Lectures 12
Cytokines and Immune Response

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Reading: Janeway - as indicated
Abbas - Chapter 11

- Small proteins that bind to specific receptors on target cells.
- The expression of cytokines and their receptors is tightly regulated (temporally and geographically).
- They direct the development, maturation, localization, interactions, activation and life span of immune cells.
- These ligands function at three distinct ranges: autocrine, paracrine and endocrine.

Quick review of cytokines, chemokines & growth factors

- Pleiotropism - activate numerous types of responses, e.g., differentiation, growth, activation and chemotaxis.
- Redundancy - i.e., functional overlap.
- Synergy - between cytokines to maximize a response.
- Antagonism - to regulate duration and potency of response. It is critical to maintain a delicate balance to avoid autoimmunity.
- Feedback and Feedforward Loops - for negative and positive (e.g., signal amplification) regulation.

Properties of cytokines and chemokines

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Properties of Cytokines

- Growth Factors (direct hematopoiesis and endothelial cell growth/activity)
- IL-1 Family (e.g., IL-1 & "Toll-like")
- TNF Family (e.g., TNF-α, CD40L, FasL)
- TGF-β Family (e.g., TGF-β)
- Chemokines (e.g., CC and CXC families)
- Hematopoietins / a.k.a. Four Helix Bundle (e.g., IL-2, IL-4, IL-6, IL-10, IL-12, IFN-γ, IFN-α/β)

Cytokines, chemokines and growth factors can be placed into several structurally & functionally related families

- Growth Factors (direct hematopoiesis and endothelial cell growth/activity)
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Cytokines and the Th1-Th2 paradigm

- Naive CD4+ T-helper cells are activated into different types of effector T-cells.
- We will focus on the development of Th1 and Th2 effector cells.
**Important Th1 effector cytokines**

**The IL-2 autocrine loop**

- Stimulation of the low affinity IL-2 receptor leads to induction of high-affinity IL-2 receptor (IL-2Rα, γ chain) and IL-2.
- IL-2 induces T-cell proliferation.

**CD4 T cells:**
- Peptide + MHC class II

**T<sub>H</sub>1 cells:**
- Activates macrophages; induces B cells to produce neutralizing antibody; has various effects on macrophages

**T<sub>H</sub>2 cells:**
- Activates B cells to produce neutralizing antibody; has various effects on macrophages

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**CD4 T cell network:**
- Proliferating T cell
- Immature effector T cell (T<sub>eff</sub>)

**T<sub>H</sub>1 cell**
- Activates macrophages; does various effects on macrophages

**T<sub>H</sub>2 cell**
- Activates B cells to produce neutralizing antibody; does neutral effects on macrophages

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**Naive CD4 T cell**
- Activates macrophages; induces B cells to produce neutralizing antibody

**Proliferating T cell**
- Activates B cells to produce neutralizing antibody; does various effects on macrophages

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**Figure 8-24**

**Figure 8-27**

**Figure 8-31**

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**Most of Fig. 8-19**

**Most of Fig. 8-27**

**Most of Fig. 8-31**

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**Activated T<sub>H</sub>1 cell**
- IL-2
  - IL-2 receptor
  - Activates T cell

**IL-2 loop**
- Stimulation of the low affinity IL-2 receptor leads to induction of high-affinity IL-2 receptor (IL-2Rα, γ chain) and IL-2, culminating in potent T-cell proliferation.
Let’s digress to review TCR signaling for an important clinical pearl!

TCR-mediated Signal Transduction: A Tyrosine Kinase Cascade

NF-AT and TCR-mediated Signal Transduction

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

IFN-γ is considered the Th1 signature cytokine.

