Cytokines

Definition

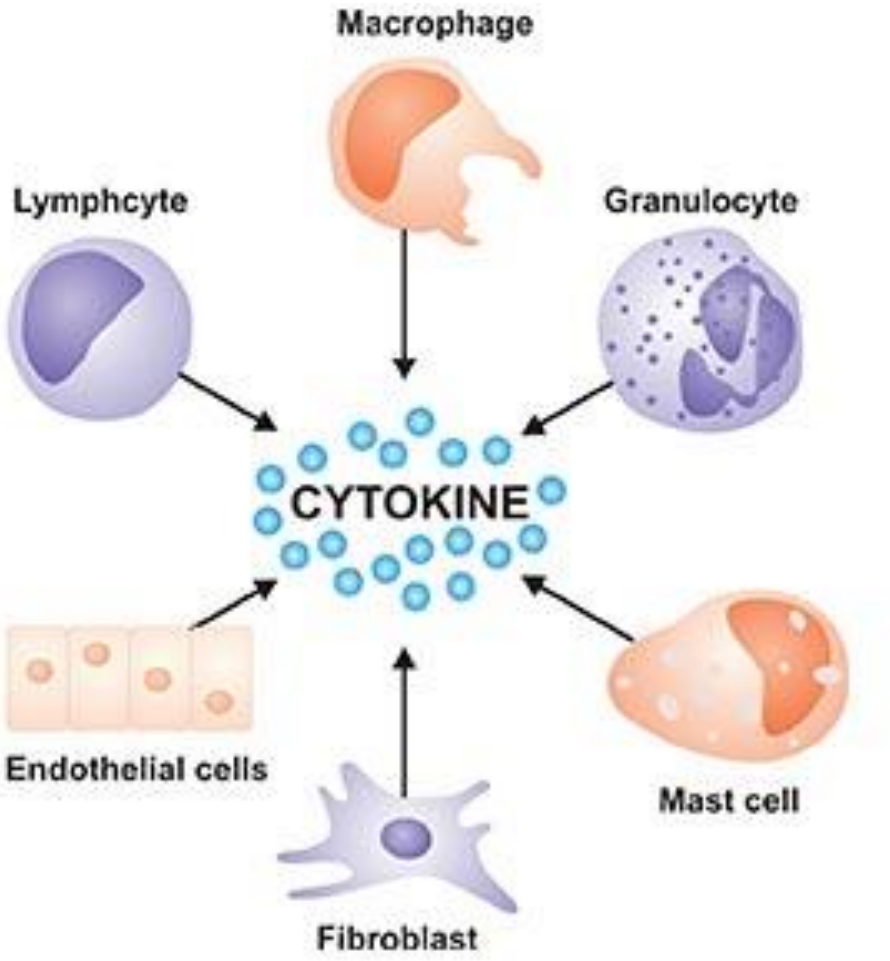
*Cytokines are **small proteins** released by cells that have a **specific** effect on the **interactions between cells**, on **communications between cells** or on **the behaviour of cells**.*

-- There are nearly **200** known cytokines.

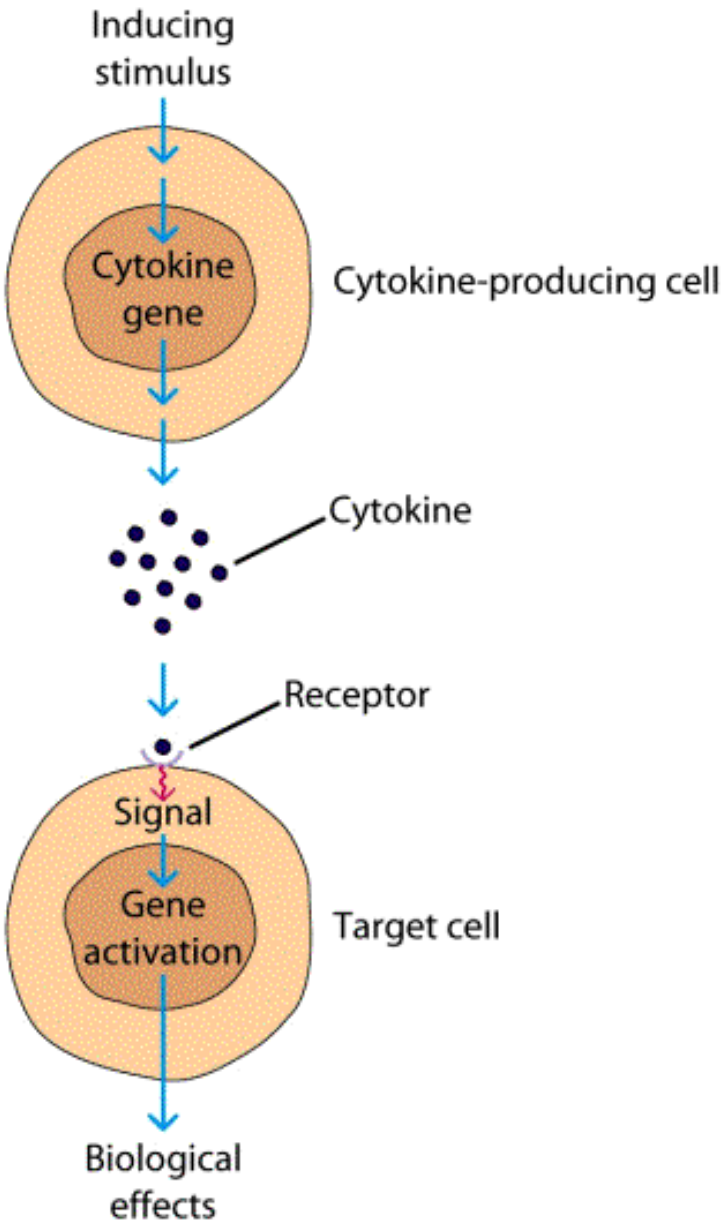
-- Among them **33** are interleukines (cytokines secreted by leukocytes).

