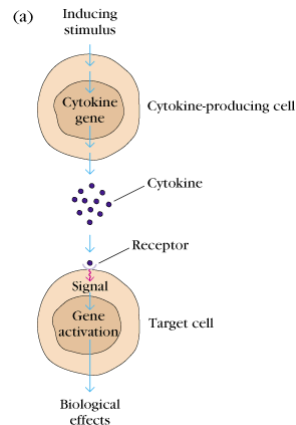


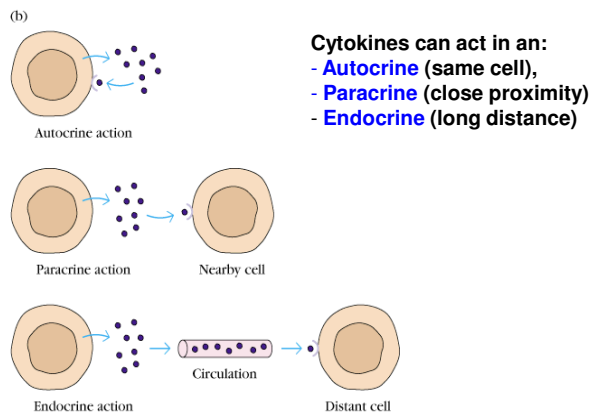
Chapter 13: Cytokines

Definition: secreted, low-molecular-weight proteins that regulate the nature, intensity and duration of the immune response by exerting a variety of effects on lymphocytes and/or other cells.

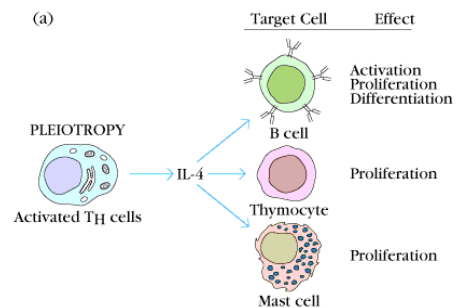
- Cytokines bind to specific **receptors** on target cells.
- Originally were called **lymphokines** because they were initially thought to be produced only by lymphocytes. Then **monokines** because they were secreted by monocytes and macrophages. Then **interleukin** because they are produced by some leukocytes and affect other leukocytes. The term "**cytokine**" is now used more widely and covers all of the above.
- Don't forget **chemokines**, they are also considered cytokines.



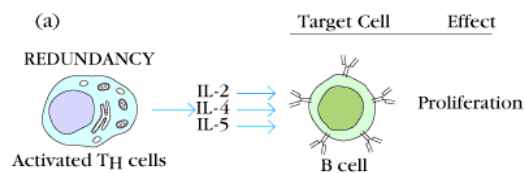
- Cytokines act only on cells bearing **specific receptors**.
- Expression of cytokines and their receptors is highly **regulated**.
- E.g. IL-2 receptor



1. Cytokines are **pleiotropic** ... one cytokine can have different effects on different cells.

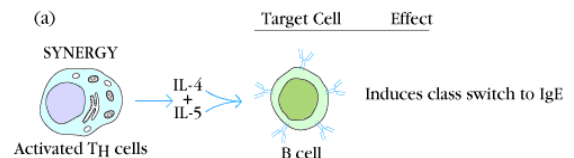


2. Cytokines can be **redundant** ... different cytokines can have the same effects.

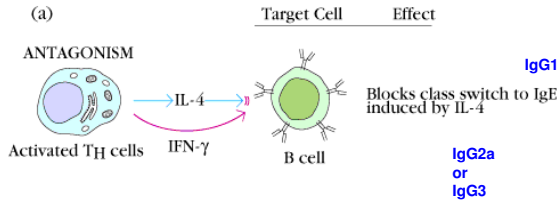


Kuby Fig 12-2a

3. Cytokines can **synergize** with each other.



4. Cytokines can **antagonize** each other.



5. Cascade effect, cytokines can stimulate the production of other cytokines.

CASCADE INDUCTION

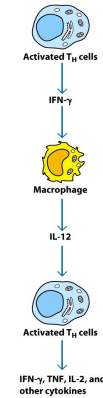


Figure 12-2b
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6. Cytokines can influence the expression of **cytokine receptors**.

