

Lecture 10

T-cell Polarization & Cytokine Signaling

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Chris Schindler
cws1@columbia.edu

What controls T-cell maturation and activity?

- Antigen Presenting Cells (APCs), which present peptide fragments in MHC I or MHC II.
- Co-receptors (e.g., CD28, CD84 & CD86)
- Cytokines (and chemokines).

What are cytokines & chemokines?

- Small (10-30 kDa), usually secreted and usually glycosylated peptides.
- Bind specific, high affinity (e.g., K_d of 10^{-10} - 10^{-12} M) receptors found on target cells.
- Expression of cytokines and their cognate receptors is usually tightly regulated (i.e., temporally & spatially).
- **Cytokine receptors define the specific type of biological response a cytokine stimulates.**
- Four helix bundle cytokines are usually referred to as interleukins (ILs; e.g., IL-2, IL-3 ...). Anachronistic terms include monokines & lymphokines.

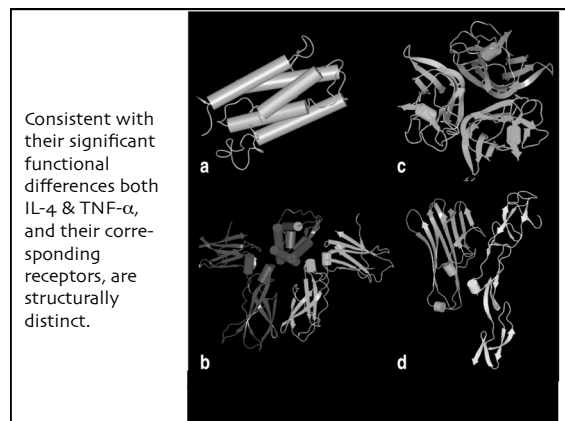
What do cytokines do?

- They direct the development, maturation, localization, interactions, activation and life span of immune cells.
- Thus they play an essential role in regulating both immunity adaptive and innate.
- (Chemokines and Growth Factors also participate).

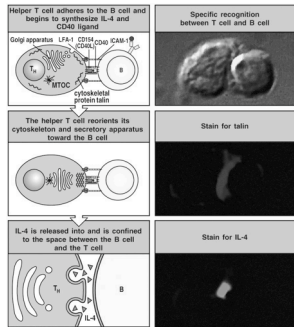
Cytokines subfamilies are functionally distinct

- Cytokines can be divided into functionally distinct groups based on the receptors they bind.
 - Growth Factors (e.g., CSF-1, SCF, RANKL, Flt₃L)
 - IL-1 Family (e.g., IL-1, IL-18 & natural products/PAMPs)
 - TNF Family (e.g., TNF- α , CD40L, FasL, LT- α , LT- β , BAFF)
 - TGF- β Family (e.g., TGF- β)
 - **Type I & II Cytokines (4 Helix Bundle Cytokines; e.g., IL-2, IL-4, IL-6, IL-10, IL-12, IL-23, IL-27, GM-CSF, IFN- γ , IFN- α/β)**
 - Chemokines (e.g., CC and CXC families)
 - Other (e.g., steroid hormones, prostaglandins and IL-17)
- There are significant functional similarities within each receptor family. The same is true for corresponding ligands.
- There are important functional differences between receptor families.

*Underlined cytokines are of particular importance



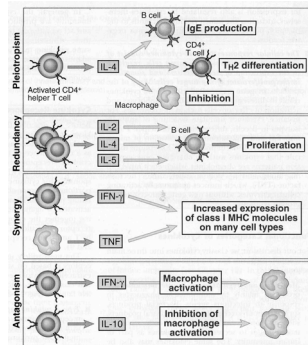
Localized release of IL-4 in the cleft between T cell and APC ("The immunological synapse")



