**Lec. 1 Cytokines Dr.Refif Al-Shawk**

Molecules that communicate among cells of the immune system are referred to as **cytokines**.

 In general, cytokines are soluble molecules, although some also exist in membrane-bound forms.

**Chemokine** is used specifically to describe that subpopulation of cytokines that share the specific purpose of mobilizing immune cells from one organ, or indeed, from one part of an organ, to another.

Like all signaling molecules, cytokines can be further classified on the basis of the **distance between the cell secreting** & **the cell receiving that chemical signal**:

* Cytokines that act on cells some distance away from the secreting cell, such that they must pass through the bloodstream before reaching their target, are referred to as **endocrine**
* Those that act on cells near the secreting cell, such that the cytokine merely has to diff use a few Ångstroms through tissue fluids or across an immunological synapse, are referred to as **paracrine**.
* Sometimes, a cell needs to receive a signal through its own membrane receptors from a cytokine that it, itself, has secreted. This type of signaling is referred to as **autocrine**.

**Of note**, the T-cell interleukin IL-2 acts effectively in all three modes.

**General Properties of Cytokines and Chemokines**

1. **Cytokines Mediate the Activation, Proliferation, and Differentiation of Target Cells:**
* Cytokines bind to specific receptors on the membranes of target cells, triggering signal transduction pathways that ultimately alter enzyme activity and gene expression. The susceptibility of a target cell to a particular cytokine is determined by the presence **of specific membrane receptors** and exhibit **very high affinity** for one another.
* Cytokines regulate the **intensity**and **duration**of the immune response by
* stimulating or inhibiting the activation, proliferation, and/or differentiation of various cells, by regulating the secretion of other cytokines or of antibodies, or in some cases by actually inducing programmed cell death in the target cell
* cytokines can modulate the expression of various cell-surface receptors for chemokines, other cytokines, or even for themselves.
* Cytokines exhibit the attributes of **pleiotropy, redundancy, synergism, antagonism**, and **cascade induction:**
* A cytokine that induces different biological effects depending on the nature of the target cells is said to have a **pleiotropic** action
* Two or more cytokines that mediate similar functions are said to be **redundant**
* Cytokine **synergy** occurs when the combined effect of two cytokines on cellular activity is greater than the additive effects of the individual cytokines
* The effects of one cytokine inhibit or **antagonize** the effects of another
* **Cascade induction** occurs when the action of one cytokine on a target cell induces that cell to produce one or more additional cytokines.
1. Cytokines Can Elicit and Support the Activation of Specific T-Cell Subpopulations;

As we know helper T cells can be classified into subpopulations, each of which is responsible for the support of a different set of immune functions.

* TH1 cells secrete cytokines that ▬▬▬▬► promote the differentiation and activity of macrophages and cytotoxic Tcells, in which cells that have been infected with viruses and intracellular bacteria are recognized and destroyed.

**How** ?? The cytokines IL-12 and interferon (IFN) γ induce TH1 differentiation.

* TH2 cells activate B cells to make antibodies, which ▬▬▬▬► neutralize and bind extracellular pathogens, ▬▬▬▬►making them susceptible to phagocytosis and complement-mediated lysis.

**How** ?? IL-4 and IL-5 support the generation of TH2 cells.

* TH17 cells promote the ▬▬▬▬► differentiation of activated macrophages and neutrophils, and support the inflammatory state;

**How** ?? their generation is induced by IL-17 and IL-23.

1. **Cell Activation May Alter the Expression of Receptors and Adhesion Molecules;**

**What keeps cytokines from activating all T cells, for example, in a nonspecific fashion during the immune response?**

In order for a cell to respond to a signaling molecule, it must express **receptors** for that molecule, and **responsiveness** to a molecular signal can thus be controlled by signal receptor expression.

For example, antigen stimulation of a T cell induces alterations in the T-cell surface expression of chemokine receptors. Reception of chemokine signals through these receptors therefore instructs only those cells that have previously been activated by antigen to migrate to nearby lymph nodes or to the spleen, ensures that stimulated cells migrate, and then remain in the location, and up-regulates the expression of the receptors for cytokines that provide **proliferative signals**, such as **IL-2**, and also for **differentiative** cytokines such as **IL-4.** In this way, following antigen encounter, only those T cells that have been activated by antigen are primed to relocate and to receive the proliferative and differentiative signals they need to function as a mature immune effector cell. This is a common strategy employed by the immune system.