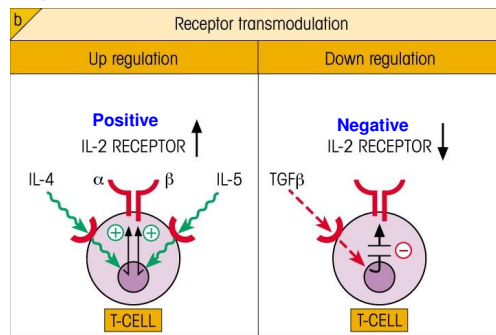


Figure 10.5b

7. Cytokines play key roles in regulating **hematopoiesis, innate immunity and acquired immunity**.

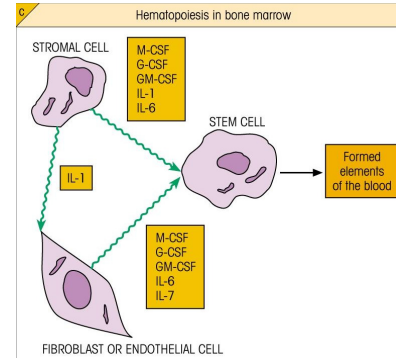
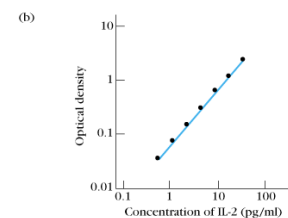
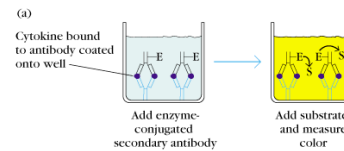


Figure 10.4c

SO...cytokines can have many effects, depending on:

- the target cell
- the state of differentiation/activation of the target cell
- the presence or absence of other cytokines

Sandwich ELISA



Cytokine levels in serum or in tissue culture supernatants can be measured with a **Sandwich ELISA** assay.

Exam Question!!!!

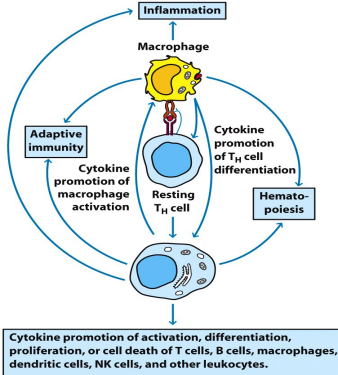


Figure 12-5
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There are many cytokines, including...

IL-1	IL-2	IL-3	IL-4
IL-5	IL-6	IL-7	IL-8
IL-9	IL-10	IL-11	IL-12
IL-13	IL-15	IL-16	IL-17
IL-18	IL-19	IL-20	IL-21
IL-22	IL-23		
IFN- α	IFN- β	IFN- γ	
TNF- α	TNF- β		
TGF- β 1			
M-CSF	G-CSF	GM-CSF	

TABLE 12-1 Functional groups of selected cytokines^a

Cytokine ^a	Secreted by ^b	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_H 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_H 2 cells, mast cells	Promotes T_H 2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T_H 2 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_H 1 cells, CD8 ⁺ cells, NK cells	Activates macrophages; increases expression MHC class I and class II molecules; increases antigen presentation

^aMany cytokines play roles in more than one functional category.
^bOnly 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.
^cAlso note that activated cells generally secrete greater amounts of cytokine than unactivated cells.

Table 12-1
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Best way to learn about cytokines.... is by their action !!!

