Signal transmission in cells

There are 2 mechanisms of this **cell-to-cell** interaction.

- The first communication system takes place via a **direct contact** (ligand-receptor) pathway using adhesion molecules located on the cell surface.
- The second is realized by soluble factors such as cytokines.

Adhesion molecules

The different types of **embryonic tissues** (which separate into individual cells much more easily than adult tissues) reunite after dissociation into individual cells (in tissue culture), so that they always adhere to each other. **Cells of the same origin**, such as liver, kidney, retina, etc. **Cell adhesion is conditioned by the participation of adhesion proteins**. It is a diverse group of proteins that also make up specific receptors on the cell surface. They are important for:

- organization of the extracellular matrix,
- regulation of cell interaction,
- influencing migration and cell shape formation.

Adhesion proteins contain several **specialized domains**. All contain a domain that binds to the cell surface, another domain interacts with collagen and another binds to proteoglycans. The tripeptide sequence arginine - glycine - aspartate (**RGD-sequence**) is essential for the adhesion of cells to the extracellular matrix.

According to the structure, they are divided into several families:

Immunoglobulin superfamily

It has more than 70 members, including receptors T-cells, immunoglobulins, MHC-molecules, CD2, CD3, CD4, CD8 , NCAM, ICAM1-5, VCAM-1, PECAM-1. All **contain one or more Ig-domains** as the basic amino acid sequence motif. Immunoglobulin family members can bind to each other, e.g. MHC molecules bind to T-cell receptors or with integrins such as ICAM-1 bind to LFA-1 and Mac-1 or with various additional receptors such as the interaction of ICAM-1 and CD43. Its members occur mainly in nervous tissue. They have 2 basic domains in their structure:

1. repeating loop homologous to immunoglobulins linked by a disulfide bond,
2. repeating sequence (about 100 amino acids) homologous to fibronectin.

The most famous include:

N-CAM (nerve-cell adhesion molecule)

The name says they are very important for nerve tissue. They appear at the beginning of morphogenesis, evenly distributed along the **neural tube**. When nerve cells begin to migrate, N-CAM disappears but reappears when migration ceases and ganglia appear. The adhesion properties of N-CAM are modulated by the long-chain sialic acids. The more salinized lose their haemophilia for the repulsion between the negative charges of sialic acid.

Selectins

It forms a small family consisting of 3 members: **selectin E, P and L** . Unlike other adhesion molecules that bind to various proteins, selectins **bind to carbohydrates** such as e.g. and PSGL-1 (P-selectin Glycoprotein Ligand-1). The structure of selection consists of:

- N-terminal Ca-dependent lectin domain,
- epidermal growth factor-like domain (EGF-like domain) linked to several repeats,
- transmembrane area,
- cytoplasmic end.

The contact between leukocytes circulating in the blood and the endothelial cells of the vascular wall is mediated by specific adhesion molecules, where **P-selectin** plays an important role. It is a lectin, ie a protein that binds to carbohydrate molecules. Selectins bind to specific oligosaccharide sequences of glycoproteins and glycolipids. The ligand for P-selectin is an oligosaccharide sequence called a **sialyl-Lewis-x antigen**, which occurs in abundant amounts on the surface of leukocytes. Sialyl-Lewis antigen contains 4 carbohydrates, very specifically bound to each other (from the end: sialic acid - galactose - N-acetylglucosamine (and fucose) - the rest of the oligosaccharide chain).

Integrins

Integrins are **major mediators of cell-cell adhesion and extracellular matrix** (integrins *integrate* the intracellular cytoskeleton with the extracellular matrix). These are membrane glycoproteins formed by **two subunits (a and b)**. Individual integrins can bind multiple ligands and individual matrix molecules are able to bind

multiple integrins. Chemically, these are heterodimers of α- and β-subunits.

