

Lec9 PART 2 Summary, Cytokines

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Cytokines Produced by Innate Immune Responses

Cytokine	Produced by	Function
IL-1 and TNF-alpha	Monocytes, macrophages, neutrophils	<ul style="list-style-type: none"> - Stimulate synthesis of adhesion factors on endothelial cells and leukocytes to aid cell migration. - Affect the hypothalamus to increase prostaglandin synthesis, causing fever. process inhibited by aspirin. - Stimulate production of acute phase proteins from the liver.
IL-12	Dendritic cells, macrophages	<ul style="list-style-type: none"> - Activates CD8 T cell differentiation. - Promotes TH1 cell differentiation. - Activates NK cells. - Stimulates production of IFN-gamma.
Type I Interferons	Any virus-infected cell	<ul style="list-style-type: none"> - Induces uninfected cells to produce enzymes that degrade viral mRNA. - Blocks viral protein synthesis and replication in infected cells. - Aids in CD4 differentiation into TH1 cells. - Assists in CD8 activation to kill virus-infected cells. - Activates NK cells to target the virus. - Stimulates IFN-gamma production by activated T cells.
Interferon-alpha	Monocytes, macrophages	
Interferon-beta	Virus-infected cells, fibroblasts	

Chemokines

- **Neutrophil Recruitment** → Primarily mediated by **CXC** chemokines.
- **Monocyte Recruitment** → More dependent on **CC** chemokines.
- **Lymphocyte Recruitment** → Mediated by both **CXC** and **CC** chemokines.
- infection sites to **draining lymph nodes** → CC-chemokine receptor 7 (**CCR7**).
- **Neutrophil Migration**
 - Neutrophils express receptors for **CXCL8 (IL-8)**, produced by tissue-resident macrophages, the main chemokine supporting neutrophil migration into tissues.
- **Monocyte Migration**
 - Classical monocytes express **CCR2**, which **binds CCL2**, the primary chemokine for monocyte recruitment.



Cytokines that produced by Adaptive Immune Responses

Cytokine	Produced	Function
IL-2	Dendritic cells (DC), T cells, B cells	<ul style="list-style-type: none"> - Growth factor for Th1, Th2, and CD8 lymphocytes upon activation (3rd signal). - B7 ligates T-cell CD28, activating T cell to produce IL-2 and IL-2R. - Acts autocrine, causing cell to divide and differentiate to effector T cell.
IL-4	Th2 cells, B cells	<ul style="list-style-type: none"> - Stimulates production of IgE in B cells and promotes B-cell growth. - Antagonizes interferon-gamma, inhibiting cell-mediated immunity.
IL-5	Th2 cells	<ul style="list-style-type: none"> - Growth and activating factor for eosinophils, aiding defense against helminths. - Stimulates proliferation and differentiation of antigen-activated B lymphocytes.
IL-13	Th2 cells	<ul style="list-style-type: none"> - Acts on B cells.
IFN-gamma (Type II Interferon)	Macrophages, dendritic cells (DC), activated Th1, NK, CD8 cells	<ul style="list-style-type: none"> - Activates macrophages (principal cytokine). - Promotes cell-mediated immunity by activating CD8 and NK cells. - Inhibits Th2 cell proliferation. - Stimulates IgG subclasses that activate complement pathway and promote opsonization.
TGF-beta	T-reg cells	<ul style="list-style-type: none"> - Inhibits T-lymphocyte proliferation and effector function. - Inhibits B-lymphocyte proliferation. - Inhibits macrophage function. - With IL-2, generates some regulatory T cells from CD4 cells. - With IL-6, leads to differentiation of TH17 cells.
Lymphotoxin (LT)	T-lymphocytes	<ul style="list-style-type: none"> - Recruits and activates neutrophils. - Contributes to lymphoid organogenesis. - Chemically similar to TNF; contributes to pro-inflammatory responses.
IL-6	Macrophages, monocytes	<ul style="list-style-type: none"> - Stimulates liver to produce acute-phase proteins. - Stimulates differentiation and growth of B-lymphocytes from TH2. - Aids differentiation of TH17 if TGF-beta is present.
IL-10	T-reg cells, Th2 cells	<ul style="list-style-type: none"> - Inhibits activated macrophages and dendritic cells. - Inhibits IL-12 production and co-stimulator molecules like MHC2, thus inhibiting TH1, TH2, and CD8. - Regulates innate, cell-mediated, and humoral immunity.



Cytokines of Hematopoiesis

- **Produced by Bone Marrow Stromal Cells**
 - Stimulate growth and differentiation of immature leukocytes.
 - **Examples of Cytokines:**
 - **Colony-Stimulating Factors (CSF):** Promote the production of leukocyte colonies in the bone marrow and enhance their activity.
 - **Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF):** Stimulates production of **granulocytes** (neutrophils, eosinophils, basophils) and **monocytes**.
 - **Granulocyte Colony-Stimulating Factor (G-CSF).**
 - **Macrophage Colony-Stimulating Factor (M-CSF).**
 - **Stem Cell Factor:** Increases stem cell responsiveness to various **CSFs**.
 - **Interleukin-3 and IL-7:** Support growth of **multi-lineage bone marrow stem cells**.
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Cytokine Receptors

- **5 Major Families of Cytokine Receptors**
 1. Immunoglobulin Superfamily
 2. **Hematopoietin Receptor Family (Class I)**
 3. **Interferon Receptor Family (Class II)**
 4. TNF Receptor Family
 5. Chemokine Receptor Family
 - **Class I and Class II** are the majority of the receptors.
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Immune Modulation

- **Purpose:** Alter the balance between different subsets of T cells to promote helpful responses and suppress damaging ones.
 - **Applications:**
 - Therapy for **autoimmunity** (increase **TH2 response**) or **allergy** (increase **TH1 response**).
 - Advantage: No need to know the precise autoantigen or allergen.
 - Drawback: **Unpredictable results**.
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Cytokines as Biologic Therapy

- **Suppress TH1 and Tc in Autoimmune Diseases**
 - Achieved by:
 - **Blocking antibodies against IL-2R.**
 - Using **IL-2 analogs** to prevent **IL-2 binding**.
 - Using **IL-2** to activate **lymphocytes** to attack **cancer**.

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