Cytokines and Immune Responses

Proinflammatory cytokines

TNF
IL-1
IL-6
chemokines (many)

Antiinflammatory cytokines

IL-10
IL-1ra
TGF- β

Inhibition of virus replication

IFN- α , - β

Macrophage-activating cytokines

IFN- γ

B cell-activating cytokines

IL-4
IL-5
IL-6
IL-21

T cell-activating cytokines

IL-2
IL-4
IL-12

Eosinophil- and/or mast cell-activating cytokines

IFN- γ
IL-3
IL-4
IL-13
IL-5

Four Structural Families

- Hematopoietin Family (IL-2, IL-4)
- Interferon Family (IFN- α , β , γ)
- Chemokine Family
- Tumor necrosis family

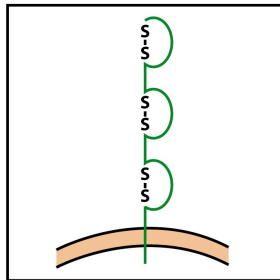
Based on structural homology, there are five major cytokine receptor families:

- Ig superfamily receptors
- Class I receptors (Hematopoietin receptor family)
- Class II receptors (Interferon receptor family)
- TNF receptor family
- Chemokine receptors
- TGF receptor family

RECEPTOR FAMILY

LIGANDS

Immunoglobulin superfamily receptors



IL-1
M-CSF
C-Kit
IL-18

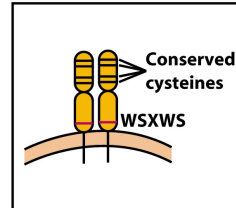
Figure 12-6a
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ruzy Fig 12-6a

RECEPTOR FAMILY

LIGANDS

Class I cytokine receptors (hematopoietin)



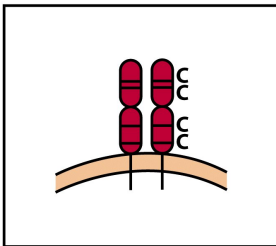
IL-2 IL-21
IL-3 IL-23
IL-4 IL-27
IL-5 GM-CSF
IL-6 G-CSF
IL-7 OSM
IL-9 LIF
IL-11 CNTF
IL-12 Growth hormone
IL-13 Prolactin
IL-15

Figure 12-6b
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RECEPTOR FAMILY

LIGANDS

Class II cytokine receptors (interferon)



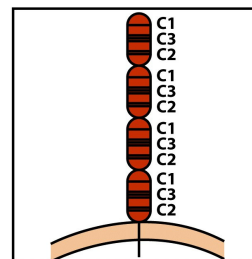
IFN- α
IFN- β
IFN- γ
IL-10
IL-19
IL-20
IL-22
IL-24
IL-26
IL-28
IL-29

Figure 12-6c
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RECEPTOR FAMILY

