CYTOKINES

Cytokines are specialized regulatory molecules of the immune system, which mainly act on cells in a short distance manner.

The classical nomenclature of cytokines includes:

(1) Interleukins (ILs),
(2) Colony Stimulating Factors (CSFs),
(3) Interferons (IFNs),
(4) Tumor Necrosis Factors (TNFs),
(5) Transforming Growth Factors (TGFs),
(6) Cytokines and chemokines, and a variety of other proteins

IL-1β, the soluble IL-1, is produced by many cell types, may act at the systemic level like a hormone, exert the property of endogenous pyrogen, and take part in the "**acute phase**" inflammation, costimulation, proliferation and differentiation of lymphocytes and other cells. IL-1 can be secreted by macrophages in response to molecular patterns to result in Toxic Shock Syndrome and "**cytokine storm**."
IL-1α, the membrane IL-1, is synthesized by a wide variety of cells, may function in the same manner as IL-1β and play an essential role in the maintenance of the skin barrier.
IL-1ra (IL-1 Receptor Antagonist) competes with IL-1 for the IL-1β receptor and downregulates IL-1β activity, i.e., exerts **anti-inflammatory effects**. It is a member of the IL-1 family of cytokines.

IL-2 is secreted by T cells, upregulates **T-cell and B-cell growth** in the course of adaptive immune responses, during clonal expansion, and activates NK cells as cells of innate immunity.

IL-3, a "Multi-Colony-Stimulating Factor," promotes the leukopoiesis at early stages. IL-3 is a member of the CSF family of cytokines.

IL-4 is produced by **type 2 helper T (Th2) cells**, follicular helper T cells, mast cells, and B cells. It is the keystone cytokine of Th2 cells and IgE antibody synthesis. Analogous to IL-21, IL-4 plays a role in the advanced B-cell-mediated immune response. IL-4 is a member of the IL-2 subfamily of the 4α-helix bundle family of cytokines.

IL-5 refers to cytokines of the Th2 profile and upregulates the **eosinophil** generation, maturation, migration, and activation. Historically, IL-5 was originally discovered as an Eosinophil Colony-Stimulating Factor (E-CSF). IL-5 is a member of the CSF family of cytokines.

IL-6 is produced by many cell types and also belongs to the Th2 profile. Analogous to IL-1β, IL-6 may act at the systemic level like a hormone, take part in the "**acute phase**" inflammation, and in the maintenance of the blood-brain barrier. IL-6 may also be secreted by macrophages in response to molecular patterns to lead to the Toxic Shock Syndrome and "**cytokine storm**." IL-6 constitutes the IL-6 family of cytokines.

IL-7 is a hemopoietic growth factor secreted by stromal and other cells in the bone marrow. IL-7 upregulates the **differentiation of multipotent stem cells** into lymphoid stem cells, which are very important for both B lymphopoiesis and T lymphopoiesis.

IL-8 (CXCL8) refers to chemokines. IL-8 is responsible for the migration of **neutrophils** toward the site of infection, activation of phagocytosis including reactive oxygen species (ROS), and angiogenesis.

IL-9 is secreted by T cells and belongs to the **type 9 helper T (Th9) cells** profile. IL-9 may activate **mast cells**, eosinophils, and epitheliocytes, and induce inflammation.

IL-10 is a **robust anti-inflammatory** and **immunosuppressive cytokine**, but it belongs to the Th2 profile. IL-10 is also produced by tolerogenic dendritic cells, peripheral regulatory T (pTreg) cells, type 1 regulatory T (Tr1) cells, and type 3 helper T (Th3) cells. IL-10 downregulates type 1 helper T (Th1) cells, and the expression of HLA molecules and costimulatory molecules required for the adaptive immune responses. IL-10 constitutes the IL-10 subfamily of the 4α-helix bundle family of cytokines.

IL-12 is produced by antigen-presenting cells and NK cells to **stimulate the Th1 formation** during T-cell-mediated responses. IL-12 upregulates the activity of cytotoxic CD8+T cells and NK cells due to the production of IFN-γ and TNF-α by these cells. IL-12 refers to pro-inflammatory cytokines.

