

Lecture 11

T-cell Effector Mechanisms-II: Cytokine Secretion & T-cell Polarization

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What do cytokines, chemokines and growth factors 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.

Blood: 4-10,000 WBC per 1 μL

Lymphocytes - 10-15 %



(T-, B- & NK cells)

Granulocytes - 35-80 %



PMNs
35-80 %



Eos
0-8 %



Basos
0-2 %

Monocytes - 0-15 %



(Macs & DCs)

How did they get there?
Where are they going?
What regulates them?

Think Cytokines, Chemo-
kines & Growth Factors !!

How many flavors regulate immunity?

- Growth Factors (e.g., CSF-1, SCF, RANKL, Flt3L)
- IL-1 Family (e.g., IL-1, IL-18 & "Toll-like")
- TNF Family (e.g., TNF- α , CD40L, FasL, LT- β , BAFF)
- TGF- β Family (e.g., TGF- β)
- Chemokines (e.g., CC and CXC families)
- Type I & II Cytokines (a.k.a. Hematopoietins or Four Helix Bundle (e.g., IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-15, GM-CSF, IFN- γ , IFN- α/β))
- Also steroid hormones and prostaglandins

What are cytokines and chemokines?

- Small (10-30 kDa), usually secreted and usually glycosylated peptides.
- They bind specific, high affinity (e.g., K_d of 10^{-10} - 10^{-12} M) receptors found on target cells.
- Expression of cytokines and their receptors is usually tightly regulated (i.e., temporally/ transiently and geographically).
- Cytokine receptors define the specific type of biological response cytokines stimulate.
- Other more anachronistic terms include monokines and lymphokines. The term interleukin (IL) is now commonly used (e.g., IL-1, IL-2, ...).

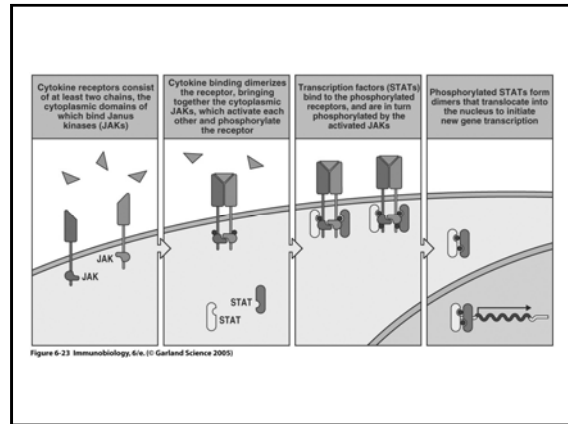
Cytokines & Chemokines can be grouped into functionally related Families

- There are significant functional similarities within each receptor family. The same is true for corresponding ligands (see summary).
- There are important functional differences between between receptor families (see summary).

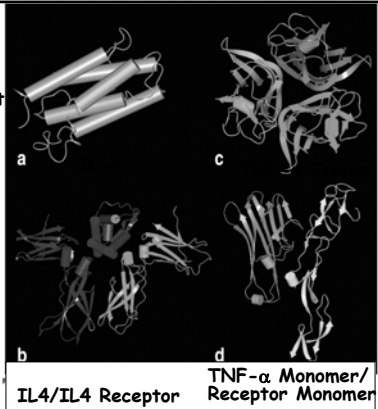
Cytokine Receptor Classes

Table 11-2. Signal Transduction Mechanisms of Cytokine Receptors

Signal transduction pathway	Cytokine receptors using this pathway	Signaling mechanism
JAK/STAT pathway	Type I and type II cytokine receptors	JAK-mediated phosphorylation and activation of STAT transcription factors (see Box 11-2)
TNF receptor signaling by TRAFs	TNF receptor family: TNF-R1, CD40	Binding of adapter proteins, activation of transcription factors (see Box 11-1)
TNF receptor signaling by death domains	TNF receptor family: TNF-R1, Fas	Binding of adapter proteins, caspase activation (see Box 11-1)
Receptor-associated tyrosine kinases	M-CSF receptor, stem cell factor receptor	Intrinsic tyrosine kinase activity in receptor
G protein signaling	Chemokine receptors	GTP exchange and dissociation of G α · GTP from G $\beta\gamma$; G α · GTP activates various cellular enzymes



