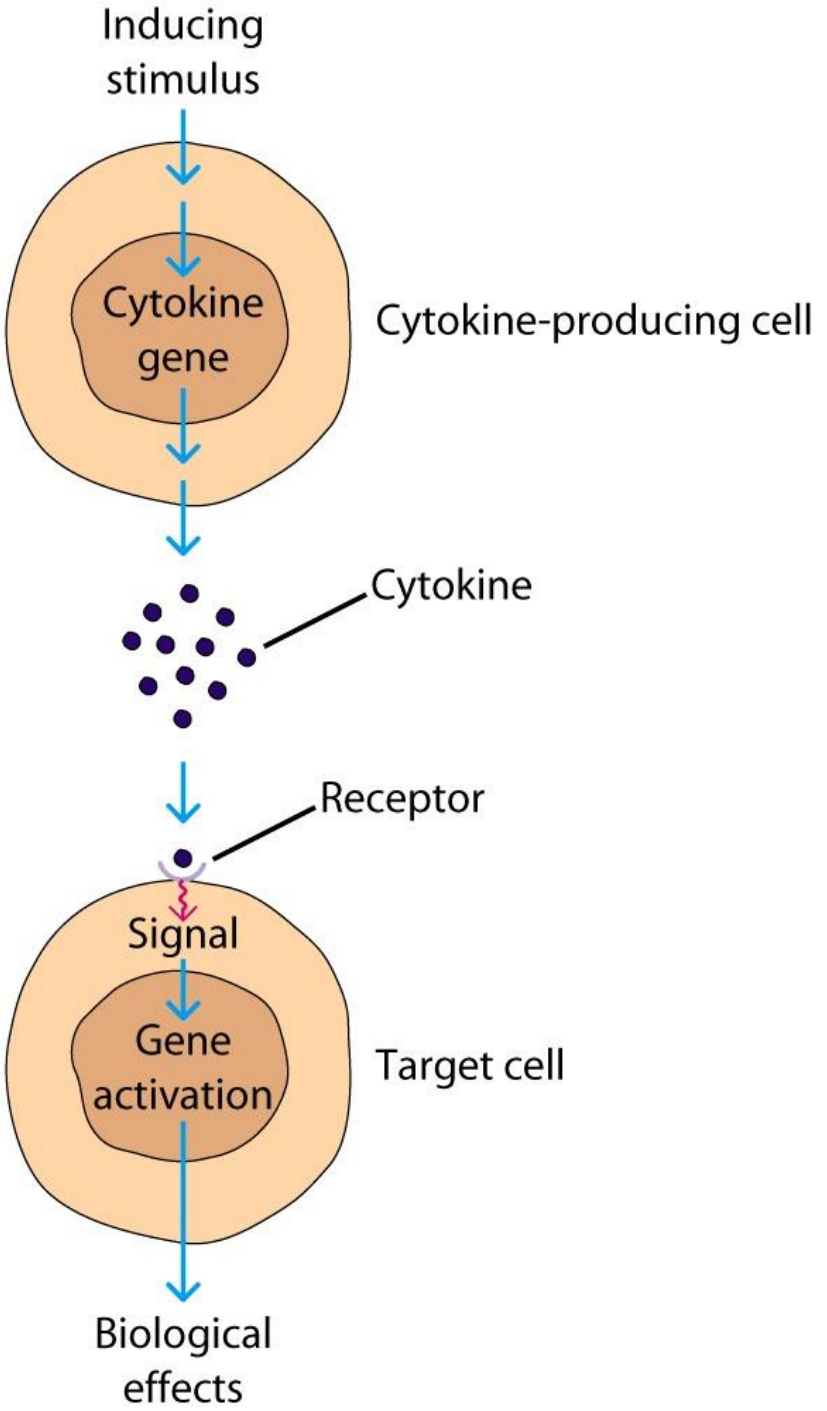
CYTOKINES

Facts

- They are low molecular weight proteins
- They are involved in immunity and inflammation where they regulate the amplitude and duration of inflammation
- They are extremely potent
- They are produced transiently