Properties of cytokines

- They are **low MW** proteins (6 to 70 kDa).
- They are **secreted** by a variety of cells.
- But they are mainly produced by **T Helper cells** and **macrophages.**


Macrophage
Lymphcyte
Granulocyte
CYTOKINE
Endothelial cells
Mast cell
Fibroblast

- Cytokines require a **stimulus** for production.
- They bind with **high affinity** to specific receptors.
- They induce **gene activation.**

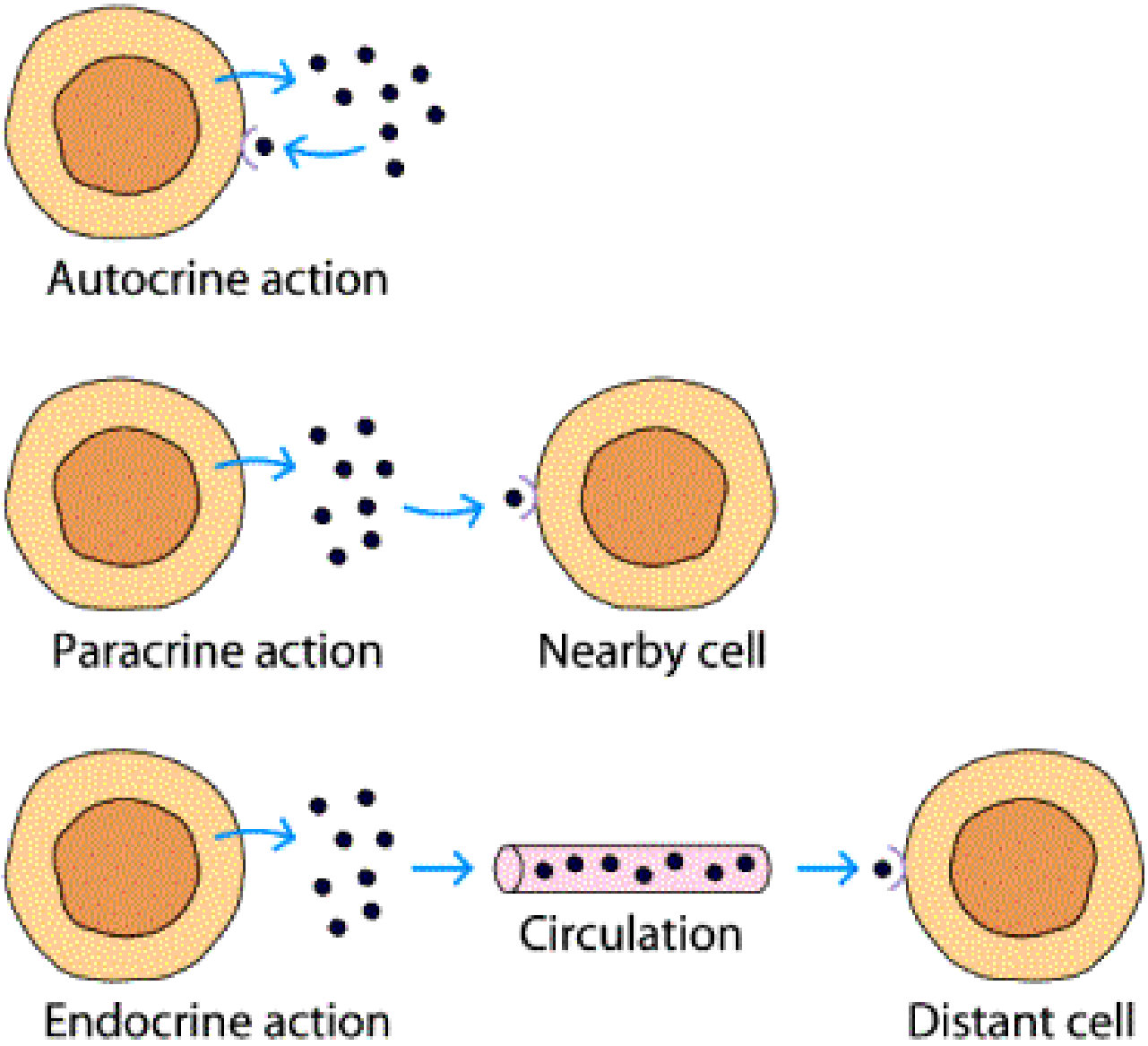

Inducing stimulus
Cytokine gene
Cytokine-producing cell
Cytokine
Receptor
Signal
Gene activation
Target cell
Biological effects

Cytokine-Receptor interactions can be:

-- **Autocrine**

-- **Paracrine**

-- **Endocrine**