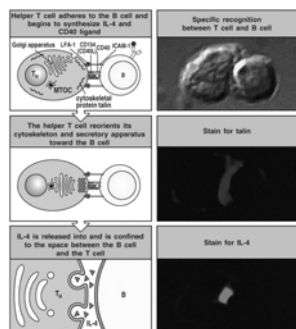
Consistent with their significant functional differences, IL-4 & TNF- α , and their corresponding receptors are structurally quite distinct.



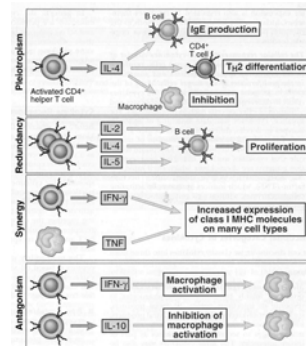
General functional properties of Cytokines and Chemokines

- Usually stimulate transient responses.
- Function at three ranges:
 - Autocrine - "self"
 - Paracrine - adjacent cells
 - Endocrine - through circulatory system
- **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).

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



Properties of Cytokines



Some Biology

Innate response to Virus Inflammatory Cytokines

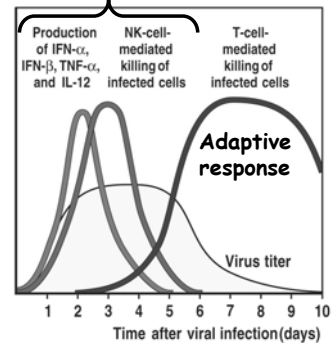
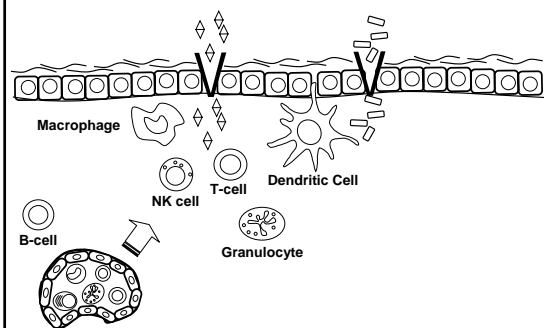
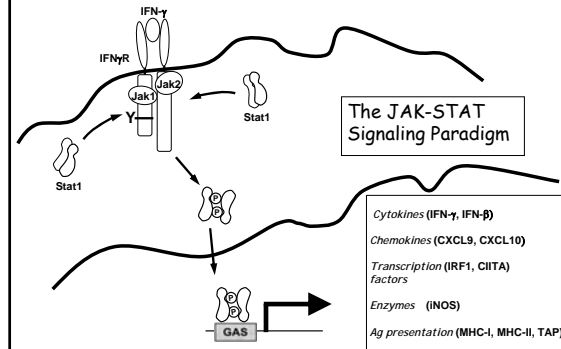


Figure 2-48 Immunobiology, 6/e. (© Garland Science 2005)

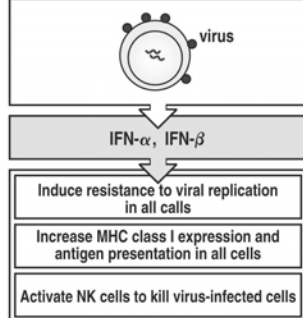
How do we protect ourselves from microbes? The antiviral response



Type I & II Cytokines mediate their biological response through the induction of genes



Virus-infected host cells



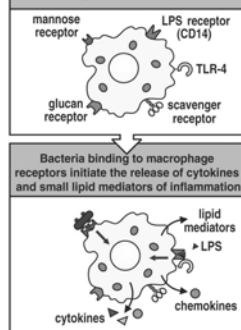
Cytokines initiate the innate immune response during a viral infection.