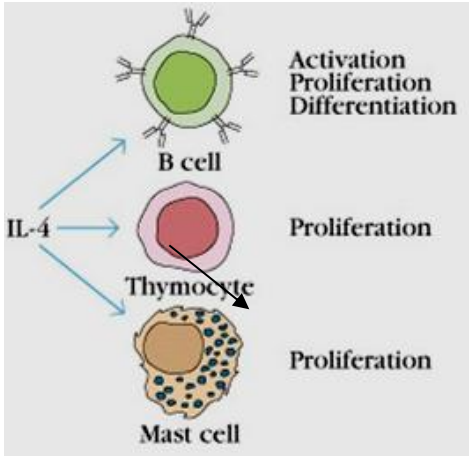
CYTOKINES

- They act with cell surface receptors specific for each cytokine group
- Their cell surface binding leads to protein synthesis and altered cell behavior

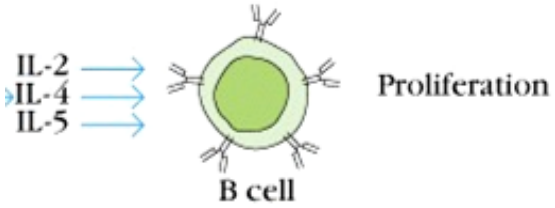


Cytokines : Mode of Action

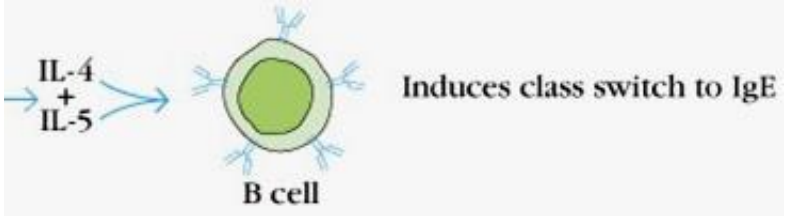
Pleiotropic



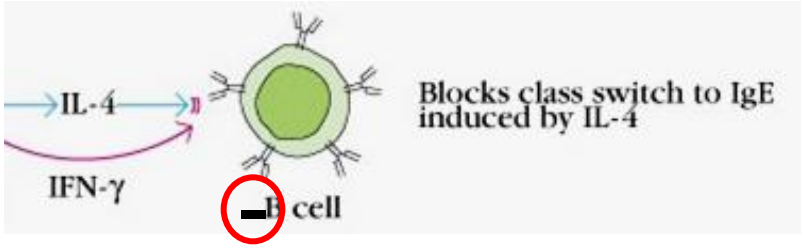
Redundant



Synergistic

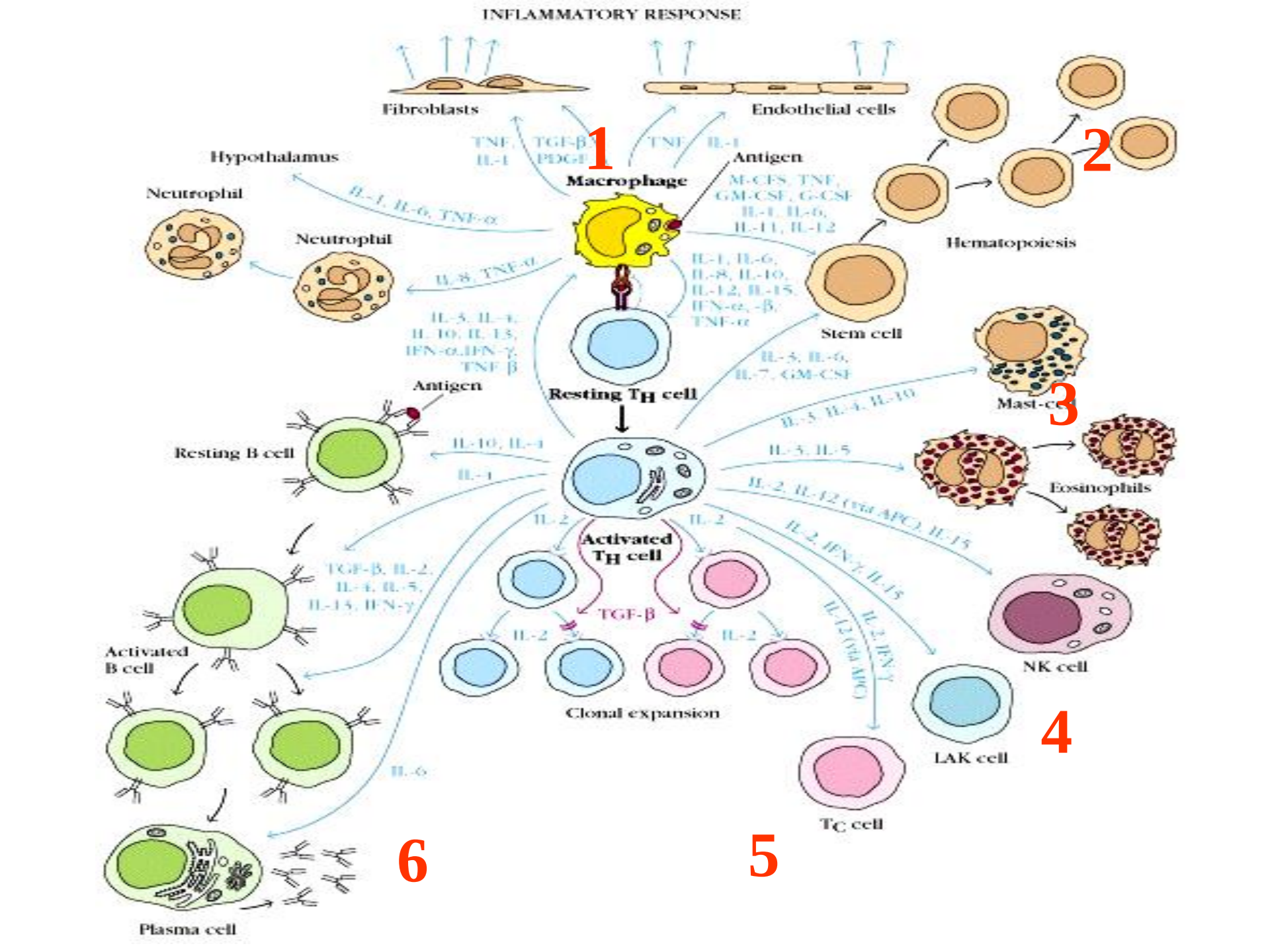


Antagonistic



CYTOKINES

- The messenger molecules of the immune system
- These are short acting soluble mediators
- Previously designated as lymphokines (lymphocyte derived), monokines (monocyte derived), chemokines, interleukins, interferon
- They have wide spectrum of effects and are produced by several different cell types


INFLAMMATORY RESPONSE
Fibroblasts
Endothelial cells
TNF, IL-1
TGF-β, PDGF
TNF, IL-1
1
2
Hypothalamus
Antigen
Macrophage