Autocrine action
Paracrine action
Nearby cell
Endocrine action
Circulation
Distant cell

Co-ordination between cytokines

Cytokines use various methods to permit cellular activity in a **coordinated fashion.** These are:

-- **pleiotropy**

-- **redundancy**

-- **synergy**

-- **antagonism**

-- **cascade induction**

Pleiotropy:

It is the production of two or more apparently unrelated effects by a single molecule.

Redundancy:

It is the phenomenon in which multiple cytokines exert similar actions.

Synergy:

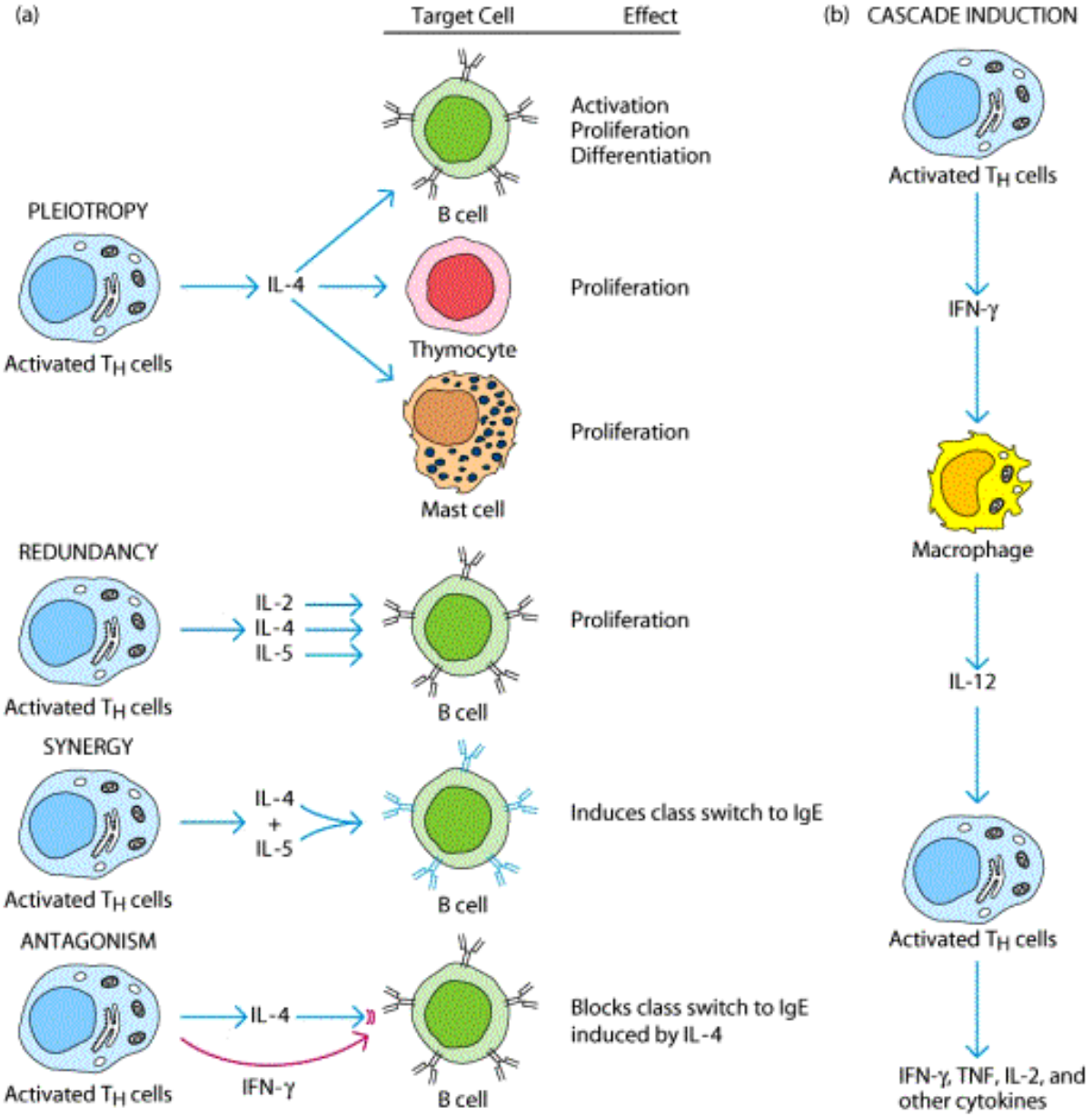
It is the interaction of biological substances that produce an overall effect greater than the sum of individual effects of any of them.