For adaptive CD8 immunity

An innate response

Figure 2-48 Immunobiology, 6/e. (© Garland Science 2005)

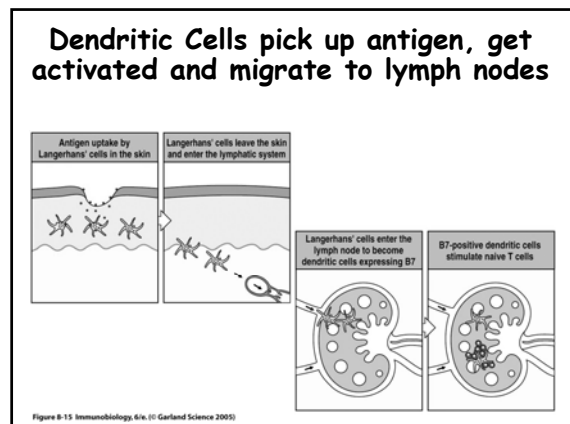
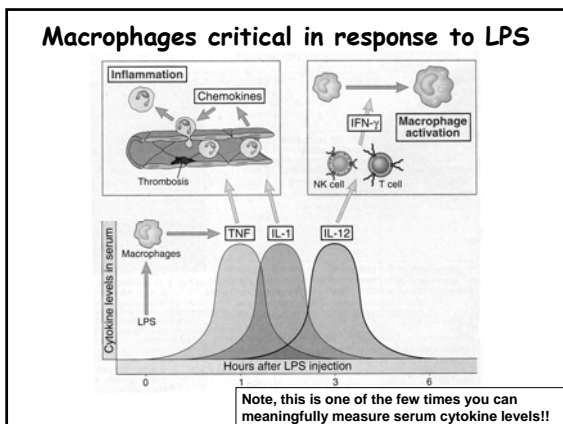
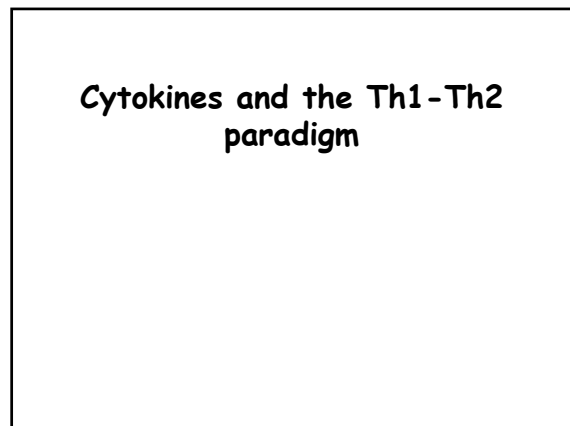
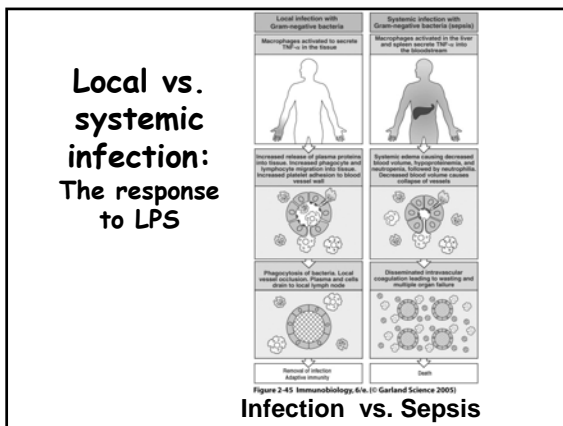
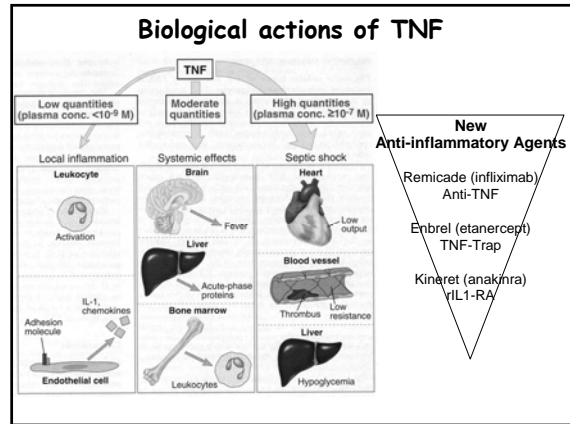
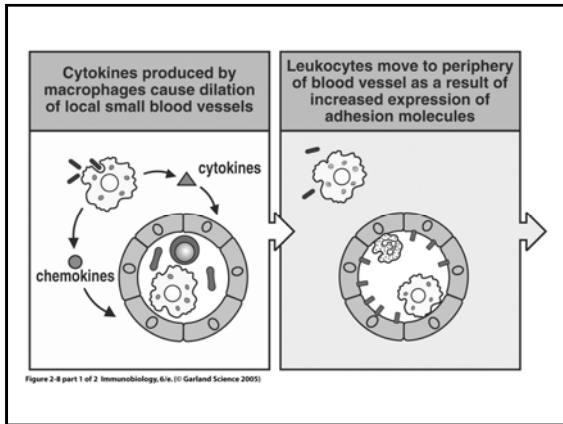
The macrophage expresses receptors for many bacterial constituents