Important general properties of Cytokines and Chemokines

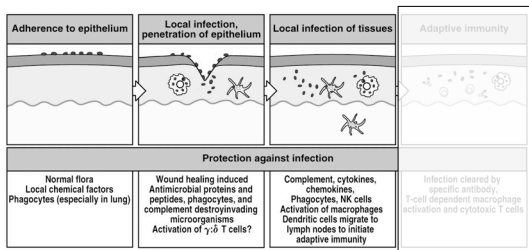
- Stimulate transient response in target cells.
- Function at three ranges:
 - Autocrine - "self"
 - Paracrine - adjacent cells
 - Endocrine - through circulatory system (e.g., septic shock: IL-1 and TNF)
- **Pleiotropism** - one ligand activate numerous types of responses (e.g., differentiation, growth & activation).
- **Redundancy** - two or more ligands exhibit functional overlap.
- **Synergy** - two or more ligands synergize to mount a single response.
- **Antagonism** - two or more cytokines mediating opposite responses to either limit a response or achieve balance (e.g. Feedback loops).

General Properties of Cytokines



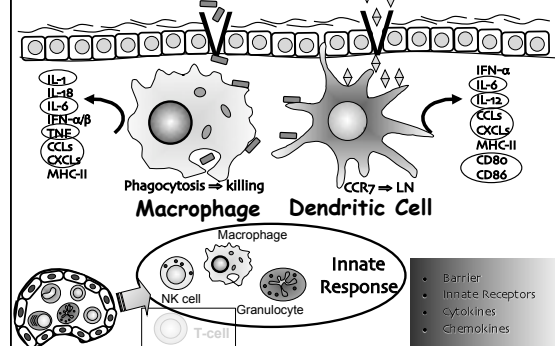
Some Biology

How do we protect ourselves from microbes?



Wound Infection: Innate \rightarrow Adaptive

What happens under the skin?



PRRs detect the infection

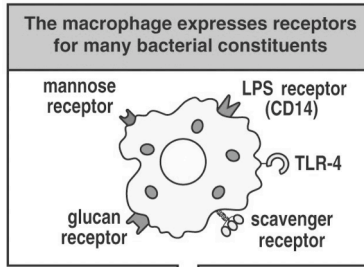


Figure 2-5 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Activated macrophages secrete cytokines & chemokines, Directing the ensuing response

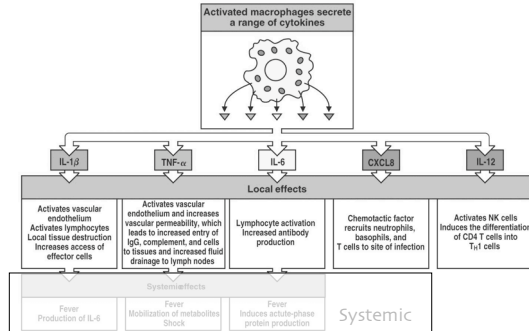


Figure 2-39 Immunobiology, 6/e. (© Garland Science 2005)

Local vs. systemic infection

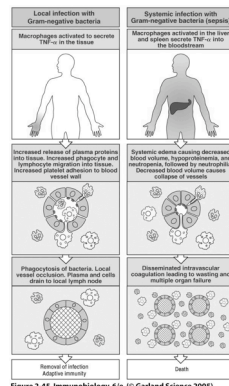
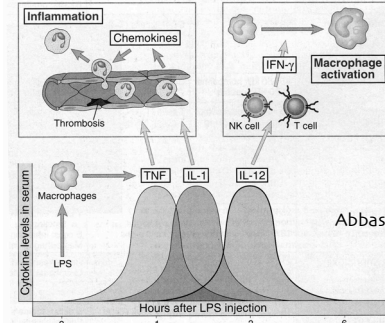


Figure 2-45 Immunobiology, 6/e. (© Garland Science 2005)

LPS stimulates macrophages to secrete cytokines that promote sepsis activities



Abbas: Chpt. 11

Note, one of the few times you can meaningfully measure serum cytokine levels!!