Antagonist:

It is a type of receptor, ligand or drug that blocks or dampens a biological response.

Cascade induction:

It occurs when the action of one cytokine on a target cell induces that cell to produce other cytokines.


(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

Structural families of cytokines

There are four structural families:

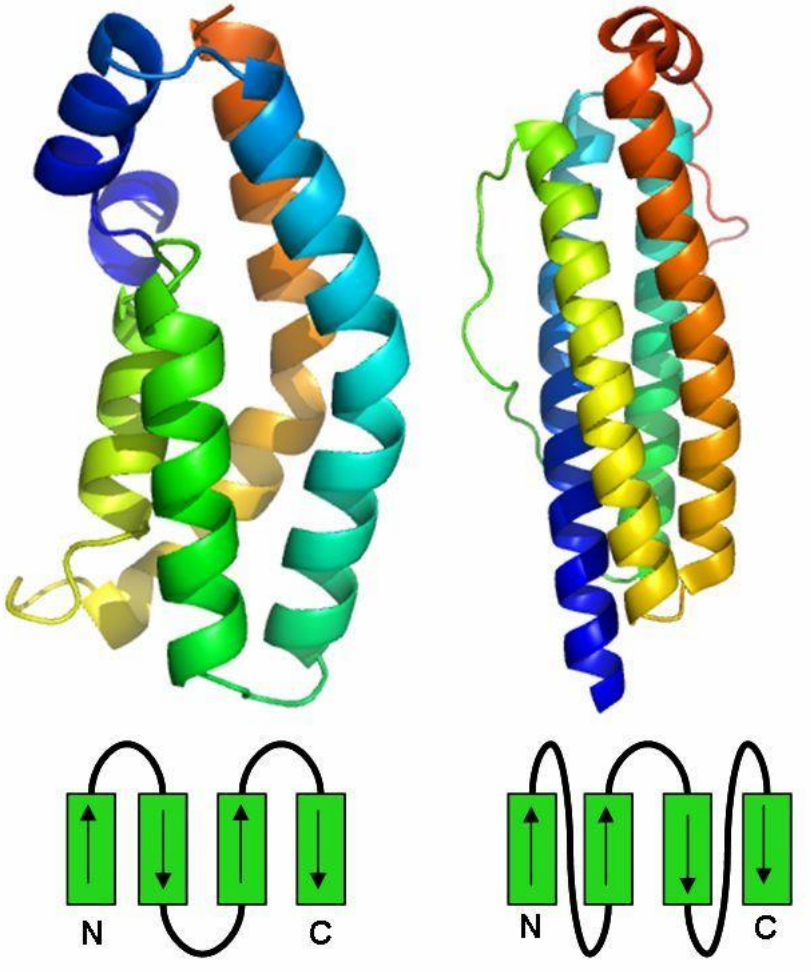
1. **Hematopoietin** family (e.g., IL-2, IL-4)
2. **Interferon** family
3. **Chemokine** family
4. **Tumor Necrosis Factor** family

1. Hematopoietin family

- This is the **largest** and **most divergent** family of cytokines that comprise around **50** distinct lymphokines, growth hormones, hemopoietins, neuropoietins and interleukins.

- In spite of minimal sequence homology, these hematopoietic cytokines have *same* **four-α-helix protein fold**.

- This four-α-helix protein fold can interact with approximately **45 receptors on different cells.**



Four-α-helix protein fold

2. Interferons (IFNs)

- These form a family of mammalian cytokines initially characterized by their **ability to inhibit viral infection.**

- In addition to their antiviral properties, IFNs have also been shown to exhibit **antiproliferative, immunomodulatory**, and many other activities.

3. Chemokines

- These are a family of **small cytokines**, or **signaling proteins** secreted by cells.

- Their name is derived from their ability to **induce directed chemotaxis** in nearby responsive cells; they are **chemotactic cytokines.**

- Cytokine proteins are classified as chemokines according to **behavior and structural characteristics**.

* Chemotaxis is movement of a motile cell or organism, or part of one, in a direction corresponding to a gradient of increasing or decreasing concentration of a particular substance.

