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)

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.

(a)

<table>
<thead>
<tr>
<th>Antagonism</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated T helper cells</td>
<td>IFN-γ blocks class switch to IgG1 induced by IL-4</td>
</tr>
<tr>
<td>B cell</td>
<td>IgG1 or IgG3</td>
</tr>
</tbody>
</table>

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

6. Cytokines can influence the expression of cytokine receptors.

<table>
<thead>
<tr>
<th>Receptor transduction</th>
<th>Up regulation</th>
<th>Down regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGFβ</td>
<td>Positive IL-2 RECEPTOR</td>
<td>Negative IL-2 RECEPTOR</td>
</tr>
<tr>
<td>IL-4</td>
<td>α</td>
<td>β</td>
</tr>
</tbody>
</table>

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:

- IL-1
- IL-2
- IL-3
- IL-4
- IL-5
- IL-6
- IL-7
- IL-8
- IL-9
- IL-10
- IL-11
- IL-12
- IL-13
- IL-15
- IL-16
- IL-17
- IL-18
- IL-19
- IL-20
- IL-21
- IL-22
- IL-23
- IFN-α
- IFN-β
- IFN-γ
- TNF-α
- TNF-β
- TGF-β1
- M-CSF
- G-CSF
- GM-CSF

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

Cytokines and Immune Responses

**Proinflammatory cytokines**
- TNF
- IL-1
- IL-6
- IL-12
- IL-18

**Antinflammatory cytokines**
- IL-10
- IL-13
- TGF-β

**Inhibition of virus replication**
- IFN-α, IFN-β

**Macrophage-activating cytokines**
- IFN-γ

**B cell-activating cytokines**
- IL-4
- IL-5
- IL-6
- IL-7
- IL-10
- IL-12
- IFN-γ

**Essential and/or mast cell-activating cytokines**
- IL-3
- IL-4
- IL-5
- IL-13

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

- Ig superfamily receptors
- Class I receptors (Hematopoietin receptor family)
- Class II receptors (Interferon receptor family)
- TNF receptor family
- Chemokine receptors
- TGF receptor family

Four Structural Families

- Hematopoietin Family (IL-2, IL-4)
- Interferon Family (IFN-α, β, γ)
- Chemokine Family
- Tumor necrosis family
Three subfamilies of the class I cytokine receptor family (hematopoietin)

(e) Chemokine receptors

LIGANDS
- IL-8
- RANTES
- MIP-1
- PF4
- MCAF
- NAP-2

(e) Chemokine receptors

G-protein

RECEPTOR FAMILY
Immunoglobulin superfamily receptors

LIGANDS
- IL-1
- M-CSF
- C-Kit
- IL-18

Class I cytokine receptors (hematopoietin)

LIGANDS
- IL-2
- IL-21
- IL-4
- IL-27
- IL-5
- IL-23
- IL-6
- IL-24
- IL-7
- G-CSF
- OSM
- IL-9
- LIF
- IL-11
- CNTF
- IL-12
- Growth hormone
- IL-13
- Prolactin
- IL-15

Class II cytokine receptors (interferon)

LIGANDS
- IFN-α
- IFN-β
- IFN-γ
- IL-10
- IL-19
- IL-20
- IL-22
- IL-24
- IL-26
- IL-28
- IL-29

TNF receptors

LIGANDS
- TNF-α
- TNF-β
- CD27L
- CD30L
- CD40L
- Nerve growth factor (NGF)
- FAS

(e) Chemokine receptors

LIGANDS
- IL-8
- RANTES
- MIP-1
- PF4
- MCAF
- NAP-2

(e) Chemokine receptors

G-protein
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.

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**Competition of ligand-binding chains of different receptors for a common subunit.**

This can result in antagonistic effects between cytokines.
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>Jak1</th>
<th>Jak2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>Jak1 and Jak2</td>
<td>Stat1*</td>
</tr>
<tr>
<td>IFN-αβ</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>Stat3</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>


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**Cytokine Antagonists**

**Action:**
1. Blocking the receptor (IL-1Ra), and
2. Binding to the cytokine (IL-2, IFN-γ)

**Table 12-3** Viral mimics of cytokines and cytokine receptors

<table>
<thead>
<tr>
<th>Virus</th>
<th>Soluble IFN-γ receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leporipoxivirus (a myxoma virus)</td>
<td>Soluble IFN-γ receptor</td>
</tr>
<tr>
<td>Several poxviruses</td>
<td>Soluble IFN-γ receptor</td>
</tr>
</tbody>
</table>

**Table 12-4** Cytokine secretion and principal functions of helper T1 (Th1) and T2 (Th2) subsets

<table>
<thead>
<tr>
<th>Cytokine secretion</th>
<th>Th1</th>
<th>Th2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INF-γ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-β</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM-CSF</td>
<td></td>
<td></td>
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<tr>
<td>IL-4</td>
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<tr>
<td>IL-5</td>
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<tr>
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<td>IL-13</td>
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</tr>
</tbody>
</table>

**Functions**

- INF-γ promotes Th2 differentiation
- IL-12 promotes Th1 differentiation
- IL-12R = β1,β2

**Figure 10.7**

**Helper T cells can be divided into two main types - Th1 and Th2 - with distinct patterns of cytokine secretion.**

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**T**h1 cells produce cytokines (IFN-γ and IL-2) that promote immune responses against intracellular pathogens (DTH, cytotoxic T cell responses, macrophage activation, opsonizing Abs).

**T**h2 cells produce cytokines (IL-4, IL-5, IL-6, IL-13) that promote immune responses against extracellular pathogens (antibody responses IgE/IgG1, eosinophilic responses, allergic reactions).

Some cytokines are produced by both Th1 and Th2 cells. These cytokines - GM-CSF and IL-3 - act on the bone marrow to increase production of leukocytes - so they are needed no matter what type of pathogen is present.
Transcription factors can be used to characterize Th lineage

Cytokine cross-regulation

- IFN-γ (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-γ (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.

Transcriptional Regulation of Cytokines

- Bacterial Septic Shock
  - Due to several Gram (-) bacteria
  - Stimulation of Macrophages by LPS → ↑ TNF-α, IL-1β
  - 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 → ↑ cytokines from T cells and activated MØ (↑ TNF-α, IL-1β)
  - Infectious Diseases
    - Leprosy, Chagas Disease (↓ IL-2Rα).

Cytokine & Diseases

- Relative predominance of T\(_{H1}\) vs T\(_{H2}\) helper T cells can influence the course of infectious disease (Mycobacterium leprae)

<table>
<thead>
<tr>
<th>T(_{H1}) activity</th>
<th>T(_{H2}) activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculoid</td>
<td>Lepromatous</td>
</tr>
<tr>
<td>Tuberculoid</td>
<td>Lepromatous</td>
</tr>
</tbody>
</table>

- IL-1, IL-6 and TNF-α can induce production of glucocorticoids by acting on the hypothalamic-pituitary-adrenal (HPA) axis.
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!!
EFFECTOR ROLE OF Th2 CELLS:
1) IgE production
2) IgA production
3) Eosinophil recruitment
4) Basophil & Mast cell recruitment

Other pathways may also be involved in cytokine signaling.