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 can act in an:
- **Autocrine** (same cell),
- **Paracrine** (close proximity),
- **Endocrine** (long distance)

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.

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

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

6. Cytokines can influence the expression of **cytokine receptors**.

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

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.
There are many cytokines, including...

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cytokine</th>
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<tbody>
<tr>
<td>IL-1</td>
<td>IL-2</td>
<td>IL-3</td>
<td>IL-4</td>
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<td>IL-5</td>
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<td>IL-18</td>
<td>IL-19</td>
<td>IL-20</td>
<td>IL-21</td>
</tr>
<tr>
<td>IL-22</td>
<td>IL-23</td>
<td>IFN-α</td>
<td>IFN-β</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>TNF-α</td>
<td>TNF-β</td>
<td>TGF-β1</td>
</tr>
<tr>
<td>M-CSF</td>
<td>G-CSF</td>
<td>GM-CSF</td>
<td></td>
</tr>
</tbody>
</table>

Four Structural Families

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

Best way to learn about cytokines... is by their action !!!

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

- Ig superfamily receptors
- Interferon receptors
- TNF receptor superfamily
- Chemokine receptors
- TGF receptor family
- Hematopoietin receptors (Cytokine receptor superfamily)
Three subfamilies of the class I cytokine receptor family (hematopoietin)
**Cytokine receptors**

- Sharing of signal transducing molecules explains the **redundancy** and **antagonism** exhibited by some 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, IL-2Rα), medium affinity (dimeric, IL-2Rαβ), and high affinity (trimeric, IL-2Rαβγ)
- Binding component: α chains
- Transducing components: β and γ chains.
Only in activated T cells

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

Kuby Fig 12-10b

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

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

*Despite its name, Tyk-2 is also a Janus kinase.

Helper T cells can be divided into two main types - T\(_H\)1 and T\(_H\)2 - with distinct patterns of cytokine secretion.

<table>
<thead>
<tr>
<th>Cytokine/Function</th>
<th>T(_H)1</th>
<th>T(_H)2</th>
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</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>IFN-(\gamma)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>TNF-(\alpha)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IL-3</td>
<td>+</td>
<td>+</td>
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<tr>
<td>IL-4</td>
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<td>IL-5</td>
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<td>IL-6</td>
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<td>IL-13</td>
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<td>+</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**T\(_H\)1/T\(_H\)2 differentiation is influenced by the levels of key cytokines:**

- **IL-4** promotes T\(_H\)2 differentiation.
- **IFN-\(\gamma\)** and **IL-12** promotes T\(_H\)1 differentiation.

**Cytokine cross-regulation**

- IFN-\(\gamma\) (Th-1) inhibits proliferation of Th-2
- IL-4 and IL-10 (Th-2) inhibits proliferation of Th-1 by decreasing IL-12 production
- INF-\(\gamma\) (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.

**Cytokine & Diseases**

- **Bacterial Septic Shock**
  - Due to several Gram (-) bacteria
  - Stimulation of Macrophages by LPS \(\rightarrow\) ↑ TNF-\(\alpha\), IL-1\(\beta\)
  - 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 \(\rightarrow\) ↑ cytokines from T cells and activated MØ
- **Infectious Diseases**
  - Leprosy, Chagas Disease.
Relative predominance of Th1 vs Th2 helper T cells can influence the course of infectious disease (Mycobacterium leprae)

<table>
<thead>
<tr>
<th>Th1 activity</th>
<th>Th2 activity</th>
</tr>
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<tbody>
<tr>
<td>Tuberculoïd</td>
<td>Lepromatous</td>
</tr>
<tr>
<td>IL-2</td>
<td>IL-4</td>
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<tr>
<td>IFN-γ</td>
<td>IL-5</td>
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<tr>
<td>TNF-β</td>
<td>IL-10</td>
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</tbody>
</table>

Tuberculoïd - ↑ CMI (granulomas) - No RIP
Lepromatous - ↑ 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

Glucocorticoid hormones can influence ongoing immune responses - particularly suppressing inflammatory responses.

Sex hormones also influence immune responses - e.g. females tend to be more prone to autoimmune disorders than males.

Stress may suppress Th1 immune responses.

The End, but interesting material next!!

Macrophage activation by Th1 Cells:

Macrophage activation by Th2 Cells:
EFFECTOR ROLE OF Th1 CELLS:
1) Cytotoxicity
2) ↑ Phagocytosis
3) ↑ Opsonizing & complement fixing Abs

EFFECTOR ROLE OF Th2 CELLS:
1) IgE production
2) IgA production
3) Eosinophil recruitment
4) Basophil & Mast cell recruitment