4. Tumor necrosis factor (TNF) superfamily

- It is a protein superfamily of **type II transmembrane proteins** containing **TNF** homology domain and forming trimers.

- Members of this superfamily can be released from the cell membrane **by extracellular proteolytic cleavage** and function as a cytokine.

- These proteins **reduce apoptosis**.

* Type II transmembrane proteins are proteins spanning the membrane once, with N-terminus on the cytoplasmic side of the membrane, whereas in Type I, C-terminus is on cytoplasmic side.

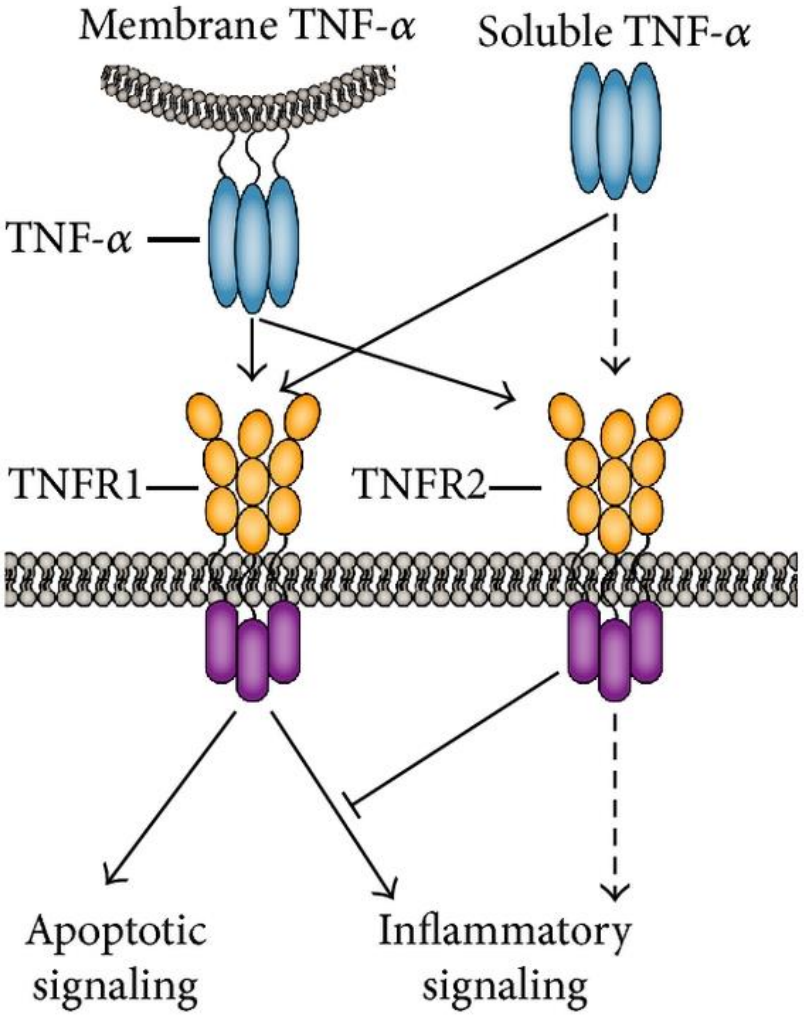

Membrane TNF-α
Soluble TNF-α
TNF-α
TNFR1
TNFR2
Apoptotic signaling
Inflammatory signaling

TABLE 12-1 Functional groups of selected cytokines[1]

Cytokine*	Secreted by**	Targets and effects
SOME CYTOKINES OF INNATE IMMUNITY		
Interleukin 1 (IL-1)	Monocytes, macrophages, endothelial cells, epithelial cells	Vasculature (inflammation); hypothalamus (fever); liver (induction of acute phase proteins)
Tumor necrosis factor-α (TNF-α)	Macrophages	Vasculature (inflammation); liver (induction of acute phase proteins); loss of muscle, body fat (cachexia); induction of death in many cell types; neutrophil activation
Interleukin 12 (IL-12)	Macrophages, dendritic cells	NK cells; influences adaptive immunity (promotes T_H1 subset)
Interleukin 6 (IL-6)	Macrophages, endothelial cells	Liver (induces acute phase proteins); influences adaptive immunity (proliferation and antibody secretion of B cell lineage)
Interferon α (IFN-α) (this is a family of molecules)	Macrophages	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK cells
Interferon β (IFN-β)	Fibroblasts	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK cells
SOME CYTOKINES OF ADAPTIVE IMMUNITY		
Interleukin 2 (IL-2)	T cells	T-cell proliferation; can promote AICD. NK cell activation and proliferation; B-cell proliferation
Interleukin 4 (IL-4)	T_H2 cells; mast cells	Promotes T_H2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T_H2 cells	Eosinophil activation and generation
Interleukin 25 (IL-25)	Unknown	Induces secretion of T_H2 cytokine profile
Transforming growth factor β (TGF-β)	T cells, macrophages, other cell types	Inhibits T-cell proliferation and effector functions; inhibits B-cell proliferation; promotes isotype switch to IgE; inhibits macrophages
Interferon γ (IFN-γ)	T_H1 cells; $CD8^+$ cells; NK cells	Activates macrophages; increases expression MHC class I and class II molecules; increases antigen presentation