Cytokines and the septic constellation

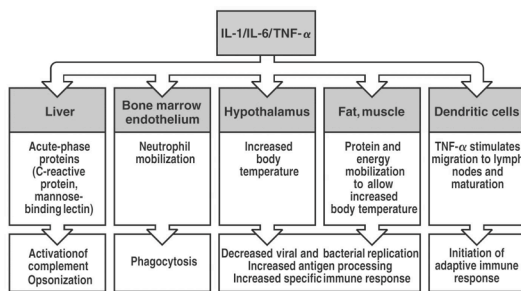
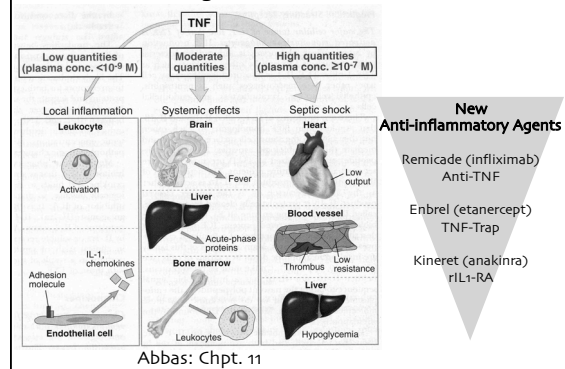
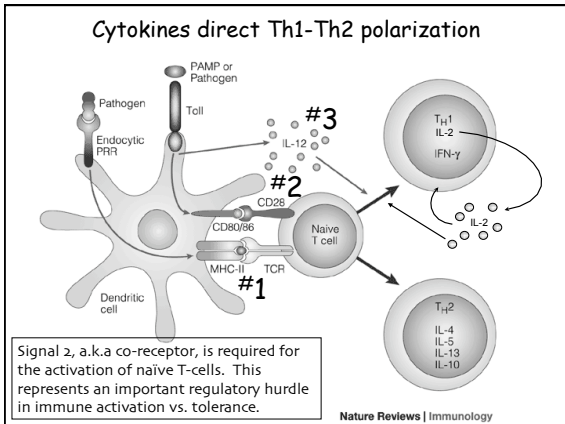
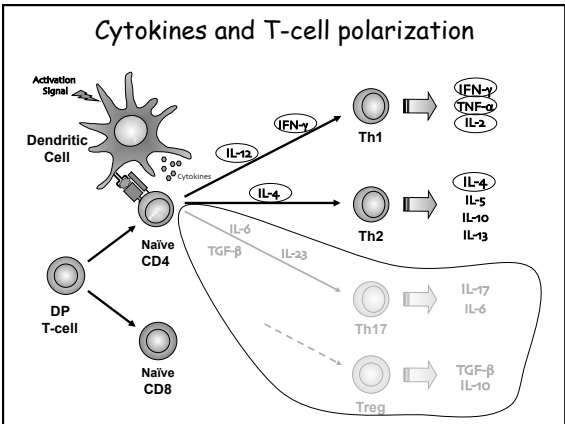
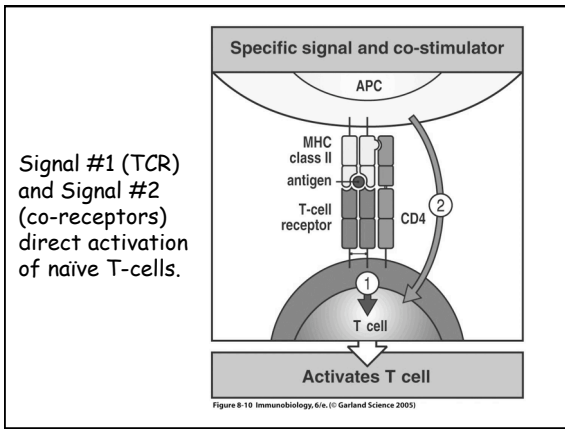
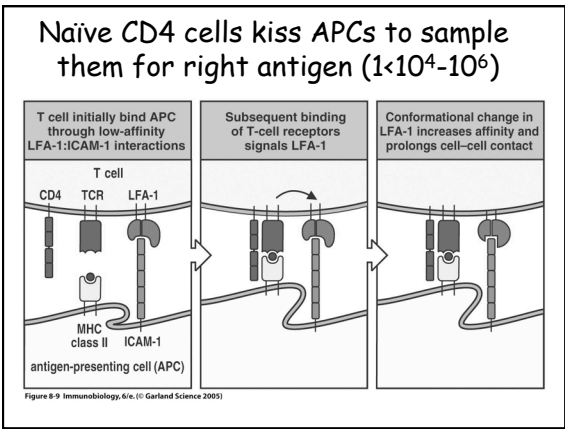
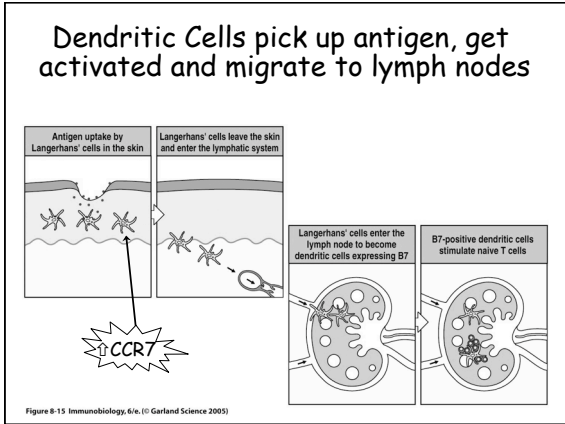