LIGANDS

TNF receptors

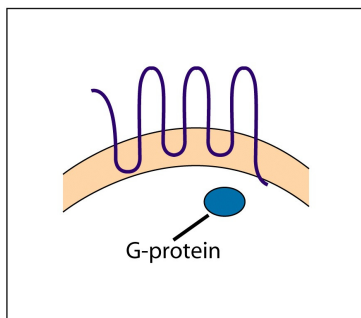


TNF- α
TNF- β
CD27L
CD30L
CD40L
Nerve growth factor (NGF)
FAS

Figure 12-6d
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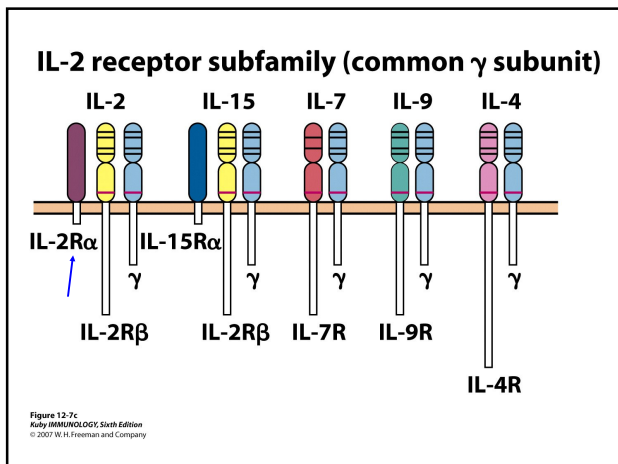
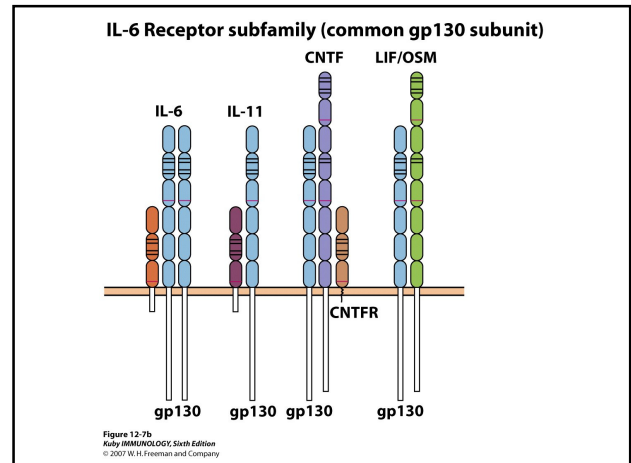
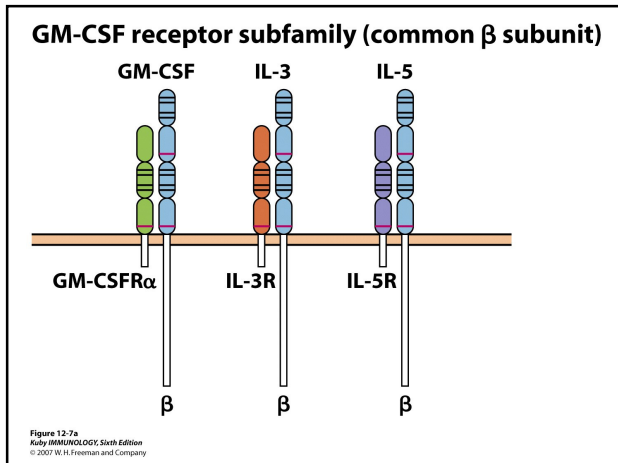
(e) Chemokine receptors

LIGANDS



IL-8
RANTES
MIP-1
PF4
MCAF
NAP-2

Three subfamilies of the class I cytokine receptor family (hematopoietin)



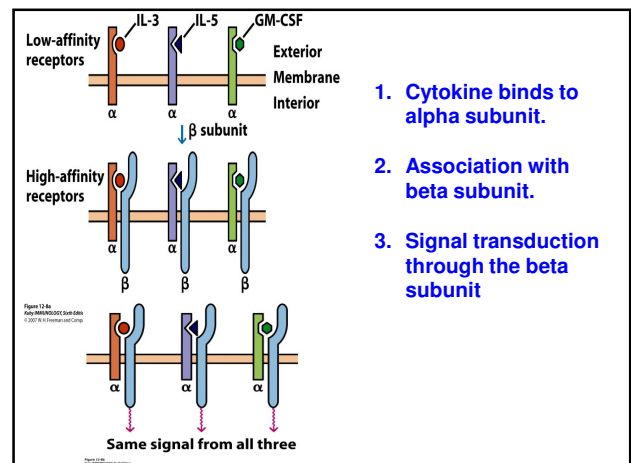
SHARED CYTOKINE RECEPTORS SUBUNITS

Shared Cytokine-Receptor Subunits	
Shared receptor chain	Cytokines recognized
C γ_c	IL-2, -4, -7, -9, -15, -21
A IL-2R β	IL-2, IL-15
IL-4R α	IL-4, -13
IL-13R α_1	IL-4, -13
β_c	IL-3, -5, GM-CSF
B gp130	IL-6, -11, -27, -31, LIF, OSM, CNTF, CT-1, GLC
IL-12R β_1	IL-12, -23
IL-10R2	IL-10, -22
IL-20R2	IL-20, -19, -24
IL-22R	IL-22, -24, -20

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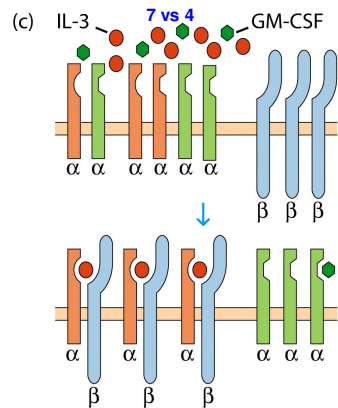
Cytokine receptors

- Sharing of signal transducing molecules explains the **redundancy** and **antagonism** exhibited by some cytokines



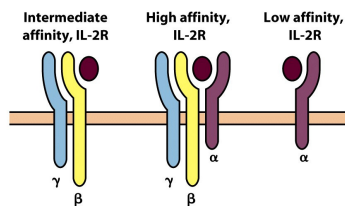
Competition of ligand-binding chains of different receptors for a common subunit.