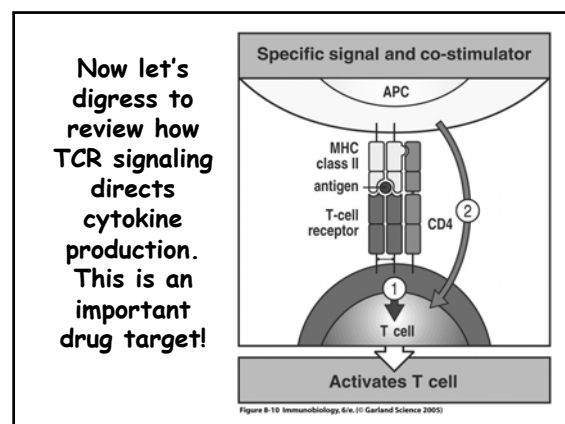
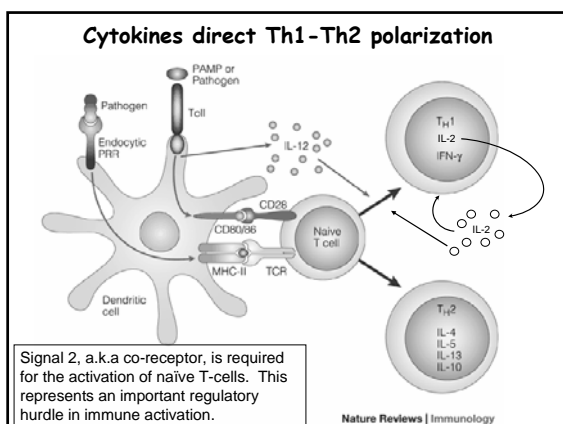
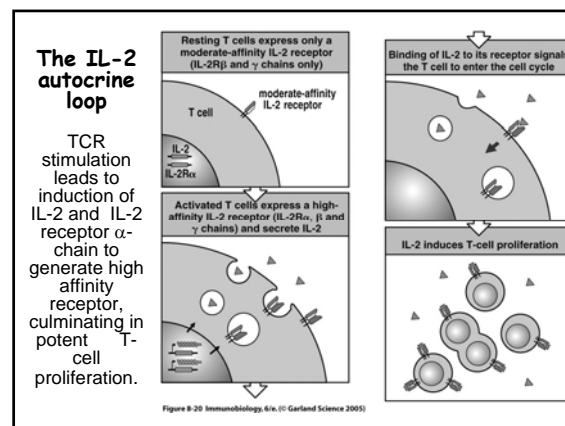
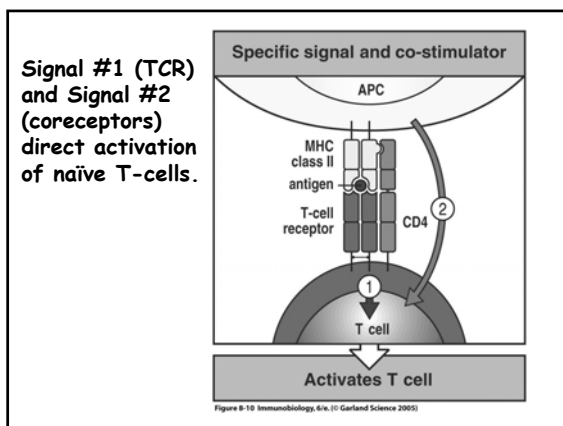
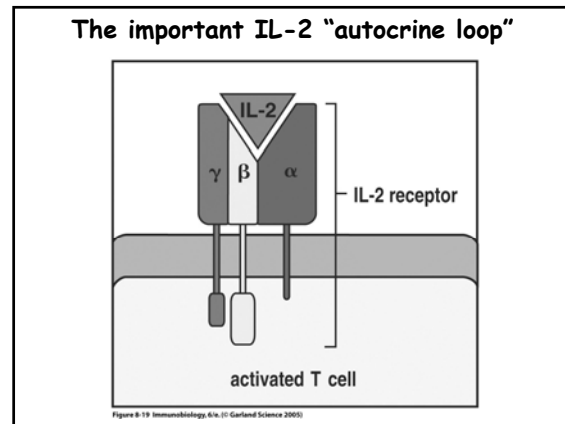
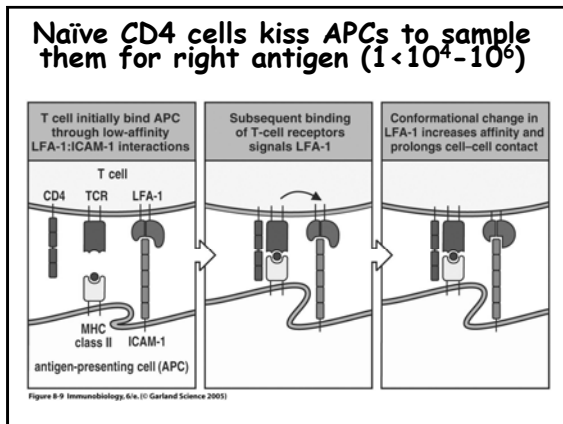


