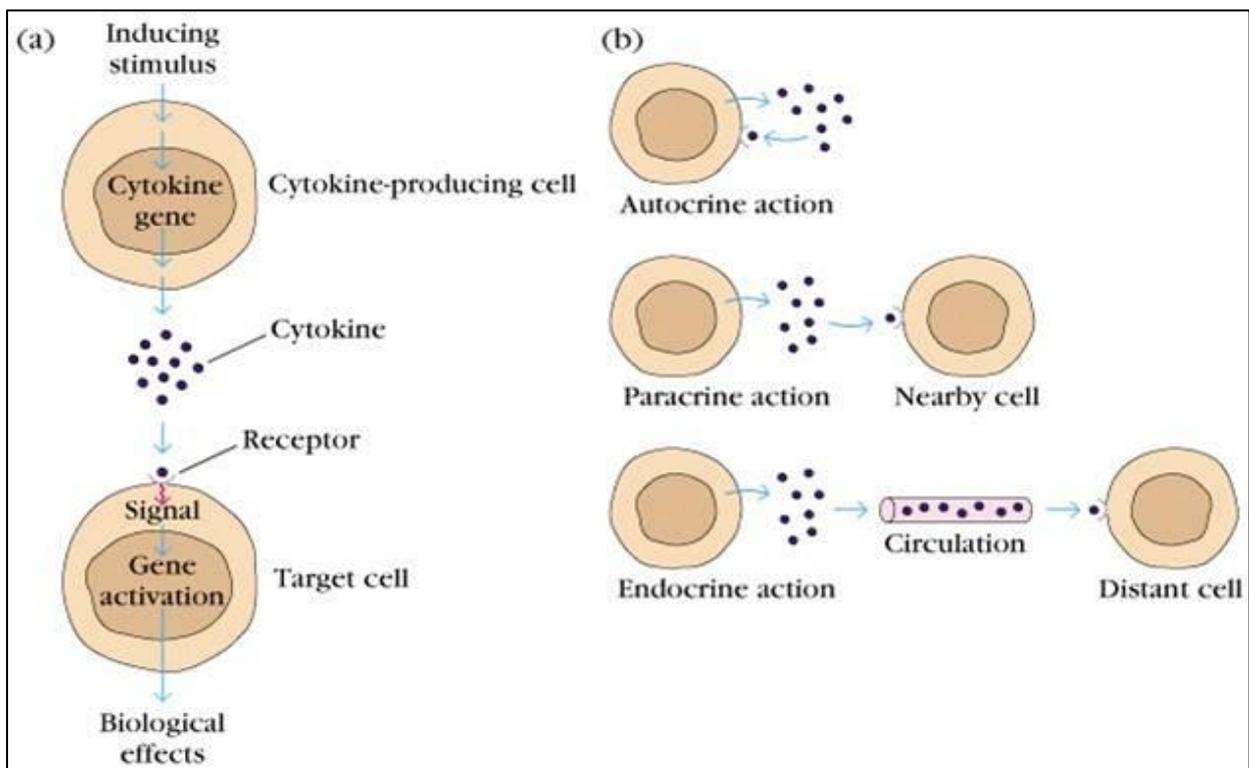
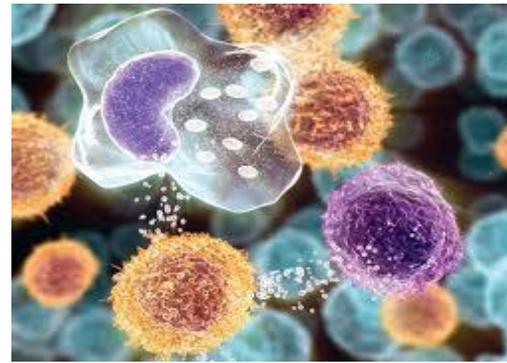


(Immunology)--- Lec # 3

((CYTOKINES))

What are the Cytokines?

- Low molecular weight soluble proteins (30 KDa)
- (polypeptides) produced in response to microbes and other antigens.
- 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



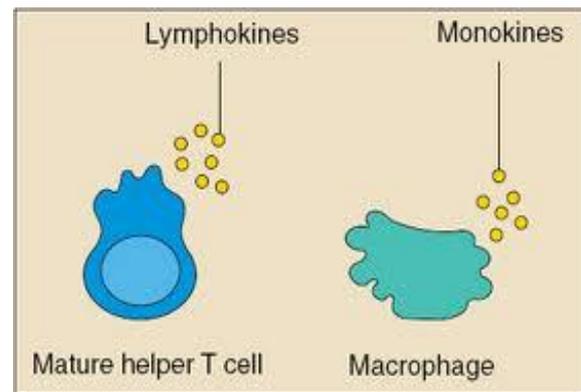
Cytokines regulate immune responses, they act via cell surface receptors to mediate and regulate the amplitude and duration of the immune-inflammatory responses, through activation of macrophages, controlling growth and differentiation of T and B cells.

When the Cytokines working? Cytokines are involved in:

- 1- Hematopoiesis
- 2- Adaptive Immunity
- 3- Innate Immunity
- 4- Inflammation

Cytokine Categories: There are 4 categories

TNF family¹, Chemokine family², Interferon family³ and Hematopoietin family⁴.