This can result in antagonistic effects between cytokines



IL-2 Receptor

- Composed of 3 subunits: α , β , and γ chains
- IL-2 receptor is present in 3 forms: low, medium, and high affinity
- The low affinity (monomeric, $\text{IL-2R}\alpha$), medium affinity (dimeric, $\text{IL-2R}\alpha\beta$), and high affinity (trimeric, $\text{IL-2R}\alpha\beta\gamma$)
- Binding component: α chains
- Transducing components: β and γ chains.



Only in activated T cells

Subunit composition:	IL-2R β IL-2R γ	IL-2R α IL-2R β IL-2R γ	IL-2R α
Dissociation constant (K_d):	10^{-9} M	10^{-11} M	10^{-8} M
Cells expressed by:	NK cells Resting T cells (low numbers)	Activated CD4 ⁺ and CD8 ⁺ T cells Activated B cells (low numbers)	

Figure 12-9a
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A number of cytokine receptors signal via the **JAK/STAT pathway**. These include the receptors for IL-2, IL-3, IL-4, IL-6, IL-10, IL-12 and IFN- γ .

Cytokine receptor subunits are associated with **JAK kinases**.

- 1.- Binding of cytokine causes **dimerization** of receptors and **activation of JAK kinases**.
- 2.- Activated JAK kinases **phosphorylate receptor sites** and **create docking sites for STAT molecules**.

JAK = Janus Kinase - OR - Just Another Kinase

STAT = Signal Transducers and Activators of Transcription

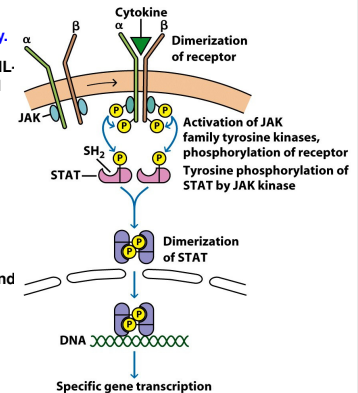
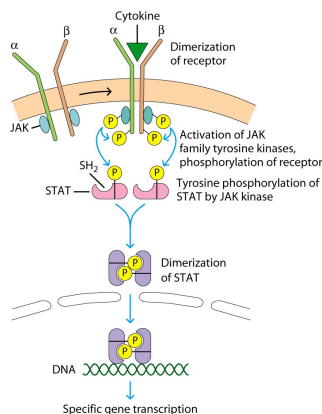
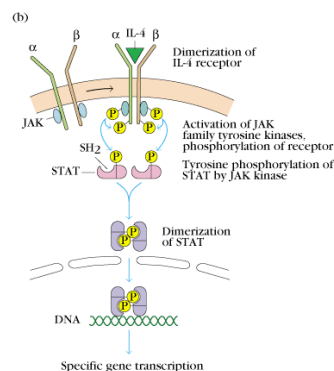


Figure 12-10
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3. After binding to the **receptor (α chain)**, **STATs** are phosphorylated by **JAK** kinases.
4. They then **dissociate from the receptor**, **dimerize** and **translocate to the nucleus**, where they **mediate transcription of target genes**.



Similar JAK/STAT signaling in the IL-4 receptor.

Kuby Fig 12-10b

Different receptors associate with different JAK/STAT combinations

TABLE 12-2 STAT AND JAK INTERACTION WITH SELECTED CYTOKINE RECEPTORS DURING SIGNAL TRANSDUCTION

Cytokine receptor	JAK	STAT
IFN- γ	JAK1 and JAK2	Stat1*
IFN- α/β	JAK1 and Tyk-2	Stat2
IL-2	JAK1 and JAK3	Stat5
IL-3	JAK2	Stat5
IL-4	JAK1 and JAK3	Stat6*
IL-6	JAK1 (and sometimes others)	Stat3
IL-10	JAK1 and Tyk-2*	Stat3
IL-12	JAK2 and Tyk-2*	Stat4*

*Despite its name, Tyk-2 is also a Janus kinase.
SOURCE: Adapted from Bach, Aguet, and Schreiber, 1997, *Annu. Rev. Immun.* 15:563.