[1]Many cytokines play roles in more than one functional category.
*Only the major cell types providing cytokines for the indicated activity are listed; other cell types may also have the capacity to synthesize the given cytokine.
**Also note that activated cells generally secrete greater amounts of cytokine than unactivated cells.

Cytokine receptors

Cytokine receptors are **diverse** and belong to one of **five** families:

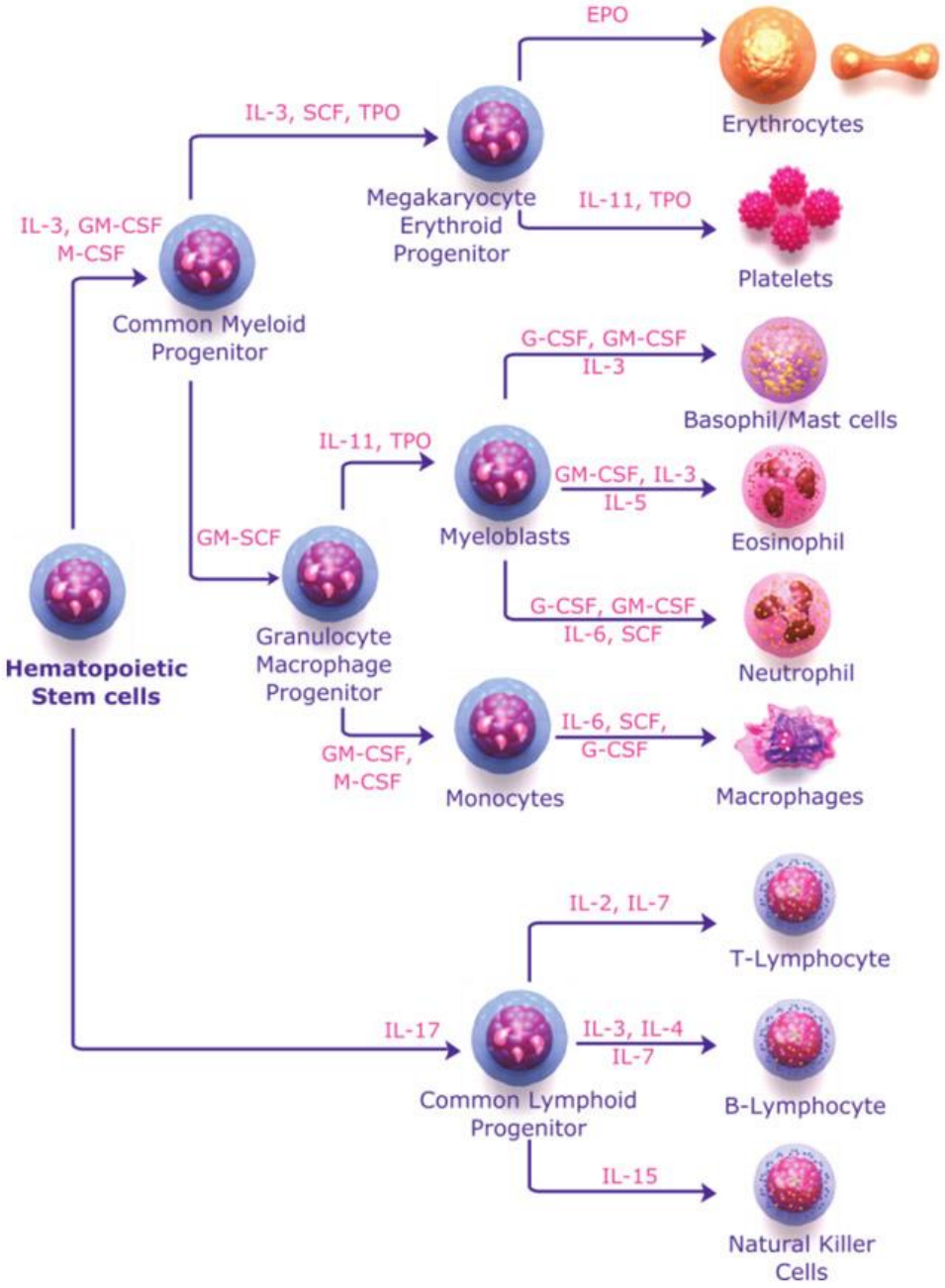
- Immunoglobulin superfamily
  (any molecule with some resemblance with Ig)
- Class I cytokine receptors (hematopoietin)
- Class II cytokine receptors (interferon)
- Tumor Necrosis Receptors
- Chemokine Receptors

