Lecture 4: Cytokines & TLR

Cytokines (chemokines, lymphokines, interleukins [IL]):

Small glycoproteins secreted by immune and other cells that influence cellular behavior by facilitating communication between cells. Many have trivial, uninformative, names e.g. TNFα - tissue necrosis factor α, IL-8, etc.

Key Cell Types: T<sub>H</sub> cells, dendritic cells, macrophages

Nomenclature of Cytokine Families:

- Receptors: Most cytokine receptors contain multiple chains:
  1. one specific for the cytokine
  2. involved in signaling, often shared.

Effects:

1. Form concentration gradients leading to chemotaxis of cells (chemokines).

2. These are often very powerful mediators of cell function. Yet they are specific and avoid affecting cells (innocent bystanders) they shouldn’t.

3. Show a wide range of action at a distance.
   1. autocrine
   2. paracrine
   3. endocrine

4. Exhibit pleiotropy, one cytokine can have many different effects.
   IL-4 activates both B cells & Mast cells.

5. Redundant- different cytokines have same effect. IL-2 and IL-4 all activate B-cells.

6. Synergistic – combination of IL-4 & IL-5 induce production of certain antibodies.
7. Antagonistic: INF-γ blocks production of a certain antibody type by B cells.

8. Receptors may contain different numbers of chains (IL2Rγ, IL2Rαγ), with different affinities

**Cytokine Signal Pathways:**

**Chemokines:** Typically signal via G-protein coupled receptors.

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**Cytokines: Dimerization and activation of kinases (JAK/STAT)**
- JAK- Janus (two faced) kinase.
- STAT-signal transduction and activation of transcription (STAT 1-6)
Toll-like receptors (TLR) have specificity for components of pathogens. These components are additional examples of PAMPs (pathogen associated molecular patterns).

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ligand</th>
<th>Path.</th>
<th>Cell types</th>
<th>Location of receptor</th>
<th>Cytokines produced</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR3</td>
<td>dsRNA</td>
<td>viruses</td>
<td>NK &amp; others</td>
<td>Endosome</td>
<td>IFN-α, IFN-β</td>
</tr>
<tr>
<td>TLR4</td>
<td>Lipopolysaccharide</td>
<td>bacteria</td>
<td>Macrophage</td>
<td>Surface</td>
<td>TNFα + inflammatory cytokines.</td>
</tr>
</tbody>
</table>

![Diagram showing TLRs and their ligands](image)

Peptidoglycan (Gram-positive)
Lipoteichoic acids (Gram-negative)
Lipoproteins
Lipoteichoic acids
Lipoarabinomannan
(Mycobacterium)
Zymosan (yeast)

LPS (Gram-negative)
Endogenous ligands
Flagellin

TLR3, TLR4
TLR5
TLR7
TLR9

Endosome

TLR3: KLC specific to pathogens

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