Cytokine Antagonists

Action:

- 1) Blocking the receptor (IL-1Ra), and
- 2) Binding to the cytokine (IL-2, IFN- γ)

TABLE 12-3 Viral mimics of cytokines and cytokine receptors

Virus	Products
Leporipoxvirus (a myxoma virus)	Soluble IFN- γ receptor
Several poxviruses	Soluble IFN- γ receptor
Vaccinia, smallpox virus	Soluble IL-1 β receptor
Epstein-Barr	IL-10 homolog
Human herpesvirus-8	IL-6 homolog; also homologs of the chemokines MIP-1 and MIP-2
Cytomegalovirus	Three different chemokine receptor homologs, one of which binds three different soluble chemokines (RANTES, MCP-1, and MIP-1 α)

Table 12-3
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CD4⁺ helper T cell

Th1

Th2

CTL response

Viral infections

DTH

Intracellular bacteria

IL-2
IFN- γ
TNF- β
IL-3
GM-CSF

IL-4
IL-5
IL-6
IL-10
IL-13
IL-3
GM-CSF

B cell response

Extracellular bacteria

Eosinophilia

Helminthic parasites

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_H -cell activation	++	-

Table 12-4
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Helper T cells can be divided into two main types - T_H1 and T_H2 - with distinct patterns of cytokine secretion.

T_H1 cells produce cytokines (IFN- γ and IL-2) that promote immune responses against intracellular pathogens (DTH, cytotoxic T cell responses, macrophage activation, opsonizing Abs).

T_H2 cells produce cytokines (IL-4, IL-5, IL-6, IL-13) that promote immune responses against extracellular pathogens (antibody responses IgE/IgG1, eosinophilic responses, allergic reactions).

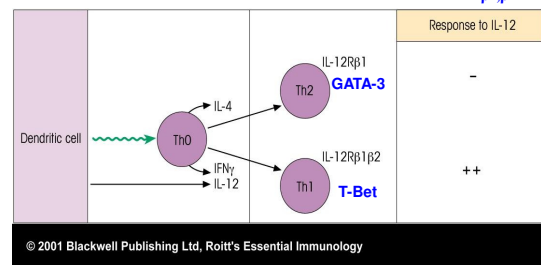
Some cytokines are produced by both T_H1 and T_H2 cells. These cytokines - GM-CSF and IL-3 - act on the bone marrow to increase production of leukocytes - so they are needed no matter what type of pathogen is present.

T_H1/T_H2 differentiation is influenced by the levels of key cytokines.

- IL-4 promotes T_H2 differentiation.

- IFN- γ and IL-12 promotes T_H1 differentiation.

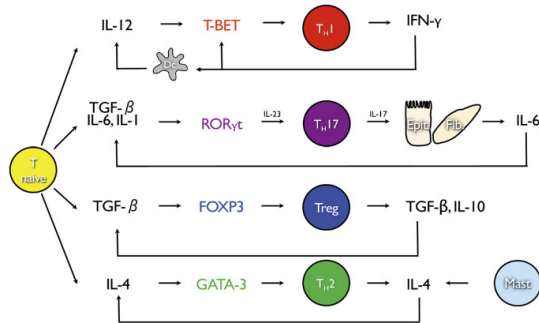
IL-12R = $\beta1, \beta2$



© 2001 Blackwell Publishing Ltd, Roitt's Essential Immunology

Figure 10.7

Transcription factors can be used to characterize Th lineage



Cytokine cross-regulation

- IFN-γ (Th-1) inhibits proliferation of Th-2
- IL-4 and IL-10 (Th-2) inhibits proliferation of Th-1 by decreasing IL-12 production
- IFN-γ (Th-1) promotes IgG2a production and decreases IgE by B cells
- IL-4 (Th-2) promotes production of IgE and IgG1 by B cells and decreases IgG2a.