M-CFS, TNF, GM-CSF, G-CSF, IL-1, IL-6, IL-11, IL-12
Neutrophil
IL-1, IL-6, TNF-α
Neutrophil
IL-8, TNF-α
IL-1, IL-6, IL-8, IL-10, IL-12, IL-15, IFN-α, -β, TNF-α
Hematopoiesis
Stem cell
IL-3, IL-4, IL-10, IL-13, IFN-α, IFN-γ, TNF β
Resting TH cell
IL-5, IL-6, IL-7, GM-CSF
Antigen
Mast-cell
3
IL-5, IL-4, IL-10
Resting B cell
IL-10, IL-4
IL-4
IL-5, IL-5
Eosinophils
IL-2, IL-12 (via APC), IL-15
IL-2
Activated TH cell
IL-2
IL-2, IFN-γ, IL-15
TGF-β, IL-2, IL-4, IL-5, IL-13, IFN-γ
TGF-β
Activated B cell
IL-2
IL-2
IL-12 (via APC)
IL-2, IFN-γ
NK cell
Clonal expansion
LAK cell
4
TC cell
IL-6
6
5
Plasma cell

WORKING CLASSIFICATION OF CYTOKINES

Cytokines that mediate natural immunity

- Interleukin-1 (IL-1), tumor necrosis factor alpha (TNFα), interferons and IL-6

Cytokines that regulate lymphocyte growth, activation and differentiation

- IL-2, IL-4, IL-5, IL-12, IL-15 and transforming growth factor-β (TGF- β)