Regulation of integrin activity

The mere presence of integrin on the cell surface is not sufficient to bind the respective ligands. This **requires activation**. An example is platelets. Only after activation of platelets by collagen or thrombin em can integrin αIIbb3 bind fibrinogen. This interaction accelerates thrombus formation. Upon this activation, conformational changes of the platelet cytoskeletal proteins occur, allowing the cytoskeletal protein to bind to the cytosolic domain of the integrin. Patients with a genetic defect of the b3-integrin subunit are prone to excessive bleeding. Integrins have a relatively low affinity for their ligands. This low binding is compensated by the large number (hundreds to thousands per cell) of integrin molecules that anchor the cells to the extracellular matrix. On the other hand, in a situation where the cell is to travel (migration), this relatively weak binding of individual integrins with different ligands allows simultaneous detachment (deactivation) e.g. from the extracellular matrix and capture (upon activation) to a specific cytosolic protein.

Cadherin family

it consists of **Ca-dependent adhesion molecules** that primarily mediate cell-cell homotypic adhesion. Thus, they can be both a ligand and a receptor. They are responsible for:

- selective cell adhesion or cell sorting (which is necessary to place different cell types in a predetermined location during development),
- maintaining the integrity of multicellular organisms,
- cell differentiation and structure formation.

They are widespread in virtually all tissues. There is the largest number of different types in the brain; there is a number of very specific contacts between the cells. Although more than 30 different types of cadherins are known, 50-60% of the amino acid sequence is identical.

E-cadherin

Also referred to as **uvomorulin**, it is an intercellular linkage that holds layers of epithelial cells together. Layers of polarized epithelial cells, such as intestinal or renal tubular epithelium, contain abundant amounts of E-cadherin on the lateral side of the cells.

Other adhesion molecules

CD44

Widespread glycoprotein. It is on hematopoietic cells (B- and T-cells, monocyte y, neutrophil y), epithelial cells, fibroblasts, and neuroglia. There are different variants of CD44. The standard type **binds hyaluronate**, the variants fibronectin, laminin, collagen. CD44s also show a homotypic interaction. They are important for a number of immune responses, especially for the interaction between leukocytes and endothelial cells in the migration of leukocytes to inflammation sites.

VAP-1 (Vascular Adhesion Protein-1)

It mediates the **binding of lymphocytes to the endothelial cell** (especially to the endothelial cells of the venules of the peripheral lymph nodes). VAP-1 expression is induced in **chronic inflammation** in blood vessels tonsillus, intestines, skin and synovium. It is also found in the hepatic sinusoids, cervix and vaginal mucosa. It is not on circulating leukocytes in the blood. It is highly expressed in psoriasis and allergic lesions, as well as in inflammation of the colon, and chronic dermatoses. Elevated levels are also in liver disease.

Extravasation

Monocytes (macrophage precursors), which absorb and digest foreign substances, neutrophils releasing antibacterial proteins and T- and B-lymphocytes involved in the immune defense mechanism, must reach the affected area where they provoke a defense reaction (inflammation). The above-mentioned cells circulating in the blood must accumulate at the affected site, penetrate the vessel wall and initiate the interstitial defense process. This phenomenon is called *extravasation* (**wall capture and penetration**).

A sequence of processes during extravasation

Free leukocyte in the bloodstream → rolling leukocyte along with the vessel wall → adhesion to the endothelium → extravasation → invasion of the interstitium.

Cytokines

Cytokines are a numerous but unique group of protein mediators that are **secreted mostly by T-lymphocytes (CD4 +) and macrophages** but also by other cells. The cytokines produced by leukocytes are called interleukins (leukocytes interact with each other). Lymphokines are secreted from lymphocytes and monokines from macrophages and monocytes. Cytokines play an important role in:

- activation of the innate effector phase and specific immunity,
- control the development and function of cells of the immune system, as well as other cells,
- are important molecules that can affect proliferation, differentiation and cell migration.