General Properties of Cytokines:

- * Cytokine secretion is a self-limited event (transient)
- * They are potent in minute amounts
- * One cytokine can act on different cells (pleiotropic)
- * Multiple cytokines may have the same functional effects (redundant)
- * Cytokines often influence synthesis and action of other cytokines
- * Two cytokines may antagonize each other's action (produce additive or synergetic effects)
- * Action of cytokine may be local or systemic
 - * Their action is not antigen specific
 - It is initiated by binding to specific cytokine receptors on the membrane of target cells
- * They act as intracellular messengers
- * The response to cytokine is:
 - a- Expression of new functions**
 - b- Proliferation of target cells**

Functional Categories of Cytokines: Cytokines classified according to their biologic actions into three groups:

(1) Mediators and regulators of innate immunity

- Produced by activated macrophages and NK cells in response to microbial infection
- They act mainly on endothelial cells and leukocytes to stimulate the early inflammatory response to microbes.

(2) Mediators and regulators of acquired immunity

- Produced mainly by T lymphocytes in response to specific recognition of foreign antigens
- They include IL-2, IL-4, IL-5,, IL-13, IFN, Transforming growth factor- β (TGF- β) and lymphotoxin (TNF- β)

(3) Stimulators of haematopoiesis

- Produced by bone marrow, stromal cells, leukocytes
- Stimulate growth and differentiation of leukocytes
- Stem cell factor, IL-3, IL-7, GM-CSF (Granulocyte Macrophage-Colony stimulating Factor).

Interferons (IFNs)

* Interferons (IFNs): are proteins secreted in response to viral infections or other stimuli

* They include:

- INF- α produced by leucocytes

→ induced by virus infected cells

- INF- β produced by fibroblasts

- INF- γ produced by NK cells, TH1 cells, CD8 T-cells

Action of INF- α and IFN- β :

- Prevent viral replication
- Increase MHC-I expression on viral infected cells helping their recognition by CD8 T-cells
- Increase cytotoxic action of Nk cells
- Inhibit cell proliferation and tumor growth

Action of IFN- γ :

- Activate Macrophages
- Increase expression of MHC-I and II on APCs
- Enhance cytotoxic actions of Nk cells
- Promote production of TH1 and inhibits proliferation of TH2

Could we use the cytokines as a drug???

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- γ , TNF- α
- (3) IL-2 and lymphokine activating killer cells (LAK) in treatment of cancer
- (4) GM-CSF induces increase in white cell count, it is used:
 - a- To restore leukocytic count after cytotoxic chemotherapy induced neutropenia
 - b- After bone marrow transplantation
 - c- To correct AIDS-associated leukopenia
- (5) Anti-cytokines antibodies in management of autoimmune diseases and transplant rejection:
 - a- Anti-TNF in treatment rheumatoid arthritis
 - b- Anti-IL2R to reduce graft rejection

- 6) Anti-TNF antibodies in treating septic shock
- 7) Anti-IL-2R α in treating adult T-cell leukemia
- 8) Anti-IL-4 is under trial for treatment of allergies

CYTOKINE SUMMARY (Review only)

IL-1

- Inflammation signal
- Secreted by macrophage and endothelial cells
- Stops DC macropinocytosis (danger signal)
- Neutrophil production and release from bone marrow
- Activate endothelial cells for neutrophil rolling/binding etc
- Causes fever

TNF- α

- Inflammation signal
- Secreted by macrophage and endothelial cells, and most cells
- Neutrophil production and release from marrow
- Activate endothelial cells and neutrophils for rolling/binding etc
- Loosens tight jxns to facilitate diapedesis \rightarrow can lead to anaphylactic shock from vascular leakage
- Locally clots blood vessels to limit spread of infection
- Sepsis (systemic infection)
 - Vasodilation \rightarrow decrease blood pressure
 - Widespread edema \rightarrow dangerous decrease in blood volume and bp
 - Wide spread clotting causes ischemic organ injury \rightarrow death

IFN- γ

- Strong activator of Macrophages
- Released by Th (Th1) cells
- Delayed Type Hypersensitivity rxn

IL-2

- Activate T cells to proliferate (mostly autocrine signaling)

IL-12

- Released by dendritic cells and macrophages
- Activates Th cells (Th1)—brings in adaptive response
- Activates NK cells

IL-4

- Activate Th2 cells

- Activates B cells to class switch

IL-5

- B cell class switching

IL-6

- Lymphocyte activation
- Increased Ab production

IL-10

- Blocks Th1 production
- immunosuppressive

TGF- β

- Suppresses T cells
- Secreted by Treg

IL-7

- Development of B and T cell precursors

IL-3

- Monocyte production

IL-8

- Strong chemotactic for neutrophils

C5a

- Chemotactic
- Attracts neutrophils
- Increases neutrophil expression of integrin for tight binding
- Anaphylatoxin

C3a

- Anaphylatoxin
- Chemoattractant- mast cells, basophils, eosinophils

CCL2

- Attracts macrophage

IL-15

- NK cell development