CYTOKINES

- Cytokines that activate inflammatory cells
  - IFN-γ, TNFα, lymphotoxin (TNF-β) and migratory inhibitory factor

- Cytokines that affect leukocyte movements also called "chemokines"
  - C-C and C-X-C chemokines on the bases of cysteine residues
  - C-X-C are produced by macrophage – IL-8
  - C-C are produced by T cells – MIP, MCP

CYTOKINES

Cytokines that stimulate hematopoiesis

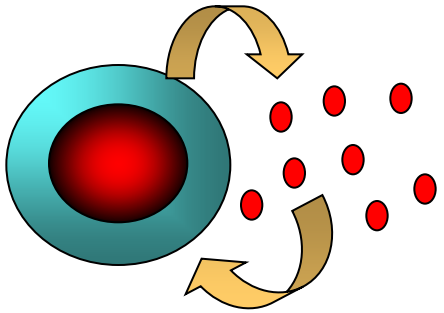
- Derived from lymphocytes or stromal cells stimulate the production of blood cells by acting on hematopoietic progenitor cells.
- The members of this family are called "colony-stimulating factors" (CSFs) eg, granulocyte-monocyte colony stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF)

GENERAL PROPERTIES OF CYTOKINES

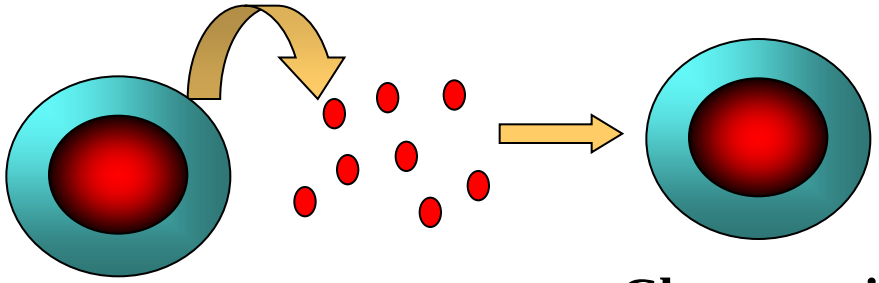
Cytokines induce their effects in three ways:

- ***Autocrine effect***: i.e. they act on the same cell that produces the cytokine e.g. IL-2
- ***Paracrine effect***: that effect other cells in the vicinity eg, IL-7 in the bone marrow act on B cells progenitors
- ***Endocrine effect***: they affect many cells systemically eg, IL-1 and TNF-α which produce acute-phase response during inflammation

General Properties of Cytokines
Mode of Action I

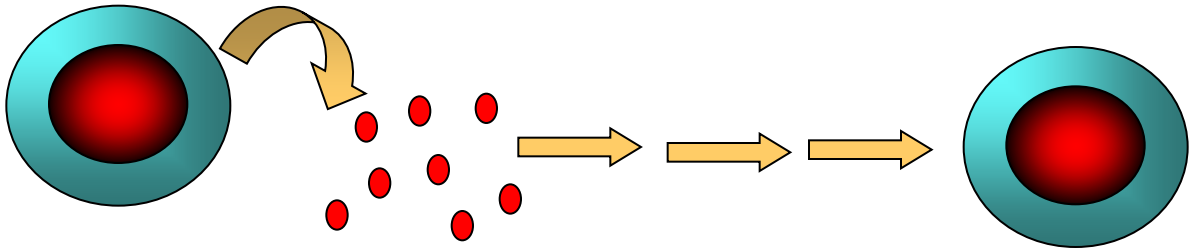


Autocrine



Paracrine

Close proximity



Endocrine

Distant cells

GENERAL PROPERTIES OF CYTOKINES

Cytokines mediate their effect by binding to specific receptors on the cell surface

- For example, IL-2 activates T cells by binding to its specific high-affinity receptor on the target cells

Mediators Affecting Lymphocytes

IL-1

- Protein produced by macrophages
- Activates T & B cells, neutrophils, epithelial cells and fibroblasts
- Activates T cells to produce IL-2
- It is an endogenous pyrogen

INTERLEUKIN-2 (IL-2)

It is a protein produced by helper T cells

Stimulates both helper and cytotoxic T cells

IL-2 acts through the induction of a specific receptor (IL-2 receptor) on the cell surface