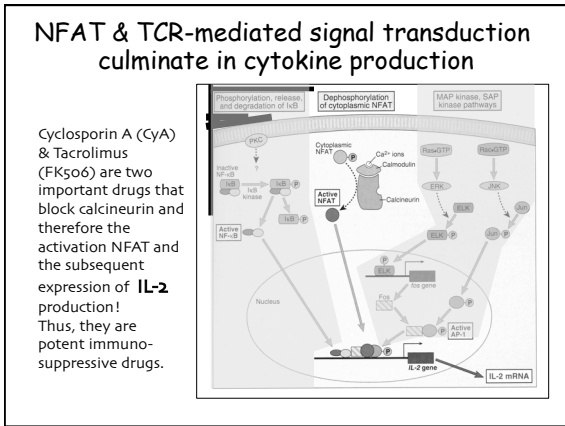
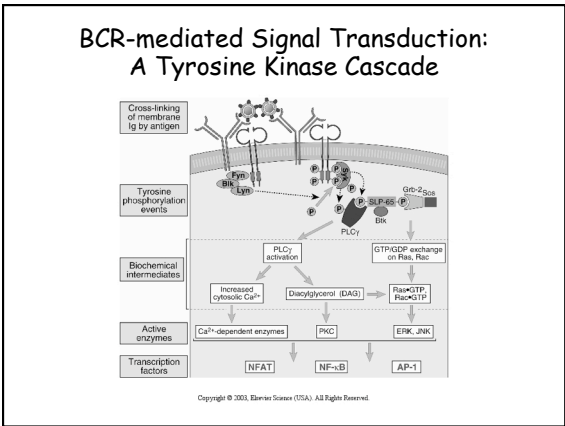
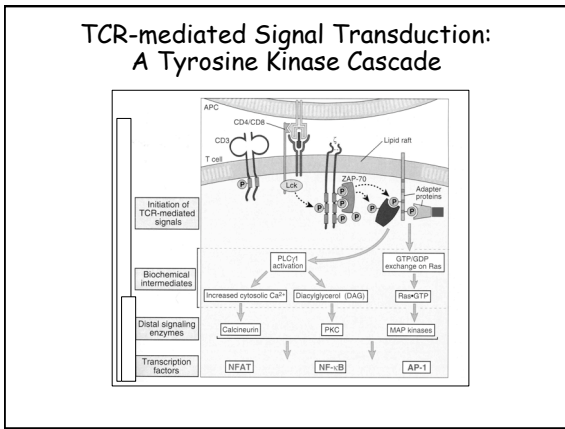
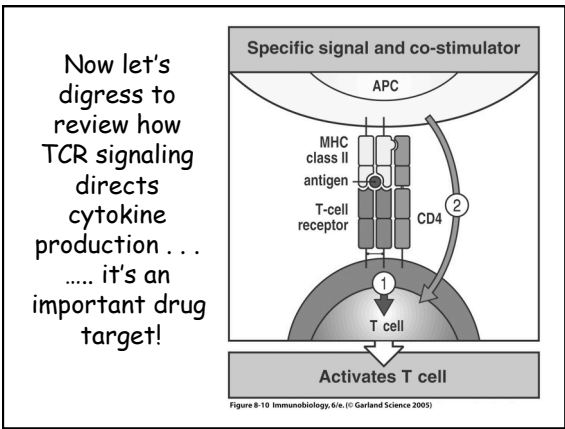
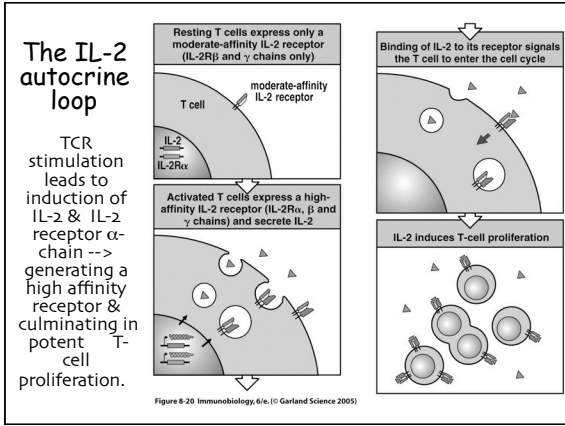
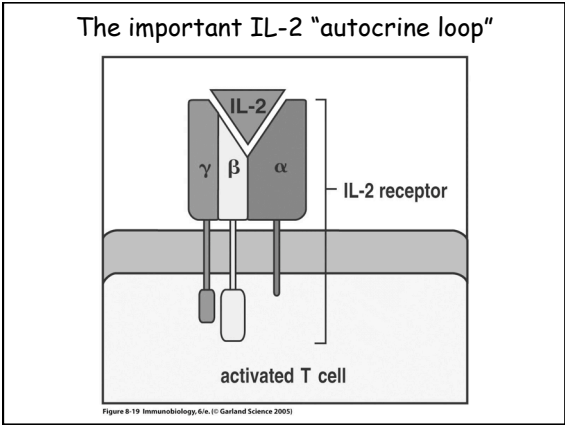
Figure 2-46 Immunobiology, 6/e. (© Garland Science 2005)