What about during a bacterial infection, how do macrophage and DC sentries sense and respond?

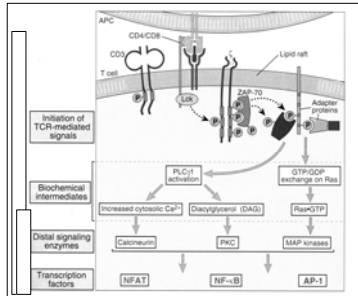
Local vs Systemic Response

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





TCR-mediated Signal Transduction: A Tyrosine Kinase Cascade



Important Th1 effector cytokines

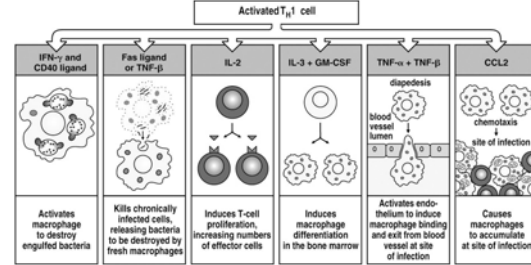
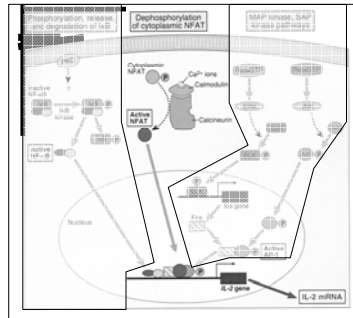