IL-2 reacts in combination with IL-4 to stimulate growth of B cells

INTERLEUKINS- 4 & 5

Are proteins produced by helper T cells

They promote growth and differentiation of B cells respectively

IL-4 enhances humoral immunity by increasing number of Th-2 cells

IL-4 is required for class switching of Igs and enhances IgE production

IL-5 increases IgA production and helps in activation of eosinophils – defense against helminths

OTHER CYTOKINES
IL-6, IL-10, IL-12 & IL-13

IL-6 produced by helper T cells and macrophages

Stimulates B cells to differentiate

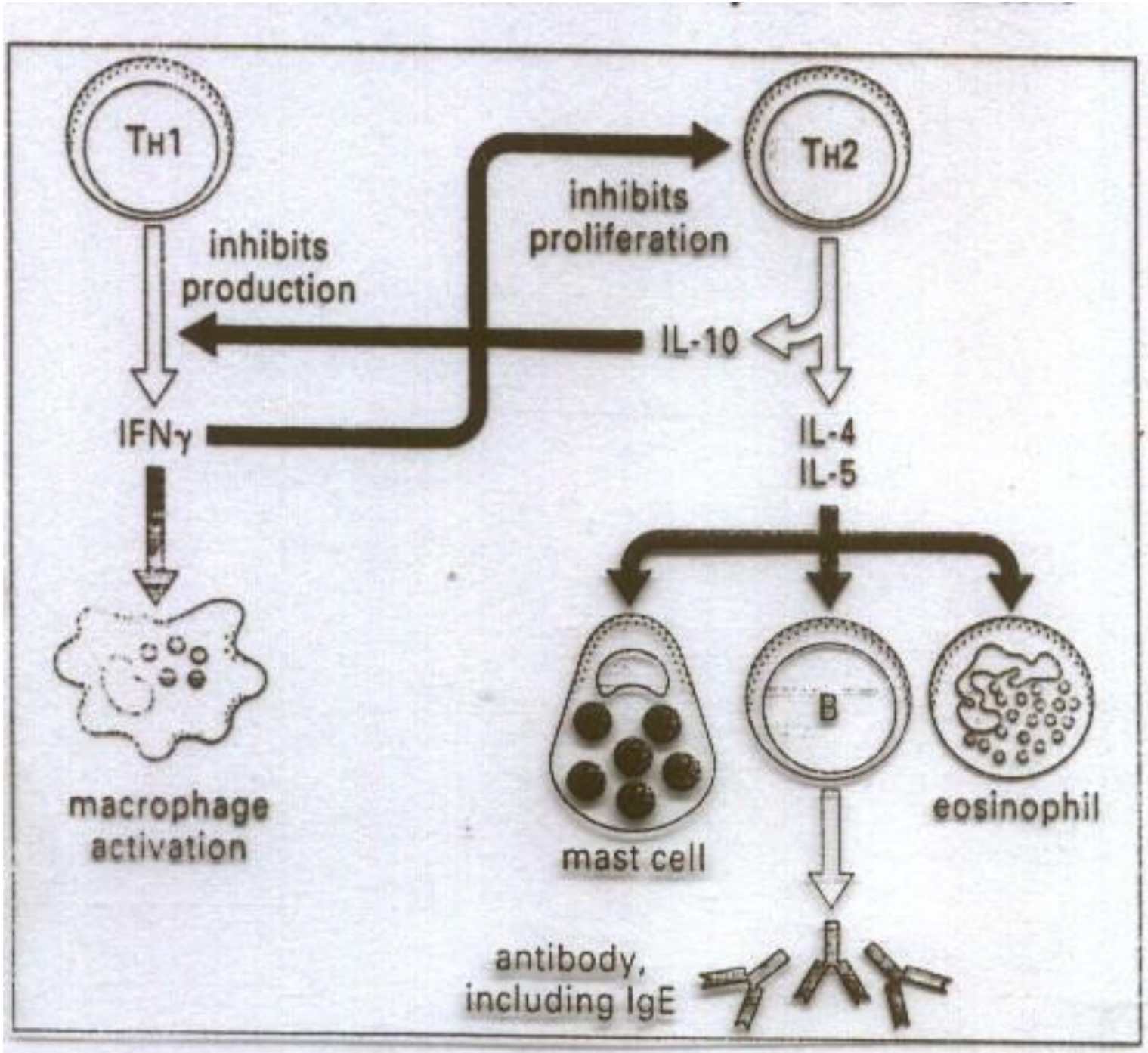
Induces fever by acting on hypothalamus

Induces the production of acute phase proteins by liver

IL-10 & IL-12

- These cytokines regulate the production of Th-1 cells
- IL-12 is produced by macrophages and promotes the development of Th-1 cells
- IL-10 is produced by Th2 cells and inhibits the development of Th-1 by limiting the production of IFγ

The relative amounts of IL-4, IL-10 & IL-12 drive the differentiation of Th-1 & Th-2 cells and enhance either cell mediated or humoral immunity respectively


TH1
TH2
inhibits production
inhibits proliferation
IL-10
IFNγ
IL-4
IL-5
B
macrophage activation
mast cell
eosinophil
antibody, including IgE

IL-13

It is produced by Th-2 cells

It is one of the main mediators of allergic airway disease (asthma)

IL-13 is associated with airway hyper-responsiveness in asthma

It has no effect on IgE production

TRANSFORMING GROWTH FACTOR-β (TGF- β)

- TGF- β inhibits the growth and activities of T cells
- It is also called anti-cytokine as it also inhibits many functions of macrophages, B cells, neutrophils and natural killer cells
- These effects are brought about by counteracting the actions of other activating factors
- It enhances synthesis of collagen (wound healing)
- Produced by many cell types including macrophages, T and B cells

MEDIATORS EFFECTING MACROPHAGES AND MONOCYTES

- ***Chemokines*** attract neutrophils and macrophages to the site of inflammation
- They are produced by endothelial cells and macrophages
- They activate "***integrins***" on the surface of macorphages and neutrophils that bind to intercellular adhesion molecule-1 (ICAM-1) on the surface of endothelium
