



Cytokines

- **Small (low molecular weight) proteins that assist in regulating the development of immune effector cell**
- **Secreted by activated lymphocytes, macrophages (white blood cells and some others)**
- **Many cytokines exert biological effect by binding to receptors on target cells and triggering signal transduction responses**
 - cytokines act locally within a small microenvironment
 - high affinity for receptors (10^{-10} to 10^{-12} M)



Action of Cytokines

- **The action of cytokines may be**
 - autocrine
 - paracrine
 - endocrine
- **Cytokines action may be**
 - **Pleiotropic-** any given cytokine may have different biological effect on different target cells
 - **Redundant-** two or more cytokines that mediate similar functions
 - **Synergism-** combined effect of two cytokines is greater than the additive effect of each alone
 - **Antagonism-** the effects of one cytokine inhibit or offset the effects of another

Cytokine Action

- Short lived
- secreted only when cell is activated, not constitutively (like growth factors)
- Most act in an autocrine or paracrine fashion

- Function as intercellular messengers:
Should know the following: cytokine, secreted by, target cell, and actions of:
 - IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-16, IFN-a, b, g and TGF-b, and TNF-a and b

Cytokine Receptors

- 5 Families of Receptors
 - Immunoglobulin superfamily receptors
 - Class I cytokine receptor family
 - class II cytokine receptor family
 - Interferon receptor family
 - TNF receptor family
 - Chemokine receptor family
- Receptors of different types may have same signal transduction action

IL-2 Receptor

- Trimeric receptor composed of **a, b, g** chains.
- Occurs in 3 forms that exhibit different affinities for IL-2
 - low affinity monomeric IL-2Ra
 - intermediate affinity dimeric IL-2Rbg
 - High affinity receptor IL-2Rabg
- the **a** chain is expressed by activated, but not resting, T cells (TAC=T cell activation antigen)
- Signal transduction by IL-2R requires both the **b** and **g** chains, but only the trimeric has high affinity for IL-2

IL-2 Receptor

- The **g** chain is constitutively expressed on most lymphoid cells
- The **b** chain is expressed on most cells constitutively, but is expressed in higher concentration when the cell is activated
- The **a** chain is expressed only on activated lymphocytes
 - the **a** receptor- activated CD4⁺ and CD8⁺ cells and in low levels on activated B cells
 - the **bg** receptor- on NK cells and resting T cells
 - the **abg** receptor- activated CD4⁺, CD8⁺ and B cells

Cytokine Antagonists

- **Act by binding:**
 - directly to a cytokine receptor, but fail to activate cell (competition for receptor)
 - bind directly to cytokine inhibiting its binding
 - *IL-1Ra binds to IL-1 receptor but has no activity (role in regulating inflammatory response)*
 - soluble cytokine receptors (made from enzymatic cleavage of the receptor from the cell membrane) can bind to cytokines
 - some viruses produce cytokine binding proteins (Pox- soluble TNF and IL-1)

T_H1 and T_H2 Subset Cytokines

- **Cytokine secretion by T_H subsets help regulate whether the response is humoral or cell mediated**
 - Both CD4⁺ and CD8⁺ cells secrete IL-3 and GM-CSF
 - T_H1 responsible for classical cell-mediated functions (i.e., DTH and activation of T_C cells, viral cell clearance)
 - *IL-2, IFN- γ , TNF- β , (GM-CSF and IL-3)*
 - T_H2 subset responsible as helper for B-cell activation (clears free living bacteria and helminthic parasites, and allergic reactions through IgE class switch by IL-4 and IL-5)
 - *IL-4, IL-5, IL-10, IL-13, (GM-CSF and IL-3)*

T_H1 and T_H2 Cell Development

- **IL-4 and IL-12 act on TH cells when TH are activated by antigen:**
 - IL-4 cells develop into T_H2 subset
 - IL-12 cells develop into T_H1 subset
 - These two subsets develop from a common TH0 precursor cell that can secrete IL-2, IL-2 and IFN- γ
- **Cytokines secreted by one subset can block the cytokines secreted by the other subset**
 - IFN- γ inhibits proliferation of T_H2 cells and secretion of IL-10
 - IL-10 down-regulates secretion of IL-2 and IFN- γ

T_H1 and T_H2 Cell Development

- **Cytokine Cross-Regulation**
 - *IFN- γ and IL-2 (secreted by T_H1 subset) promote IgG2a production by B cells but inhibit IgG1 and IgE production*
 - *IL-4 (secreted by T_H2 cells) promotes production of IgG1 and IgE and suppresses production of IgG2a*
 - *IL-10 does not inhibit TH1 directly but acts on macrophage and interferes with their ability to stimulate T_H1 cells*
- **Progression of some diseases may depend on the balance between T_H1 and T_H2 subsets**

Therapeutic Uses of Cytokines

■ Purified Cytokines

- regulation of response to alloantigens (organ transplants)
 - *try to block activation of T_H and T_C cells to prolong transplants*
 - *use of IL-1 soluble receptors to block T_H activation*
 - *Use of anti-TAC antibodies to block IL-2 receptor*
 - *toxin tagged cytokines (IL-2) to kill T_H cells (only responding cells have IL-2R)*
 - *Use in LAK cell stimulation*
 - *Treatment of allergy (block IL-4 using IL-12)*