Figure 8-41 Immunobiology, 6/e. (© Garland Science 2005)

IFN-γ is the Th1 signature cytokine

NF-AT & TCR-mediated signal transduction culminate in cytokine production

Cyclosporin A (CyA) & Tacrolimus (FK506) are two important drugs that block calcineurin activation of NFAT activation of IL-2 production! They are therefore potent immunosuppressive drugs.



Important Th2 effector cytokines IL-4, IL-5 & IL-6 promote humoral immunity

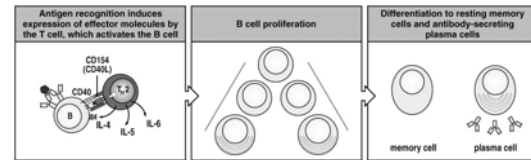
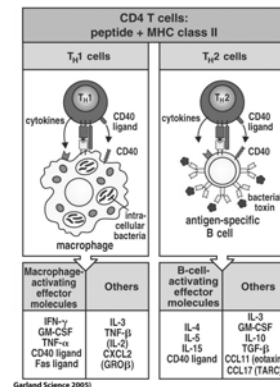


Figure 9-5 Immunobiology, 6/e. (© Garland Science 2005)

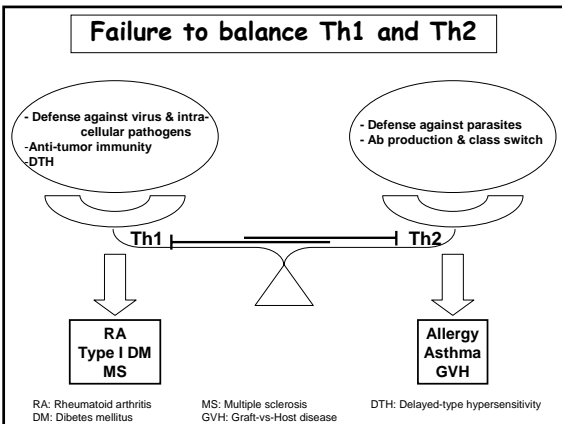
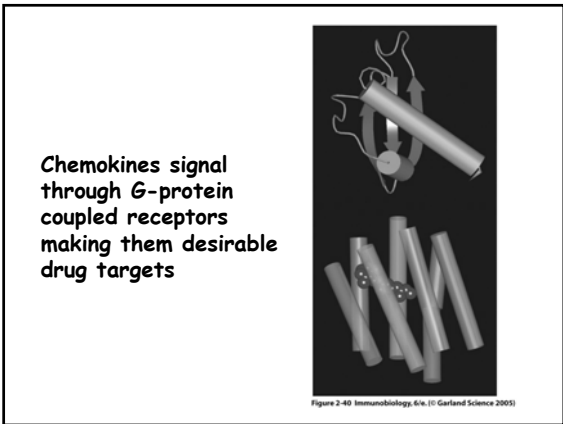
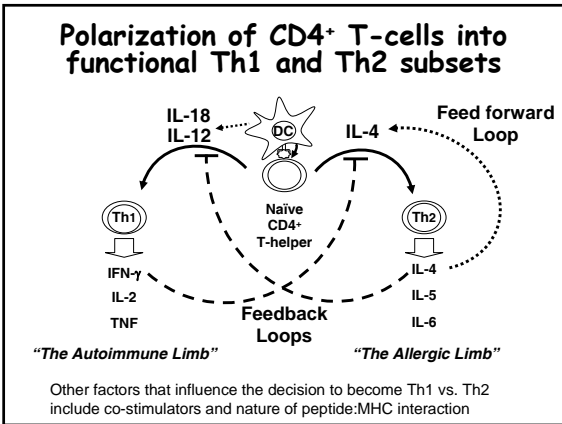
Th1 and Th2 cells each secrete signature cytokines & chemokines that define their effector functions.