- This interaction leads to migration of cells into the infected or inflamed area

CHEMOKINES

- Approximately 50 chemokines have been identified
- They are polypeptides of size from 68 to 120 amino acids
- Alpha chemokines have two cysteines separated by an amino acid (C-X-C group)
  - Attract neutrophils
- Beta chemokines have two adjacent cysteines
- (C-C group)
  - Attract macrophages

MEDIATORS AFFECTING POLYMORPHONUCLEAR LEUKOCYTES

1. ***Tumor Necrosis Factor (TNF)***
   - Activates phagocytic and killing activities of neutrophils
   - Increases synthesis of adhesion molecules by endothelial cells
   - Thus mediating extra-vascular migration of neutrophils

MEDIATORS AFFECTING POLYMORPHONUCLEAR LEUKOCYTES

2. Interleukin-8 and complement component C5a are important attractants for neutrophils

3. Leukocyte-inhibitory factor inhibits migration of neutrophils from the site of inflammation

MEDIATORS AFFECTING STEM CELLS

IL-3 produced by activated helper T cells supports the growth and differentiation of stem cells in the bone marrow

Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

- **Used in bone marrow transplantation**

Granulocyte Colony Stimulating Factor (G-CSF)

- **Used in cancer chemotherapy**

MEDIATORS PRODUCED BY MACROPHAGES THAT AFFECT OTHER CELLS

1. **TNF-α**
   - Extra-vascular migration of inflammatory cells through induction of adhesion molecules
   - Activates respiratory burst within neutrophils
   - Enhances lymphokine production by Th cells
   - Stimulates growth of B cells
   - High concentrations mediate endotoxin-induced septic shock

MEDIATORS PRODUCED BY MACROPHAGES THAT AFFECT OTHER CELLS

- Anti TNF-α antibodies prevents the action of endotoxin
- TNF-α is also known as "***cachectin***" because it causes "***cachexia***"
- It causes death and necrosis of certain tumors in experimental animals

MEDIATORS PRODUCED BY MACROPHAGES THAT AFFECT OTHER CELLS

2.**Nitric Oxide (NO)**

- Produced mainly by macorphages in response lipopolysaccharide (LPS) found in cell wall of gram-negative bacteria
- NO cause vasodilatation which contributes to hypotension associated with septic shock
- Inhibitors of NO synthtase inhibits NO production thus preventing hypotension