Unlike hormones, cytokines are produced not in glandular formations, but by various individual cells, mainly acting locally: paracrine or autocrine, not as endocrine hormones. Cytokines have a **pleiotropic effect** (one cytokine has multiple effects); it also has a **redundant** (multiple cytokines have the same effect) and sometimes an **antagonistic** (one cytokine inhibits another). Their activity can be divided into five major areas:

- development of humoral and cellular immune response,
- induction of an inflammatory reaction,
- regulation hematopoiesis,
- control of cell proliferation and differentiation,
- induction of wound healing.

The effect of individual cytokines is quite difficult to predict. They do not perform it alone but together with other cytokines or other molecules, both synergistically and antagonistically. Cytokines usually **initiate a cascade of production of other cytokines**, in which the next cytokine may affect the previous one. Although cytokines do not themselves have antigen specificity, cytokine receptors that are expressed on the surface of cells that have been previously activated by the antigen exert an antigen-specific immune response. Cytokines secreted primarily from leukocytes stimulate humoral and cellular immune responses, as well as phagocyte activation. Some cytokines are expressed on the cell surface, others may be stored in the extracellular matrix. They are usually produced for a very short period of time after cell activation in an immune or inflammatory response.

Historically, cytokines can be divided into five classes according to their main effect:

- Interleukins (IL-1 to IL-18) - regulate the interaction between leukocytes; some are growth factors targeting hematopoietic cells.
- Interferons (a, b, g, w) - are produced in response to a viral infection. However, they are also potent immunomodulators. They can promote or inhibit the production of antibodies from activated B-lymphocytes, they can also activate macrophages, NK cells and T-lymphocytes. They also have direct antiproliferative activity and are cytostatic or cytotoxic to various types of tumor cells.
- Chemokines - acts in chemotaxis or inflammation (eg IL-8). They are multipotent cytokines that localize or promote the inflammatory response by inducing chemotaxis (by attracting inflammatory cells to the site of affection) and, above all, by activating inflammatory cells at the affected site. They are also essential mediators for normal leukocyte migration.
- **Colony-Stimulating Factors (CSF)** - affect the growth and proliferation of certain types of progenitor cells. E.g. G-CSF is a granulocyte progenitor cell colony-stimulating factor for proliferation and differentiation. M-CSF affects the proliferation and differentiation of stem cells into macrophages, especially the differentiation into monocytes. GM-CSF is responsible for the growth and development of both granulocytes and macrophages progenitors.
- **Tumor-necrotizing factors (TNF)** - are derived from macrophages, and have antitumor activity. The TNF family consists of two molecular individuals, TNFα and TNFβ. TNFα induces the expression of other autocrine growth factors, increases the response of cells to growth factors, and induces signalling pathways that lead to proliferation. In addition, it induces the expression of a number of proto-oncogenes in the nucleus, as well as other interleukins. TNFb is characterized by the ability to destroy a number of different cell types or to induce terminal differentiation in others. Induction of TNFb results in an increase in IL-2 and antigen interaction with T-cell receptors.

According to the main effect, we can classify cytokines into 4 large groups:

Proinflammatory cytokines

These include **TNF, IL-1, IL-6**. They are the main molecules that induce and strengthen every inflammatory response. They are secreted by most cells in the initial phase of inflammation. Their effect lies in changes in the place of disability:

- mobilization of antigen-presenting cells,
- activation of endothelial cells to express adhesion molecules.

This is manifested by the development and proliferation of inflammatory cells (leukocytes and monocytes / macrophages). IL-1 and TNF also act systemically and induce an acute phase response, including fever.

Chemokines

IL-8 is a prototype, has a chemoattractant effect for all known migrating immunocompetent cells, **IL-16** induces migration in T-lymphocytes (CD4 +), also in monocytes and eosinophils ; **IL-3** is a chemoattractant for eosinophils. Chemokines form a network over endothelial cells and are needed for the formation of adhesion molecules on the surface of leukocytes. They also create a chemotactic gradient for the movement of inflammatory cells.