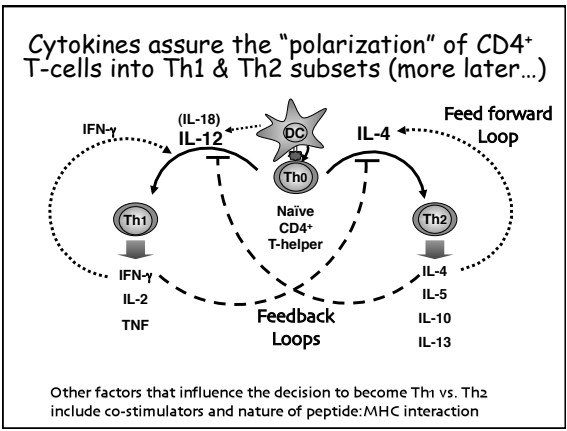
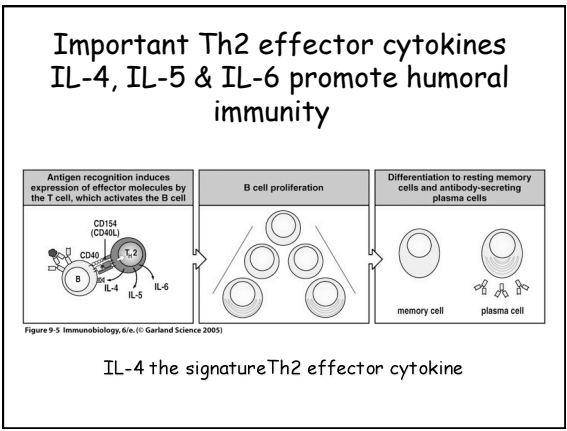
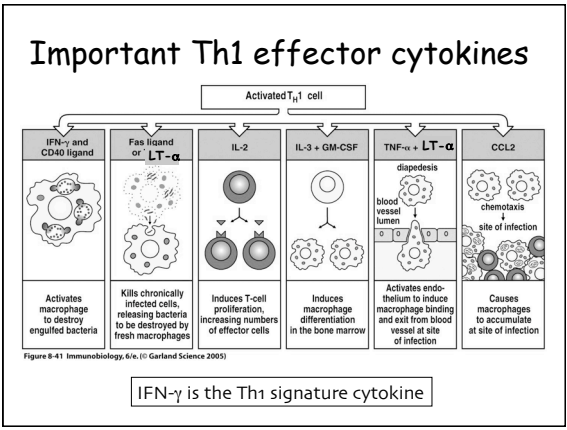
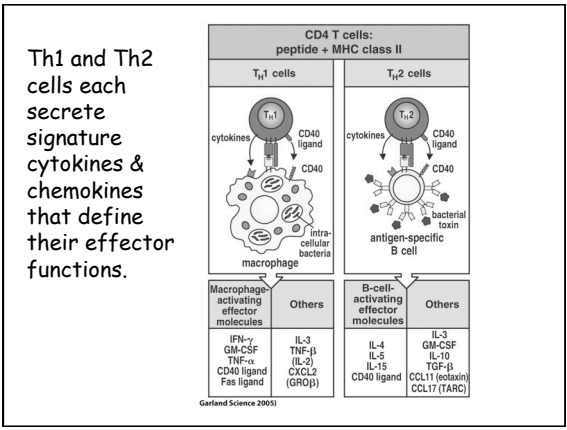
Biological actions of TNF