MEDIATORS PRODUCED BY MACROPHAGES THAT AFFECT OTHER CELLS

3. **Macrophage migration inhibition factor (MIF)**
   - Produced by macorphages in response to endotoxin
   - Plays a major role in the induction of septic shock
   - Anti-MIF antibodies can prevent septic shock

MEDIATORS WITH OTHER EFFECTS

- **Interferons**
  - These are glycoproteins that block viral replication
  - Alpha interferon from leukocytes and beta interferon from fibroblasts have anti-viral activity
  - Gamma interferon produced by Th-1 lymphocytes activates macrophages (phagocytosis), NK cells (tumor cells) and neutrophils
  - Enhances the expression of Class I & II MHC

CYTOKINES AND DISEASE

Bacterial Septic Shock

- Cell wall endotoxin stimulate macrophages to overproduce IL-1 and TNF alpha
- Treatment is with antibodies against TNF alpha and use of recombinant IL-1 receptor antagonists

CYTOKINES AND DISEASE

Lymphoid and Myeloid Cancers

- High levels of IL-6 are produced by
- Cardiac myxoma cells, myeloma, plasmacytoma cells, cervical and bladder cancer cells

IL-6 works in an autocrine manner to stimulate cell proliferation

CYTOKINES AND DISEASE

- T cell leukemia is associated with HTLV-1 retrovirus
  - HTLV-1 protein called “Tax” induces factors that bind to the promotor regions of genes encoding IL2 and IL2 receptors and activating them

CYTOKINE RELATED THERAPIES

Soluble form of IL-1 receptor inhibits Th cell activation – prolongs graft survival in heart transplantation

IL-2 conjugated with toxin diminishes rejection of kidney and heart transplants

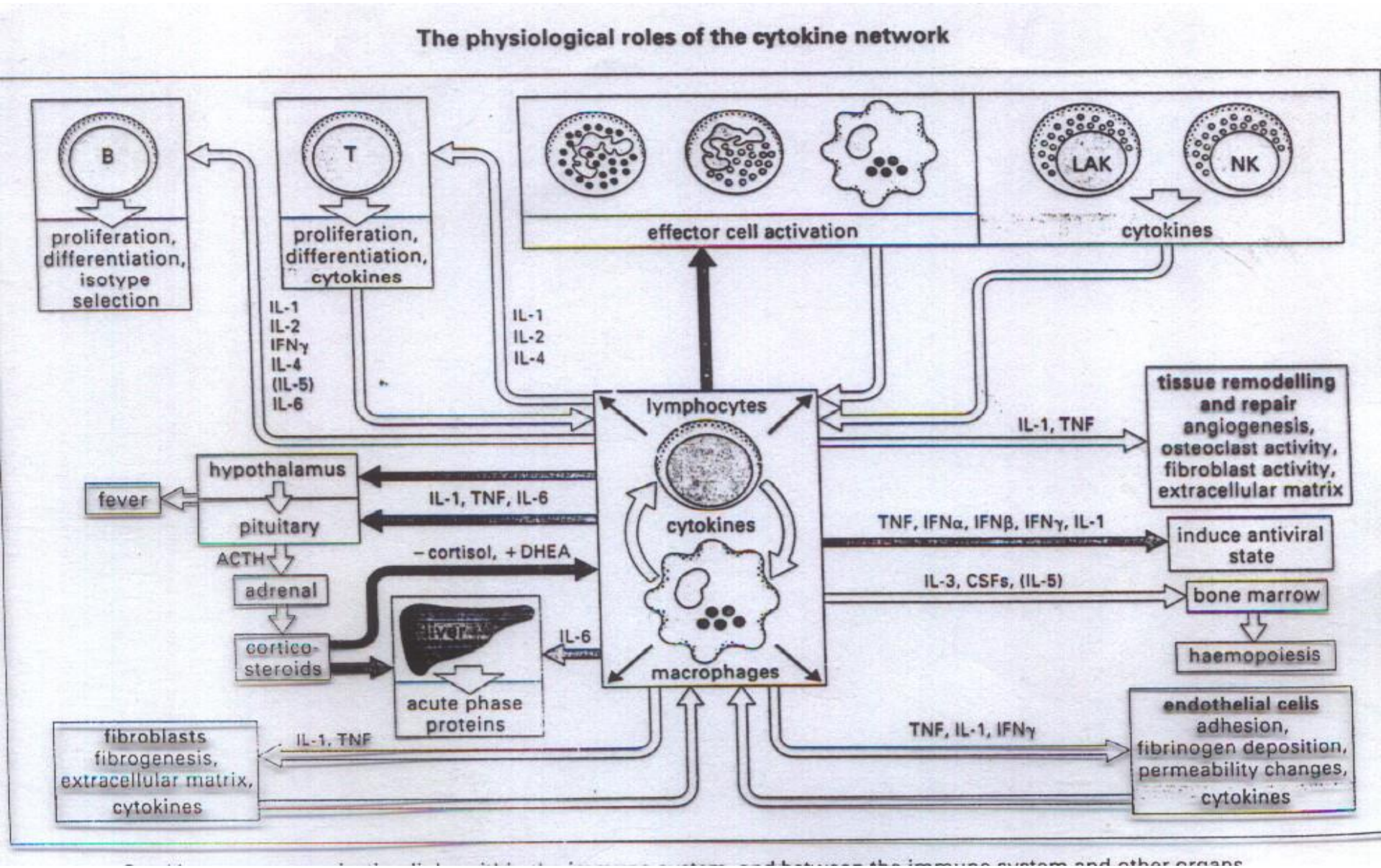
Lymphokine activated killer cells in tumor therapy