Effect of cytokine concentration:

Cytokine concentration in microenvironment of the naive T cell influences **T cell differentiation**

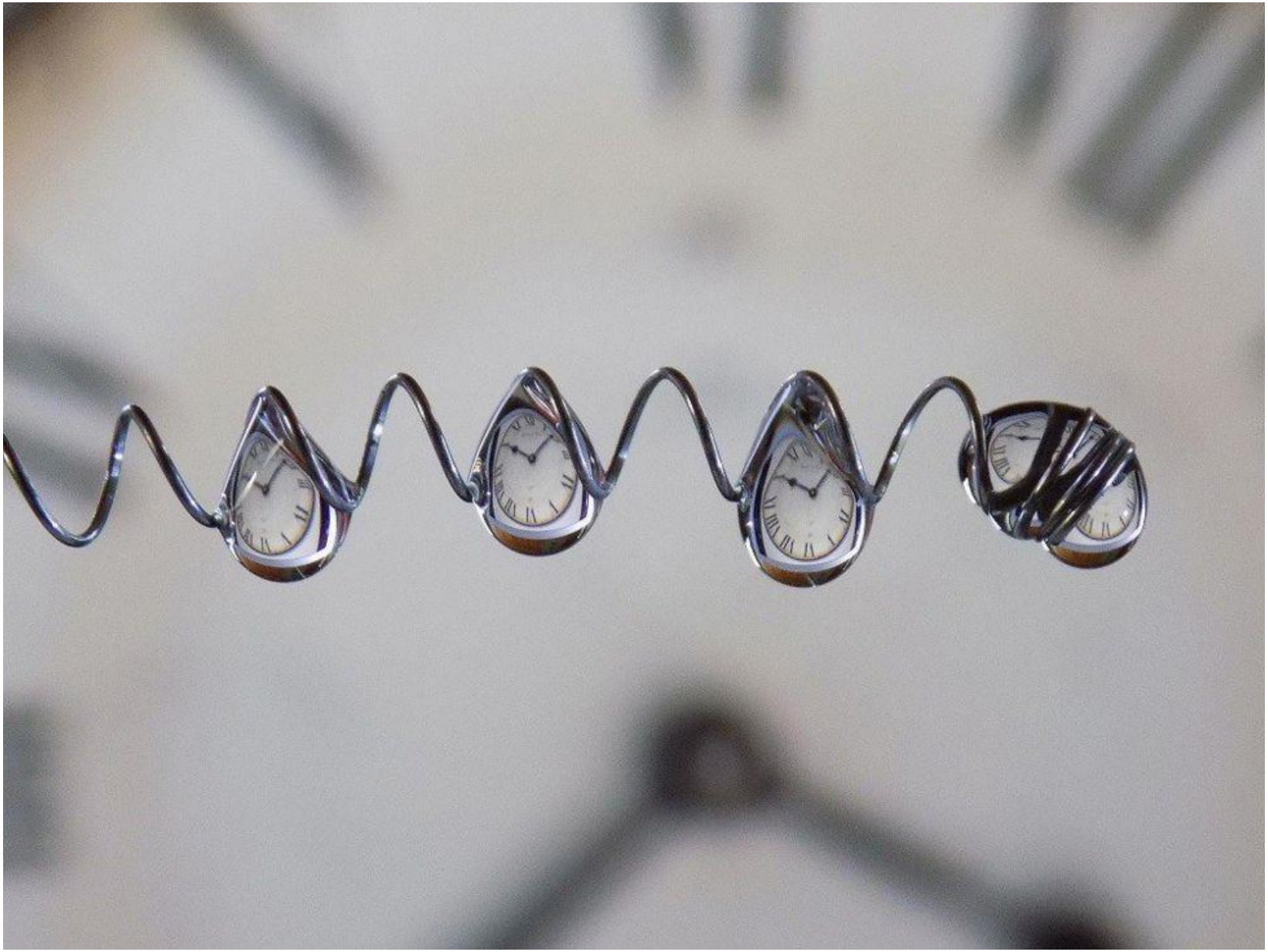
-- Role of the **APC** is important

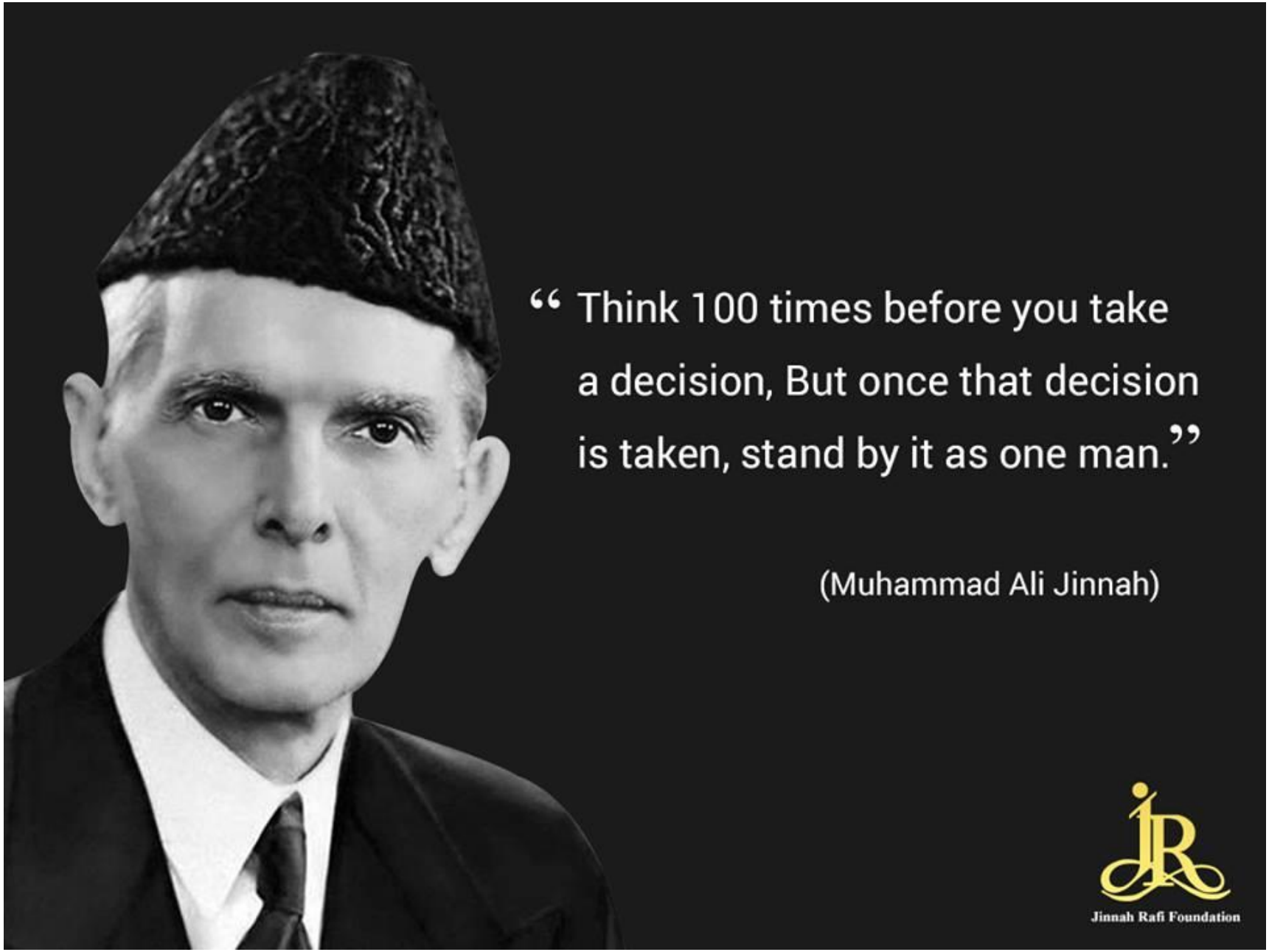
-- **IL-2, IL-12** and **IL-4** have spécial role in controlling T cell differentiation


EPO
Erythrocytes
IL-3, SCF, TPO
Megakaryocyte
Erythroid
Progenitor
IL-11, TPO
Platelets
IL-3, GM-CSF
M-CSF
Common Myeloid
Progenitor
G-CSF, GM-CSF
IL-3
Basophil/Mast cells
IL-11, TPO
GM-CSF, IL-3
IL-5
Myeloblasts
Eosinophil
GM-SCF
G-CSF, GM-CSF
IL-6, SCF
Neutrophil
Granulocyte
Macrophage
Progenitor
Hematopoietic
Stem cells
IL-6, SCF,
G-CSF
GM-CSF,
M-CSF
Monocytes
Macrophages
IL-2, IL-7
T-Lymphocyte
IL-17
IL-3, IL-4
IL-7
Common Lymphoid
Progenitor
B-Lymphocyte
IL-15
Natural Killer
Cells

Therapeutic use of cytokines:

- **Organ transplantation**
- **Inflammation**
- **Cancer therapy**
- **Infectious diseases**
- **Allergy**




“ Think 100 times before you take a decision, But once that decision is taken, stand by it as one man.”
(Muhammad Ali Jinnah)
Jinnah Rafi Foundation


Thank You!