Cytokines for hematopoiesis

Colony-stimulating factors (G-CSF, M-CSF, MG-CSF) and some cytokines (such as **IL-3** play a key role in the development of progenitor inflammatory cells in the bone marrow. Some cytokines also induce specific differentiation from hematopoietic stem cells.

Immunomodulatory cytokines

These include, in particular, **IL-2, IL-4, IL-5, IFNγ** and others. They are especially important for the development of T- and B-cells after stimulation. They induce both activations as well as determine the type of immune response.

Cytokines secreted by TH-lymphocytes (CD4 +)

Effect of Type 1 cytokines

- **IL-2** - after initial stimulation of TH-lymphocytes (helper T-lymphocytes) by antigen-presenting cells, IL-2 is secreted, which activates the cells as an antigen as well as a mitogen of mature resting T-lymphocytes. By interacting with its high-affinity receptor, IL-2 promotes the clonal expansion of antigen-activated effector T cells.
- **IL-12** directly induces the initial development of Th1 cells and the formation of IFNγ-secreting Th1 cells. IL-12 is also thought to suppress IL-4-induced IgE production. IFNγ controls a class of B-cell antibodies, reducing the expression of the MHC I. and II antigen complex. class and increases the efficiency of the destruction of intracellular parasites by macrophages.

Effect of type 2 cytokines

- **IL-4** Th2-cells induce **selective production of immunoglobulin isotypes** IgG, IgA and IgE in the humoral response. IL-4 regulates the expression of surface antigens on B-cells, resulting in the promotion of antigen-presenting capacity of B-cells.
- **IL-5** plays an important role as an eosinophilic hematopoietic growth factor. It also modifies the function of basophils and induces their differentiation. It plays a very important role in the development of hypersensitivity reactions and other diseases associated with eosinophil infiltration. IL-5 also stimulates B-cells to differentiate into immunoglobulin-secreting cells.
- **IL-10** exerts a broad spectrum of activity on a variety of cells with both immunosuppressive and immunostimulatory effects. IL-10 produced by Th2 cells inhibits the production of cytokines, mainly IFNγ, formed in Th1 cells upon antigen activation. It is also a potent regulator of cell-mediated immune responses, causing its strong anti-inflammatory effect.
- **IL-13** is a pleiotropic cytokine produced by activated Th2 cells. It probably affects the morphology and phenotypes in monocytes induced by IgE-receptor expression and suppression of MHC II complex expression. class. It is also involved in the switching of IgE and IL-4-dependent IgG4 production and IgE synthesis in the presence of T cells.

Cytokine receptors

The effect of cytokines, which affect cell growth and differentiation, depends on their recognition and binding to specific receptors. These receptors, located on the cell membrane, transfer the appropriate signal into the cell, where they trigger a signalling cascade. Binding to the appropriate ligand gives rise to an active multi-component complex, which often involves oligomerization of the ligand-binding subunits with subsequent signal transduction to the cell nucleus.

Cytokine receptors can be classified into 4 groups according to their basic structure:

- **IL-1 receptor superfamily**: IL-R1I, IL-1-RII, IL-1RAcP, IL-18Ra, IL-18Rb; CSF-1R, PDGF-Rb.
- **Class I (for hematopoietins)**: IL-2Rb, IL-2Rg, IL-3Ra, b, IL-4Ra, IL-5Ra, IL-6Ra, IL-7a, IL-9R, IL- 11R (gp130), IL-12Rb1, b2, IL-13R, IL-15R, GM-CSF-Ra, b,

G-CSF-R (contains established chain fragment composition motifs, i.e. CCCC and Trp-Ser-X-Trp-Ser or WSXWS).

- **Class II (for interferons)**: IFNg - Ra, b (contain a fixed CCCC motif).
- **The superfamily of TNF-receptors (TNF-R)**: TNF-RI, TNF-RII, CD40 (B-cells), NGF-R and Fas, CD27 (T, B-cells) (contain repeating with sequences C1, C3, C2).

Links

Sources

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