Antibody to IL-4 reduces IgE production

Examples of some cytokines functions

Cytokine	Functions
IL-5 & TGF-β	Induces class switch to IgA
IL-4	Up-regulates MHC II expression, class switch to IgE
IL-10	Down-regulates MHC II expression
IL-2 & IL-12	Synergistically induce differentiation into CTL
Interferon α/β	Inhibition of viral replication
Interferon γ	Class switching to certain IgGs

CYTOKINE NETWORK



CXCL1 has a role in angiogenesis and arteriogenesis and thus has been shown to act in the process of tumor progression. The role of CXCL1 was described by several studies in the development of various tumors, such as breast cancer, gastric and colorectal carcinoma or lung cancer.CXCL1 is secreted by human melanoma cells, has mitogenic properties and is implicated in melanoma pathogenesis.

Cytokines and their functions.

Cytokine	Major Cellular Source	Principal Effect
IFN-α	Macrophages, dendritic cells	Inhibit viral replication
IFN-β	Virally infected cells	
IFN-γ	T cells, NK cells	Upregulation of adhesion and MHC molecules, increased macrophage and antigen-presenting cell (APC) activity
IL-1	Macrophage	Endogenous pyrogen, endothelial cell activation, induces acute-phase reactants
IL-2	T cells	T-cell growth factor *and* regulatory factor, B-cell and NK cell activation
IL-3	T cells	Hematopoietic growth factor
IL-4	T cells, mast cells	Induces IgE synthesis, T_H2 responses
IL-5	T cells	Eosinophil activation and growth factor, B-cell activation factor
IL-6	Macrophages, T cells, endothelial cells	Induces Ig synthesis and acute-phase reactants
IL-7	Bone marrow	B-cell and T-cell growth and differentiation factor
IL-8	Macrophage, neutrophils, endothelial, and epithelial cells	Leukocyte chemotactic factor
IL-10	T cells, macrophages	Inhibits antigen presentation, cytokine responses
IL-12	Macrophage	Induces T_H1 responses
IL-13	T cells, mast cells	Induces IgE responses
IL-17	T_H17	Activation of CD4 T cells
GM-CSF	Macrophages, T cells	Hematopoietic growth factor for neutrophils, eosinophils, and macrophages
TGF-β	Platelets	Immune modulator for leukocytes, tissue growth factor for wound healing
TNF	Macrophage, T cell	Endogenous pyrogen; activates neutrophils, endothelial cells, and acute-phase reactants; promotes angiogenesis and coagulation

Source : Pathophysiology of Disease An Introduction to Clinical Medicine 7th Edition

REFERANCES

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2.QRS FOR BDS 3-YEAR-E BOOK

Thank you