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IL-4, the signature Th2 effector cytokine regulates B-cells, . . . and IL-10 & TGF-β potently antagonize cellular immunity (think regulatory T-cells).

CCL11/17



Chemokine Redundancy

Chemokine receptor	Legend (chemokines)	Function
HIV Co-receptor	CCR1	Original name
	CCR2	CCR2
	CCR3	CCR3
	CCR4	CCR4
	CCR5	CCR5
	CCR6	CCR6
	CCR7	CCR7
	CCR8	CCR8
	CCR9	CCR9
	CCR10	CCR10
HIV Co-receptor	CCR1	CCR1
	CCR2	CCR2
	CCR3	CCR3
	CCR4	CCR4
	CCR5	CCR5
	CCR6	CCR6
	CCR7	CCR7
	CCR8	CCR8
	CCR9	CCR9
	CCR10	CCR10

Abbott Chpt. 11

Secreted by Macrophage
Secreted by Th1 cells
Induced by IFN-γ
Secreted by Th2 cells
*Inflammatory
*Homeostatic

Chemokines

Leukocytes express unique sets of chemokines receptor signatures allowing them to be targeted to the appropriate tissues either homeostatically or drive an inflammatory response.

QuickTime™ and a GIF decompressor are needed to see this picture.

Homeostatic targeting of lymphocytes and APCs in the spleen

QuickTime™ and a GIF decompressor are needed to see this picture.

Cell	Chemokine receptor	Chemokine sensed
DC	CCR7	ELC, SLC
naïve T	CCR7	ELC, SLC
naïve B	CXCL5	BLC

Cytokines you should know

Type I & II Cytokine Receptors (JAK-STAT)	<ul style="list-style-type: none"> IL-2 -Th1 cytokine ⇒ T-cell proliferation IL-4 -Th2 cytokine ⇒ B-cell proliferation; Th2 polarization IL-6 -Th2 cytokine ⇒ B-cell proliferation; Plasma cell growth IL-10 -Th2 cytokine ⇒ antagonizes cellular immunity IL-12 -DC cytokine ⇒ drives Th1 polarization IFN-γ -Th1 cytokine ⇒ drives inflammation; Mac. Activation; DTH IFN-α -All cells make this antiviral cytokine
Toll (TLR) /IL-1 Receptors (NFκB)	<ul style="list-style-type: none"> IL-1 -Potent activator of inflammation & innate immunity TLR -Potent activators of innate and adaptive immunity
TNF Related Receptors (NFκB vs. Caspases)	<ul style="list-style-type: none"> TNF -Potent activator of inflammation & innate immunity (arthritis) CD40L - T-cell help (survival/proliferation) to B-cells FasL -Induces cell death: to achieve negative selection; to terminate an immune response
TGF-β Receptors	<ul style="list-style-type: none"> TGF-β -Antagonizes cellular immunity and promotes wound healing
Chemokine Receptors (GPCRs*)	<ul style="list-style-type: none"> Chemokines (see Fig. 11.6) Inflammatory (e.g., CCL11, CCL17, CXCL2, CXCL8/9/10) Non-inflammatory (i.e. homeostatic; e.g., CCL19, CCL21, CXCL-12, CXCL-13, S-1P)

*G-Protein Coupled Receptors -Good drug targets

CXCL12

Chemokines are much more than just chemo-attractants

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CXCR4

Of Note

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