Lectures 10 (linked to 12)
Cytokines and Immune Response
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Chris Schindler
cws4@columbia.edu
Reading: Janeway - as indicated
Abbas - Chapter 11

Blood: 4–10,000 WBC per 1 µL
Lymphocytes - 10-15 %
(T-, B- & NK cells)
Granulocytes - 35-80 %
(PMNs, Eos, Basos)
Monocytes - 0-15 %
(Macs & DCs)

How did they get there?
Where are they going?
What regulates them?
Think Cytokines, Growth Factors & Chemokines!!!

What are cytokines and chemokines?

- Small (10–30 kDa) secreted peptides (usually glycosylated).
- They bind to specific receptors on target cells to elicit a specific biological response.
- Expression of cytokines and their receptors is usually tightly regulated.
- Other more anachronistic terms include monokines and lymphokines.

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 immunity (adaptive and innate).

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-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, IL-13, GM-CSF, IFN-γ, IFN-α/β)
- Also steroid hormones and prostaglandins

Other important facts about Cytokines, Chemokines & Growth Factors

- There are functional similarities within ligand families (see summary).
- There are important functional differences between ligand families (see summary).
- These functional characteristics are determined by the class of receptors these ligands bind.
- These ligands function at three distinct ranges:
  - Autocrine*
  - Paracrine*
  - Endocrine*

*Make sure you have an example of each.
Additional important concepts

- Properties of cytokines and chemokines.
  - 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.

- Innate vs. Adaptive Immunity

  **Innate Immunity**
  - Per-wired first line of defense (more primitive)
  - Recognizes ~10^3 pathogen derived molecules (analogous to antigens)
  - Most important during initial minutes and hours of infection
  - Macrophages, Granulocytes and NK cells

  **Adaptive Immunity**
  - Second, but very potent line of defense
  - Antigen specific response - recognizes ~10^7 antigens
  - Constitutes immunological memory for specific antigens
  - T-cells and B-cells

Cytokines and the innate response to a viral infection

- The innate response is often quite effective
- The subsequent adaptive immune response is important for many viral pathogens and very important for immunization strategies

Innate Viral Interfering Activity is Discovered in Cultured Cells (1950s)

Fractionating Viral Interfering Activity Leads to the Discovery of Interferons (IFNs)

Type II IFN Signaling Paradigm
Identification of “High IFN Producing Cells” (HIPCs) in vivo

A small subset of WBCs produce most of the circulating IFN-Is

Cytokines and the innate response to a skin infection

Wound Infection: Innate - Adaptive

The macrophage expresses receptors for many bacterial constituents
Cytokines and the response to sepsis

- Injection of LPS (a molecular pattern molecule found on G- bacteria) is a model system for sepsis.
- The host response to sepsis is often referred to as the Acute Phase Response (APR).
TLR-4 and company enable macrophages to sense and respond to LPS (to be covered in detail in a later lecture)

Serum cytokine production (from Macrophages) during Septic Shock

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

IL-4 & TNF-α, and their corresponding receptors, are in two different families and have two distinct types of structures.

Top half of Fig. 2-47
### V. Cytokines you need to know

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Innate</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 (big family e.g. IL-7 &amp; IL-15)</td>
<td></td>
<td>✓ ✓</td>
</tr>
<tr>
<td>IL-4 (small family Inc. IL-13)</td>
<td></td>
<td>✓ ✓</td>
</tr>
<tr>
<td>IL-6 (large family Inc. G-CSF)</td>
<td></td>
<td>✓ ✓</td>
</tr>
<tr>
<td>IL-10 (growing family)</td>
<td></td>
<td>✓ ✓</td>
</tr>
<tr>
<td>IL-12 (small family Inc. IL-23)</td>
<td></td>
<td>✓ ✓</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>✓ ✓</td>
<td></td>
</tr>
<tr>
<td>IFN-α (large family)</td>
<td>✓ ✓</td>
<td></td>
</tr>
<tr>
<td>IL-1</td>
<td>✓ ✓</td>
<td></td>
</tr>
<tr>
<td>IL-18</td>
<td>✓ ✓</td>
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<tr>
<td>LT-α</td>
<td>✓ ✓</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>✓ ✓</td>
<td></td>
</tr>
<tr>
<td>CD40L</td>
<td>✓ ✓</td>
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</tr>
<tr>
<td>FasL</td>
<td>✓ ✓</td>
<td></td>
</tr>
<tr>
<td>TGF-β (very large family)</td>
<td>✓ ✓</td>
<td></td>
</tr>
<tr>
<td>Chemokine Receptors</td>
<td>Chemokines (see Fig. 11.8)</td>
<td>Inflammatory</td>
</tr>
<tr>
<td></td>
<td>Non-inflammatory</td>
<td></td>
</tr>
</tbody>
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