

Immunology

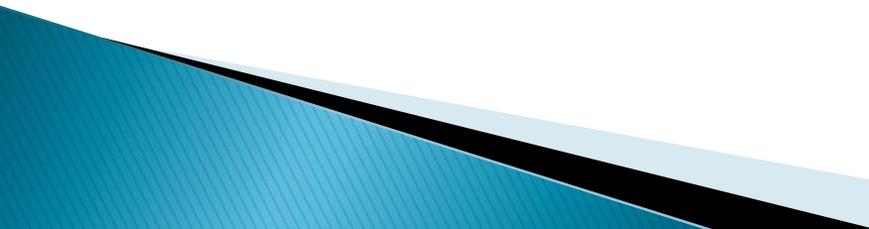
Lecture 5

Cytokines properties

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

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

Cytokines properties

- * 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
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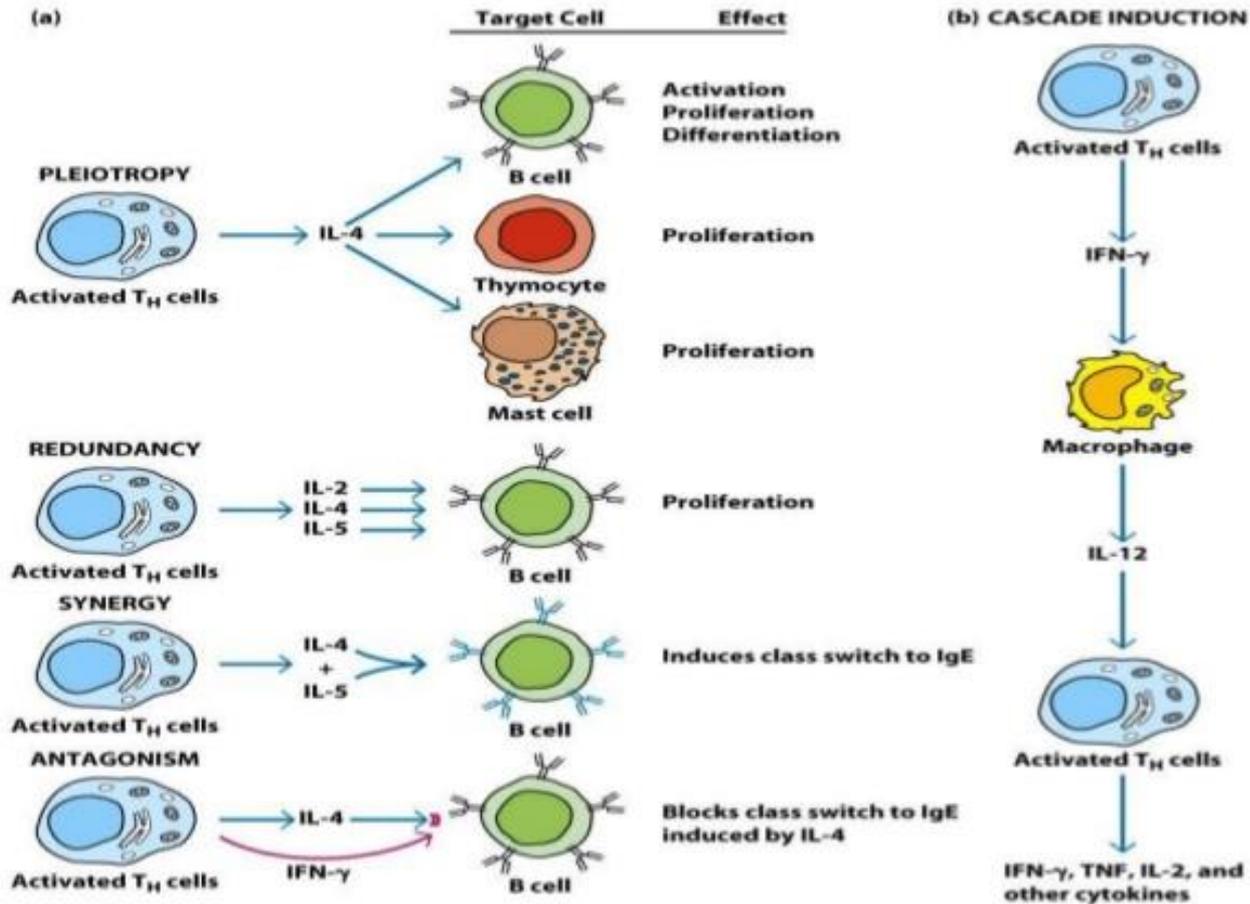
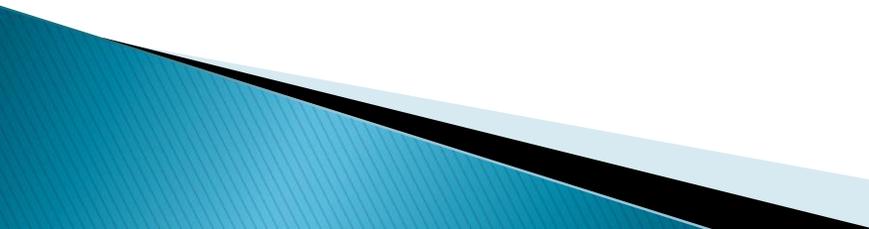
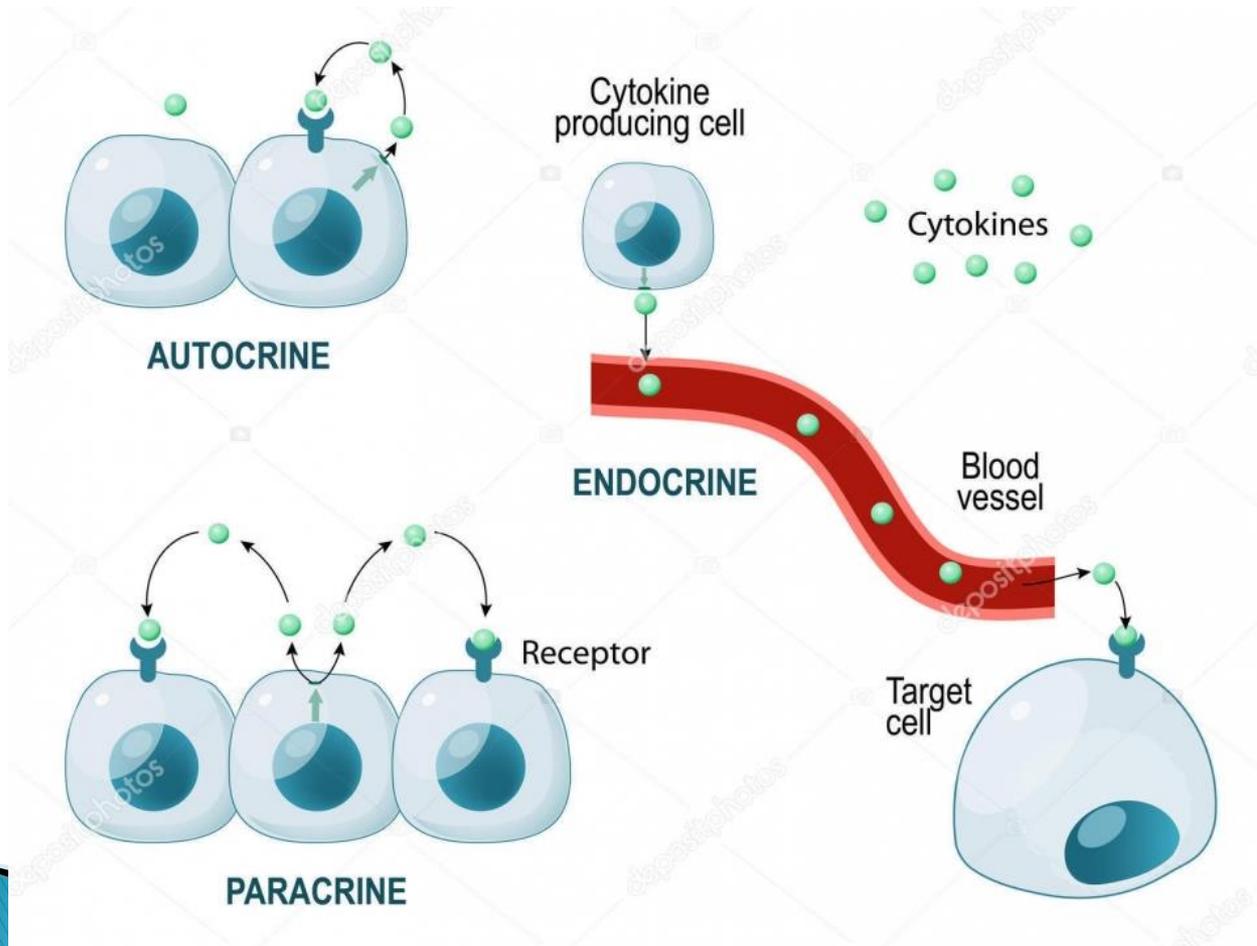