IL-4, IL-5 and IL-6 are Th2 cytokines and promote humoral immunity

IL-4 is the signature Th2 effector cytokine

IL-10 and TGF-β are also Th2 important effector cytokines that potently antagonize cellular immunity.
Polarization of CD4+ T-cells into functional Th1 and Th2 subsets

- IL-12
- IL-4
- Naïve CD4+ T-helper

Th1
- IL-2
- IFN-γ

Th2
- IL-4
- IL-5
- IL-6

"The Autoimmune Limb"  "The Allergic Limb"

Pathophysiology of the balance between Th1 and Th2

- Defense against virus & intra-cellular pathogens
- Anti-tumor immunity DTH
- Defense against parasites
- Ab production & class switch

Rheumatoid arthritis
Type I Diabetes mellitus
Multiple sclerosis

Allergy
Graft-vs-host disease

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

Leukocytes express unique sets of chemokines receptors allowing them to be targeted to the appropriate tissues.

FYI - some of the chemokine leukocyte specific activities

<table>
<thead>
<tr>
<th>Monocytes</th>
<th>Neutrophils</th>
<th>Naive T</th>
<th>Activated T</th>
<th>NK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCL2</strong></td>
<td>CCL3</td>
<td>CCL1,2</td>
<td>CCL2 (TH1)</td>
<td>CCL2</td>
</tr>
<tr>
<td>CCL4</td>
<td>CCL1,2</td>
<td>CCL12</td>
<td>CCL2</td>
<td>CCL4</td>
</tr>
<tr>
<td>CCL5</td>
<td>CCL8</td>
<td>CCL5</td>
<td>CCL3 (TH1)</td>
<td>CCL4</td>
</tr>
<tr>
<td>CXCL10</td>
<td>CXCL8</td>
<td>CXCL10</td>
<td>CCL3</td>
<td>CCL5</td>
</tr>
<tr>
<td>CXCL5</td>
<td></td>
<td>XCL1</td>
<td>CCL10 (TH1)</td>
<td>CCL5</td>
</tr>
</tbody>
</table>

** Activating chemokine

Non-inflammatory (i.e., development/homing vs. inflammatory chemokines

Chemokines are much more than just chemoattractants

CXCL12

** Activating chemokine

Chemokine Redundancy

Abbas: Chpt. 11
Of Note . . .

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

How many flavors regulate immunity?

• Growth Factors (e.g., CSF-1, SCF)
• IL-1 Family (e.g., IL-1, IL-18 & “Toll-like”)
• TNF Family (e.g., TNF-α, CD40L, FasL, LT-β)
• TGF-β Family (e.g., TGF-β1)
• Chemokines (e.g., CC and CXC families)
• Hematopoietins / a.k.a. Four Helix Bundle (e.g., IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, GM-CSF, IFN-γ, IFN-α/β)
• Also steroid hormones and prostaglandins

Cytokine Receptor Classes

<table>
<thead>
<tr>
<th>Signal transduction pathway</th>
<th>Cytokine receptors using this pathway</th>
<th>Signaling mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK/STAT pathway</td>
<td>Tyk2 and Jak1/2 receptor</td>
<td>JAK-mediated phosphorylation and activation of STAT transcription factors (see Box 15-2)</td>
</tr>
<tr>
<td>TNF receptor signaling by TRAF5</td>
<td>TNF receptor family: TRAF5, TRAF2, TRAF6</td>
<td>Binding of adapter proteins, activation of transcription factors (see Box 15-1)</td>
</tr>
<tr>
<td>TNF receptor signaling by death domain</td>
<td>TRAF receptor family: TRAF2, Fas</td>
<td>Binding of adapter proteins, caspase activation (see Box 15-1)</td>
</tr>
<tr>
<td>Receptor associated tyrosine kinases</td>
<td>M-CSF receptor, chemokine receptor</td>
<td>Mediates tyrosine kinase activity in receptor</td>
</tr>
<tr>
<td>Upstream signaling</td>
<td>Chemokine receptor</td>
<td>G-protein exchange and downstream of Gαi; GTP activates various cellular responses</td>
</tr>
</tbody>
</table>

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