IL-13 is related to cytokines of the **Th2 profile** and acts like IL-4. IL-13 enhances atopic allergic inflammatory processes even more than IL-4. However, IL-13 may induce matrix metalloproteinases in the airway to protect lungs from excessive inflammatory proteins, which prevents asphyxiation in asthma.

IL-15 is a cytokine with structural and functional similarity to IL-2, which upregulates the T cell and NK cell proliferation and activity. IL-15 is a **"partner" of the IL-2.**

IL-17 is a keystone cytokine of **type 17 helper T cells** produced by some CD4+T cells under the influence of IL-23. IL-17 is a pro-inflammatory cytokine involved

in the chronic inflammation with the participation of neutrophils and other cells and in autoimmune disorders. IL-17 acts synergistically with TNF-α, TNF-β, IL-1β, and IL-6. IL-17 constitutes the IL-17 family of cytokines, which includes IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F.

IL-21 is a keystone cytokine of **follicular helper T cells (Tfh).** IL-21 is an important cytokine in advanced B-cell-mediated response, in particular, B-cell clonal expansion, antibody switching, and memory B cell formation.

IL-22 is produced by dendritic cells, Th17, **type 22 helper T (Th22) cells** and splenocytes. IL-22 is a keystone cytokine of Th22 cells, may exert both anti-inflammatory and pro-inflammatory qualities, and play a role in skin and mucosal immunity protecting epithelial integrity. Mainly, IL-22's target cells are non-immune cells.

IL-27 is released by antigen-presenting cells as a regulator of T and B cells. IL-27 **pro-tolerogenic activity** has been described.

IL-31 is produced by CD4+T cells. IL-31 may play a role in **skin inflammation.**

IL-33 is produced by a variety of cell types, including epitheliaocytes as **alarmin**, refers to cytokines of the **Th2 profile** and **group 2 ILC**, and plays a role in atopic allergic inflammation such as asthma, allergic rhinitis, and atopic dermatitis (especially, in skin itch pathogenesis).

IL-35 is a keystone **anti-inflammatory and immunosuppressive cytokine**. IL-35 is secreted by pTreg and other regulatory T cells.

BAFF (B-cell Activating Factor) is produced by B cells and antigen-presenting cells. BAFF acts as a potent **activator of the B-cell differentiation** and antibody synthesis, and a modulator of B-cell apoptosis. It belongs to the TNF superfamily.

TGF-β (Transforming Growth Factor-β) is a **keystone anti-inflammatory and immunosuppressive cytokine**, which produced by type 3 helper T (Th3) cells, pTregs, and a variety of cell types. Besides, TGF-β upregulates the angiogenesis, tissue regeneration, embryonic development, and the growth of some human cancer cells.

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) secreted by a variety of cell types stimulates stem cells in the bone marrow to produce **granulocytes and monocytes**. Analogous to IL-1β, IL-6, TNF-α, and TNF-β, GM-CSF may function at the systemic level and affect mature cells of the immune system. GM-CSF acts in a synergic manner with IL-3.

Granulocyte Colony-Stimulating Factor (G-CSF) is secreted by many cell lineages and stimulates stem cells in the bone marrow to produce granulocytes and release granulocytes and stem cells into the bloodstream. Next, G-CSF upregulates the proliferation, maturation, and survival of **granulocytes**.

Macrophage Colony-Stimulating Factor (M-CSF) released by some cell types stimulates the proliferation, differentiation, survival, and functional activity of **monocytes and macrophages**. M-CSF acts synergistically with IL-34. In addition, M-CSF takes part in processes associated with fertility and pregnancy.

TNF-α (Tumor Necrosis Factor-α, "cachectin") is produced by macrophages (M1) and a variety of cell types. TNF-α acts synergistically with TNF-β, IL-1β, IL-6, and IFN-γ. It is a potent pro-inflammatory cytokine and even endogenous toxin pyrogen, responsible for "**cytokine storm**", and a regulator of adaptive immune responses. Historically, TNF-α was discovered and named in such manner as could lyse particular tumor cell lines.

TNF-β (Tumor Necrosis Factor-β, "lymphotoxin") is secreted by lymphocytes. Its effects are similar to TNF-α's effects (**pro-inflammatory activity**), but TNF-β is more critical for the development of lymphoid tissue.