Figure 12-2
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Cytokines properties

- * Two cytokines may antagonize each other's action (produce additive or synergetic effects)
 - * Action of cytokine may be local or systemic
 - * Cytokine act close to the site of production (autocrine act.)
 - * Cytokine act on a nearby cell (paracrine action)
 - * Large amount secretion may enter circulation and act at a distance from site of production (endocrine action)
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Cytokines properties



Cytokines function

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
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Cytokines function

- 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 Tumor necrosis factor (TNF- β)

 - 3) Stimulators of haematopoiesis
 - Produced by bon marrow, stormal cells, leukocytes
 - Stimulate growth and differentiation of leukocytes
 - Stem cell factor, IL-3, IL-7, GM-CSF
- 

Interferons

- Interferons (IFNs): are proteins secreted in response to viral infections or other stimuli
- * They include:
 - IFN- α produced by leucocytes
 - IFN- β produced by fibroblasts
 - IFN- γ produced by NK cells, TH1 cells, CD8 T-cells

Interferons

Action of IFN- α and IFN- β :

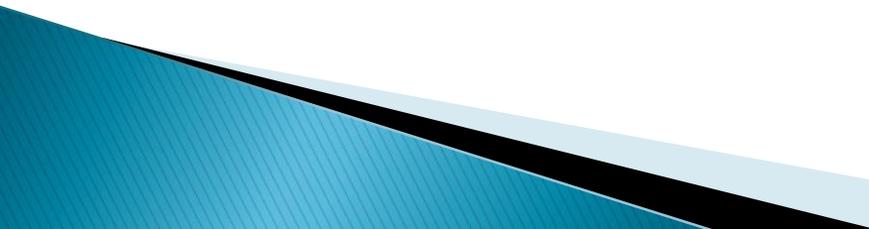
- Prevent viral replication
 - Increase MHC-I expression on viral infected cells helping their recognition by CD8 T-cells
 - Increase cytotoxic action of NK cells
 - Inhibit cell proliferation and tumor growth
- 

Interferons

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
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Cytokines 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.
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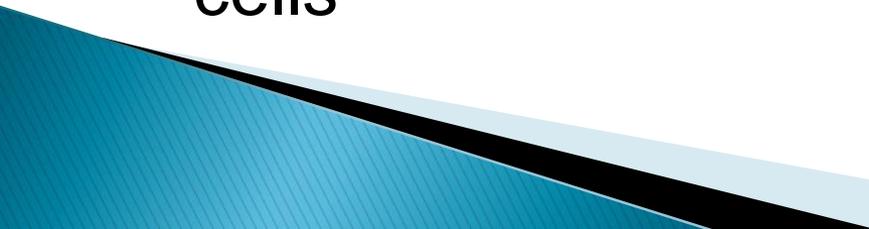
Cytokines assays