Cytokines and the evolving Th1-Th2 paradigm

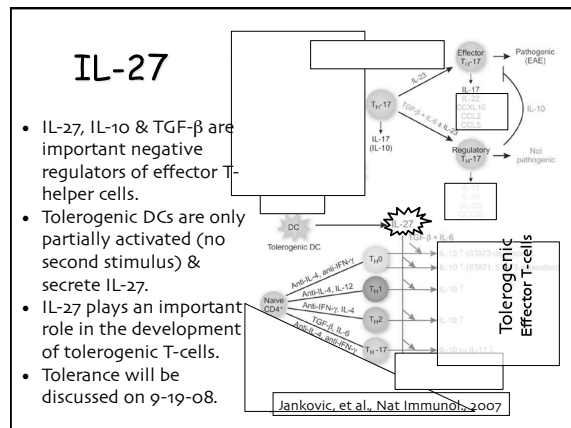
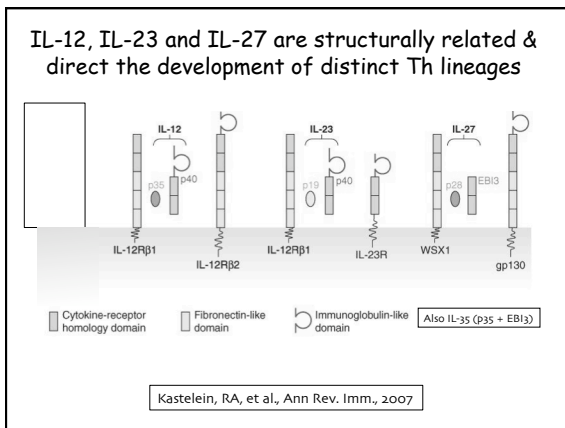
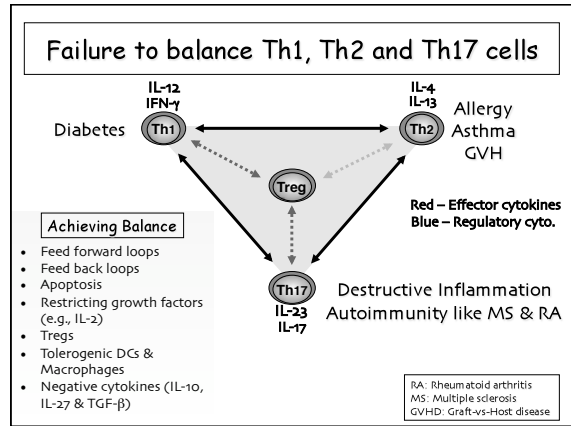
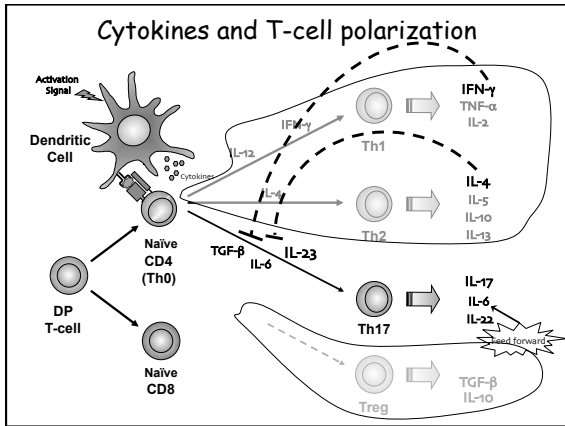