**Six Families of Cytokines and Associated Receptor Molecules;**

Cytokines characterized so far belong to one of six groups:

1. the Interleukin 1 (IL-1) family,
2. the Hematopoietin (Class I cytokine) family,
3. the Interferon (Class II cytokine) family,
4. the Tumor Necrosis Factor (TNF) family,
5. the Interleukin 17 (IL-17) family,
6. and the Chemokine family.
7. **Cytokines of the IL-1 Family Promote Proinflammatory Signals**

Cytokines of the interleukin 1 (IL-1) family are:

* typically secreted very early in the immune response
* by dendritic cells and monocytes or macrophages.
* IL-1 secretion is stimulated by recognition of viral, parasitic, or bacterial antigens **by innate immune receptors**.
* IL-1 family members are generally proinflammatory, (what does this mean)? meaning that **(1)** they induce an increase in the capillary permeability at the site of cytokine secretion, along with **(2)** an amplification of the level of leukocyte migration into the infected tissues**. (3)** In addition, IL-1 has systemic (whole body) effects and signals the liver to produce acute phase proteins such as the Type I interferons (IFNs α and β), IL-6, and the chemokine CXCL**. (4)** These proteins further induce multiple protective effects, including the destruction of viral RNA and **(5)** the generation of a systemic fever response (which helps to eliminate many temperature-sensitive bacterial strains).
* IL-1 also activates both T and B cells at the induction of **the adaptive immune response.**
1. **Hematopoietin (Class I) Family Cytokines**

Members of the hematopoietin (Class I) cytokine family are small, soluble cytokines that communicate between and among cells of the immune system.

Their cellular origins and target cells are as diverse as their ultimate functions, which range from;

* signaling the onset of T- and B-cell **proliferation** (e.g., IL-2),
* signaling the onset of B-cell **differentiation** to plasma cells and antibody secretion (e.g., IL-6),
* signaling the **differentiation** of a T helper cell along one particular differentiation pathway versus another (e.g., IL-4 TH 2 vs. IL-12 TH 1)
* initiating the **differentiation** of particular leukocyte lineages (e.g., granulocyte monocyte- colony stimulating factor GM-CSF, granulocyte - colony stimulating factor G-CSF).
1. **The Interferon (Class II) Cytokine Family Was the First to Be Discovered;**

There are two major types of interferons, Types 1 and 2, and that Type 1 interferons can be subdivided into two subgroups.

* **Type I interferons**

Are composed of **Interferons α**, and **interferon-β**, which are **secreted by** activated macrophages and dendritic cells, as well as by virus-infected cells after recognition of viral components by pattern recognition receptors (PRRs) located either at the cell surface, or inside the cell.

* **Type II interferon**

Type II interferon**, known as interferon-γ**, is **produced by** activated T and NK cells and is a powerful modulator of the adaptive immune response:

1. Interferon-γ is used medically to bias the adaptive immune system toward a cytotoxic response in diseases such as leprosy and toxoplasmosis, in which antibody responses are less effective than those that destroy infected cells.
2. and inducing the activation of macrophages, with subsequent destruction of any intracellular pathogens
3. and the differentiation of cytotoxic T cells.

[All three interferons increase the expression of MHC complex proteins on the surface of cells, thus enhancing their antigen-presentation capabilities].

**4. Members of the TNF Cytokine Family**

The Tumor Necrosis Family (TNF) family of cytokines regulates the development, effector function, and homeostasis of cells participating in the skeletal, neuronal, and immune systems, among others.

**Cytokines of the TNF Family Can Be Soluble or Membrane Bound**

There are two members of the TNF family: TNF-α and TNF-β

* **TNF-α** (frequently referred to simply as TNF) is a proinflammatory cytokine, **produced** primarily by activated macrophages, but also by other cell types including lymphocytes, in response to infection,or inflammation.
* **TNF-β** is **produced** by activated lymphocytes and can deliver a variety of signals. On binding to neutrophils, endothelial cells lead to increased expression of MHC and of adhesion molecules.