- The biological activities of cytokines can be measured by a variety of bioassays which may employ factor-dependent cell lines, or antibodies (ELISA)
- RT-PCR quantitation of cytokines detects the presence of mRNA encoding specific cytokines

IL-2

- IL-2 important actions:
 - It can **increase immunoglobulin synthesis**
 - Proliferation in B cells (with IL-4)
 - potently **augment the cytolytic activity** of natural killer (NK) cells
 - induce the cytolytic activity of lymphokine-activated killer (LAK) cells
 - Due to its effects on T-cells and B-cells IL-2 is a **central regulator** of immune response

IL-4

- IL-4, like IL-2, is produced principally by activated CD4+ T cells
 - It is also produced by natural killer cells, and by mast cells and basophils
 - IL-4 is the major B-cell growth factor
 - IL-4 induces expression of class II major histocompatibility complex (MHC) molecules on B cells
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IL-15

- Although IL-15 messenger RNA (mRNA) is produced by a range of non-lymphocytic cell types, it is difficult to detect IL-15 protein production.

IL-15 receptors are widely expressed, and it is becoming more clear that IL-15 plays a major role related to NK cell development and cytolytic activity

TABLE 12-1 Functional groups of selected cytokines*		
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
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 IgA; 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
<p>*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.</p>		

Table 12-1
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Cytokines action

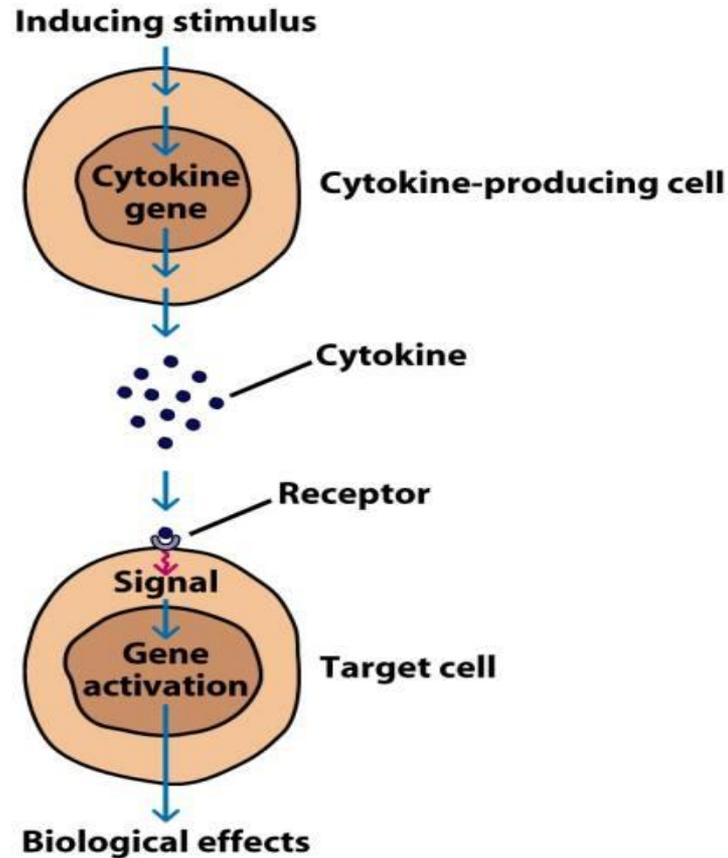


Figure 12-1a
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TH1 and TH2 cytokines

TABLE 12-4		Cytokine secretion and principal functions of mouse T_H1 and T_H2 subsets	
	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, <i>Immunology Today</i> 14:270.			

Table 12-4
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