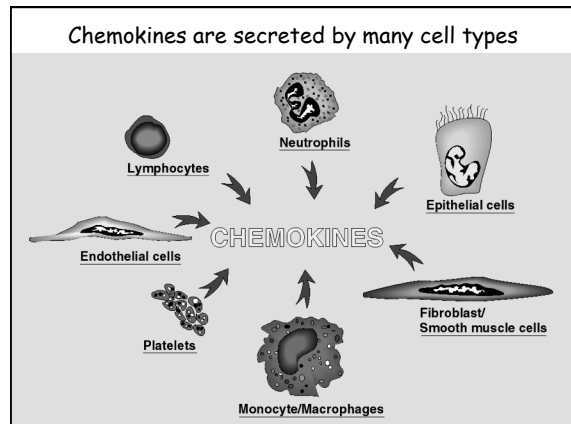


The rapidly emerging story of a new T-cell effector subsets. Th17 cells & Treg cells (on 9-19).

- ### The Th17 Cell
- An effector T-cell that arises from naïve CD4+ cells.
 - Secretes IL-6, IL-22 and prodigious quantities of IL-17.
 - Th17 cells evolved to combat pathogens not covered by Th1 (intracellular) or Th2 (helminths) cells.
 - IL-17 deficient mice are highly susceptible to extra-cellular pathogens including Klebsiella, Borrelia and Citrobacter.
 - IL-17 receptor is found on many cell types
 - IL-17 activates granulocytes (innate immunity)
 - IL-17 promotes cellular immunity by activating CD8 T-cells, NK cells and macrophages.
 - IL-17 stimulates fibroblasts, endothelial cells, macrophages, and epithelial cells to produce multiple pro-inflammatory mediators, (e.g., IL-1, IL-6, TNF- α , NOS-2, metalloproteases, and chemokines).
 - Important in autoimmune disease like Multiple Sclerosis & Rheumatoid Arthritis.



Chemokines



Chemokines signal through G-protein coupled receptors making them desirable drug targets

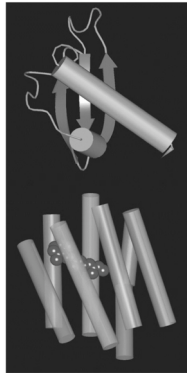
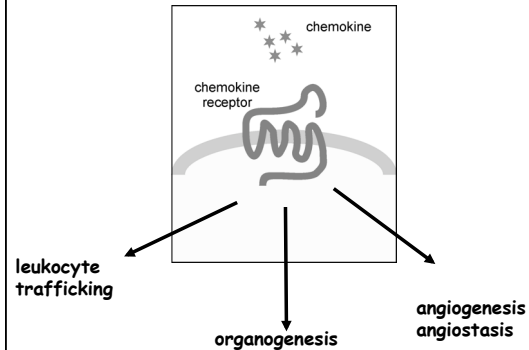
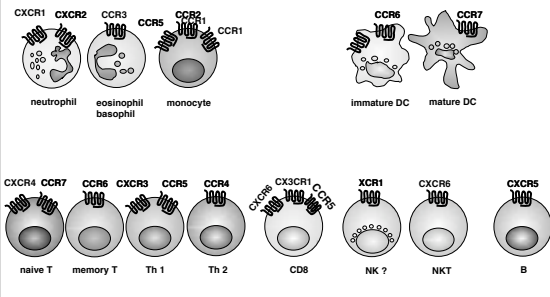


Figure 2-40 Immunobiology, 6/e. (© Garland Science 2005)