**Fas ligand (FasL)**,which is member of this family induces apoptosis on binding to its receptor.

**5. The IL-17 Family Is a Recently Discovered, Proinflammatory Cytokine Cluster;**

IL-17 family, includes:

 **interleukins 17A, 17B, 17C, 17D, and 17F**. Signaling through most members of this family culminates in the **generation of inflammation**. IL-17 receptors are found on **neutrophils, keratinocytes, and other nonlymphoid** cells.

Members of the IL-17 family therefore appear to occupy a location at the interface of innate and adaptive immunity.

**IL-17** is **released** by activated T cells and stimulates the production of factors that signal a proinflammatory state, including IL-6, CXCL8, and granulocyte colony-stimulating factor (G-CSF).

**6. Chemokines Direct the Migration of Leukocytes Through the Body;**

**Chemokines** are a structurally related family of small cytokines that bind to cell-surface receptors and induce the movement of leukocytes up a concentration toward the chemokine source. This soluble factor-directed cell movement is known as chemotaxis, and molecules that can elicit such movement are referred to as chemoattractants .

**For example**,

1. **CXC chemokines** attract **neutrophils**,
2. Members of CC groups are chemoattractants that attract **monocytes and macrophages** (although not neutrophils) to the site of infection.
* **Cytokine Antagonists**

A number of proteins that inhibit the biological activity of cytokines have been reported. These proteins act in one of two ways:

* Either they bind directly to a cytokine receptor but fail to activate the cell, thus **blocking** the active cytokine from binding, The best-characterized cytokine inhibitor is the IL-1 receptor antagonist (IL-1Ra), which binds to the IL-1 receptor **but does not** elicit activation of the signaling pathway **inhibitory properties**.( Recombinant IL-Ra has been used clinically, for the treatment of rheumatoid arthritis.)
* or they bind directly to the cytokine itself, inhibiting its ability to bind to the cognate receptor.
* **Cytokine-Related Diseases**

Defects in the expression of cytokines and cytokine receptors have been implicated in a number of diseases.

1. immunodeficiencies. Genetic defects in cytokines, their receptors, or the molecules involved in cytokine directed signal transduction lead to immunodeficiencies. For example, people with a defective receptor for IFN-γ are susceptible to mycobacterial infections that rarely occur in the general population.
2. over expression or under expression of cytokines or cytokine receptors. (not genetic defect)
3. **Septic Shock Is Relatively Common and Potentially Lethal**

Despite the widespread use of antibiotics, bacterial infections remain a major cause of septic shock, which may develop a few hours after infection by certain bacteria, including *Staphyloccocus aureus, E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa.* Bacterial septic shock is one of the conditions that falls under the general heading of sepsis.

* A common feature of sepsis: production of proinflammatory and fever-inducing cytokines such as TNF-α and IL-1β.
* The cytokine imbalance induces abnormal body temperature, alterations in the respiratory rate, and high white blood cell counts, followed by capillary leakage, tissue injury, widespread blood clotting, and lethal organ failure.
* Bacterial septic shock often develops **HOW** ?? because bacterial cell wall endotoxins bind to innate immune system pathogen receptors, such as Toll-like receptors, on dendritic cells and macrophages, causing them to produce IL-1 and TNF-α at levels that lead to pathological capillary permeability and loss of blood pressure.
* monoclonal antibodies to TNF-α will protect from endotoxin-induced shock.
* **Bacterial Toxic Shock Is Caused by Superantigen Induction of T-Cell Cytokine Secretion;**

A variety of microorganisms produce toxins that act **as superantigens. S**uperantigens results in excessive production extremely high levels of TNF-α and IL-1β. As in bacterial septic shock, these elevated concentrations of cytokines can induce systemic reactions that include fever, widespread blood clotting, and shock.

* **Cytokine-Based Therapies;**

The availability of purified cloned cytokines, monoclonal antibodies directed against cytokines, and soluble cytokine receptors offers the prospect of specific clinical therapies to modulate the immune response.

1. soluble TNF-α receptor and monoclonal antibodies against TNF-α have been used to treat **rheumatoid arthritis** and **ankylosing spondylitis** in more than a million patients. These anti–TNFα drugs reduce proinflamatory cytokine cascades; help to alleviate pain, stiffness, and joint swelling; and promote healing and tissue repair.
2. the recombinant form of IL-1Ra has been shown to be relatively effective in the treatment of rheumatoid arthritis.
3. Monoclonal antibodies directed against the α chain of the IL-2R are also in clinical use for the prevention of transplantation rejection reactions

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