Transcriptional Regulation of Cytokines

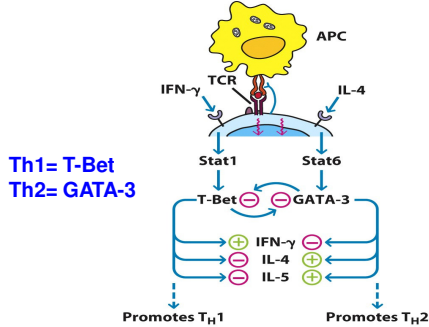


Figure 12-13
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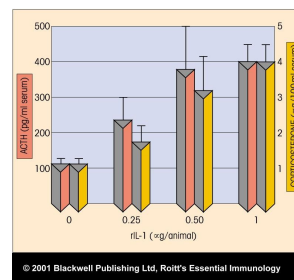
Cytokine & Diseases

- **Bacterial Septic Shock**
 - Due to several Gram (-) bacteria
 - Stimulation of Macrophages by LPS → ↑ TNF-α, IL-1β
 - Drop in blood pressure, fever, diarrhea, systemic blood clotting in various organs
- **Bacterial Toxic Shock**
 - Caused by **superantigens** (wide variety of toxins)
 - Activation of T cells → ↑ cytokines from T cells and activated MØ (↑ TNF-α, IL-1β)
- **Infectious Diseases**
 - Leprosy, Chagas Disease (↓ IL-2Rα).

Relative predominance of TH1 vs TH2 helper T cells can influence the course of infectious disease (*Mycobacterium leprae*)

TH1 activity		TH2 activity	
Tuberculoid	Lepmatous	Tuberculoid	Lepmatous
IL-2		IL-4	
IFN-γ		IL-5	
TNF-β		IL-10	
Tuberculoid - ↑ CMI (granulomas) - No RIP		Lepmatous - ↑ HI (dissemination) - RIP	

Neuroendocrine regulation



IL-1, IL-6 and TNF-α can induce production of glucocorticoids by acting on the hypothalamic-pituitary-adrenal (HPA) axis.