Chemokines are more than chemo-attractants



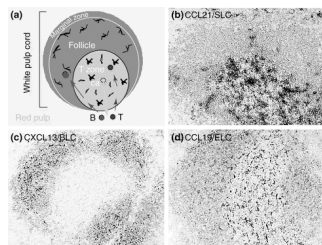
Leukocytes express unique sets of chemokine receptors that direct them to the appropriate target tissue



Functional Classification of Chemokines

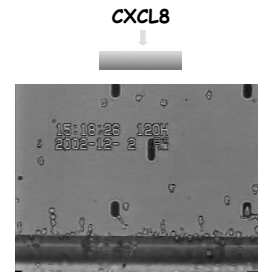
- Homeostatic Chemokines - Development of immune tissues
 - These chemokines direct the basal or homeostatic distribution of leukocytes to immune tissues.
 - Homeostatic chemokines include: "S1P", CCL19, CCL21, CXCL12, CXCL13
- Inflammatory Chemokines - Acute and chronic inflammation
 - e.g., Danger signals, many chemokines are involved in directing leukocyte traffic during infection & inflammation (chronic & acute).
 - Inflammatory chemokines include: CCL2, CCL5, CCL11, CXCL8, CXCL9, CXCL10
- There are some "double dippers"

Homeostatic chemokines target cells to appropriate compartment in the absence of inflammation e.g. lymphocytes and APCs to spleen or LN



Cell	Chemokine receptor	Chemokine sensed
DC	CCR7	CCL19, CCL21
naive T	CCR7	CCL19, CCL21
naive B	CXCR5	CXCL13

IL-8 / CXCL8 (human) is a potent inflammatory chemoattractant for PMNs



Of Note

- Two chemokine receptors serve as co-receptors for HIV infection (CXCR4 and CCR5)

Chemokine Summary*

- 8-12 kDa proteins secreted by WBCs, platelets, epithelial, endothelial, smooth muscle and fibroblast cells.
- Form **gradients** that act as chemoattractants for WBCs expressing the corresponding receptors
 - Inflammatory Chemokines - CCL2-5, CCL11, CCL17, CXCL8 (IL-8), CXCL9, CXCL10
 - Homeostatic Chemokines - S1P, CCL19, CXCL12, CCL21, CXCL13
- Bind GPCRs (G-protein coupled receptors).
- Chemokines also regulate the growth and development of some immune and non-immune tissues.
- There are several families of non-classical chemokines:
 - Lipid-based, e.g., sphingosine-1-phosphate (S1P; blocked by FTY720), LTB₄, PGD₂
 - Peptide-based, e.g., fMLP (bacterial-derived), C3a, C5a

***Do not memorize the list of individual chemokines, only the functional classes!**

Summary

1. Naive CD4⁺ T-cells mature into several distinct T cell subsets in a process that is driven by antigen and cytokines. These subsets include Th1, Th2, Th17 and Treg cells. Critical cytokine dependent feed forward and feedback loops drive/regulate this process.
2. Th1 cells - secrete IFN- γ and IL-2. IFN- γ potently activates macrophages to secrete pro-inflammatory cytokines and kill microbes. Th1 cells are also important for "Delayed Type Hypersensitivity," or DTH. IL-2 directs the proliferation of T-cells. Pathways leading to IL-2 production, especially those that activate NFAT, are important targets of immunosuppressive drugs (e.g., cyclosporin and FK506).
3. Th2 cells - secrete IL-4, which along with CD40, BAFF and MHC:Ag, potently activate B-cells. IL-4 also stimulates immunoglobulin class-switch IgG and IgE. Th2 cells, IL-4 and IL-5 afford important immunity against parasites (e.g., helminths).
4. Th17 cells - stimulate neutrophils during acute bacterial infections and many other cells during chronic inflammation (e.g., in autoimmunity).
5. Tregs - negatively regulate T-cells through secretion of IL-10 and TGF- β (More on 9-19-08)
6. Chemokines are small proteins that activate G-protein-coupled receptors and are essential for homeostatic and inflammatory leukocyte trafficking. They also regulate other important activities in target cells. GPCRs make great drug targets.