Figure 11.19

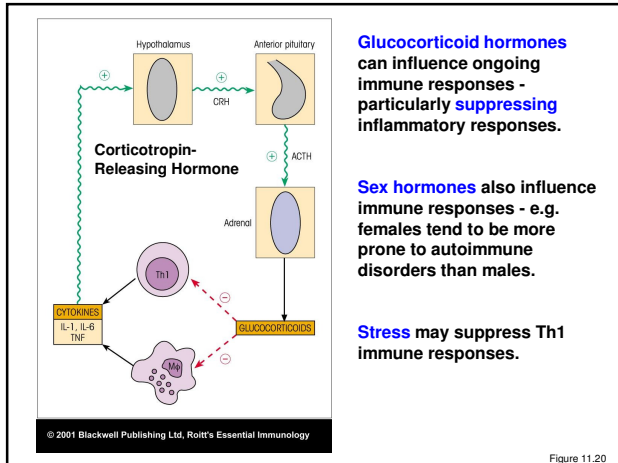
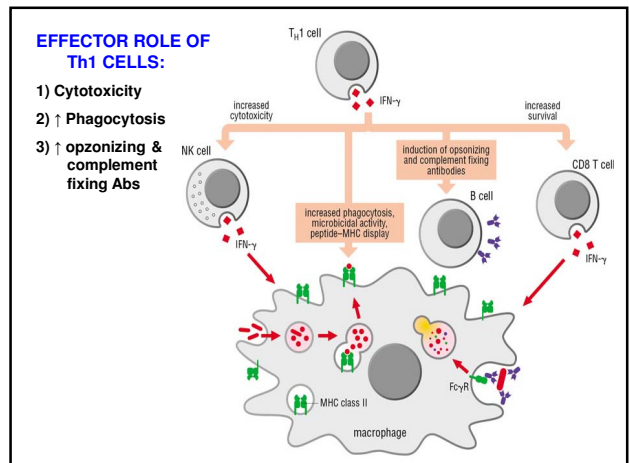
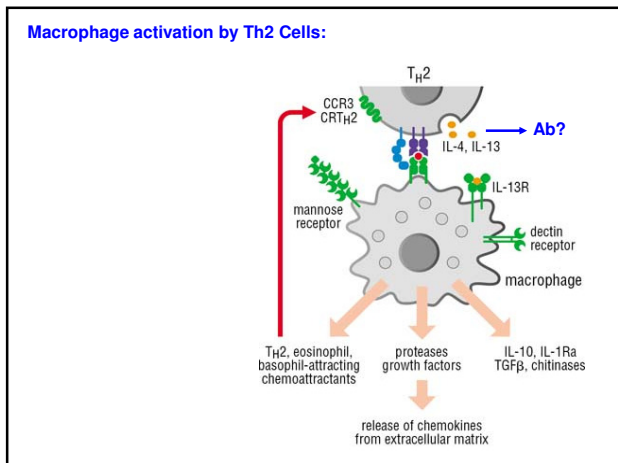
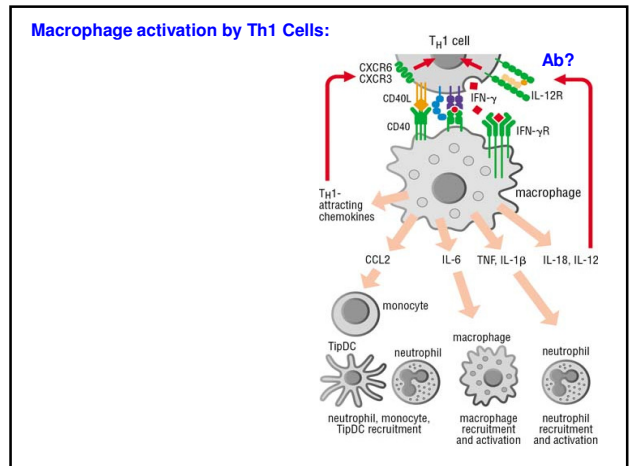
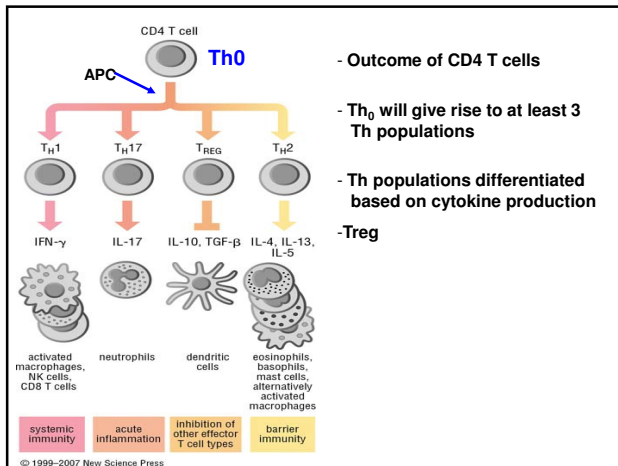


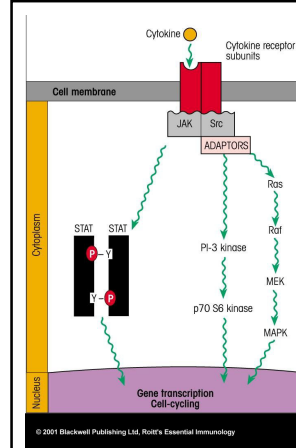
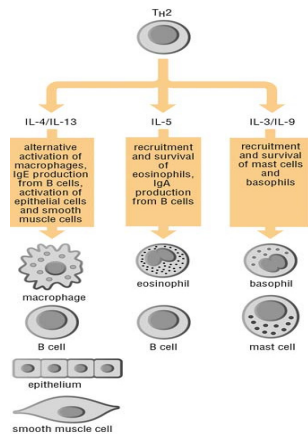
Figure 11.20

The End, but interesting material next!!



EFFECTOR ROLE OF Th2 CELLS:

- 1) IgE production
- 2) IgA production
- 3) Eosinophil recruitment
- 4) Basophil & Mast cell recruitment



Other pathways may also be involved in cytokine signaling.