Transduction of signals in cells

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

- The first communication system occurs through **direct contact** (ligand-receptor) using adhesion molecules located on the surface of cells.
- The second is realized by soluble factors such as cytokines.

Adhesion Molecules

Different types of **embryonic tissues** (which are separated into individual cells much more easily than adult tissues) after dissociation into individual cells (in tissue culture) regroup by always adhering 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 form specific receptors on the cell surface. They are important for:

- the organization of the extracellular matrix,
- regulation of cellular interaction,
- affecting migration and forming the shape of cells.

Adhesion proteins contain several **specialized domains**. They all contain a domain that binds to the cell surface, another domain that interacts with collagen, and another that binds to proteoglycans. The tripeptide sequence arginine-glycine-aspartate (**RGD-sequence**) is necessary for the adhesive ability 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-cell, immunoglobulins, MHC-molecules,CD2, CD3, CD4, CD8 , NCAM, ICAM1-5, VCAM-1, PECAM-1. All **contain one or more Ig-domains** as a basic amino acid sequence motif. Members of the immunoglobulin family can bind to each other, e.g. MHC-molecules bind to T-cell receptors or with integrins such as ICAM-1 binds to LFA-1 and Mac-1 or with various additional receptors such as the interaction of ICAM-1 and CD43. Its members are mainly found in nervous tissue. They have 2 basic domains in their structure:

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

Among the most famous are:

N-CAM (nerve-cell adhesion molecule)

The name says that they are very important for nervous 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 stops and ganglia appear. The adhesion properties of N-CAM are modulated by a long chain of sialic acids. More sialinized, they lose their homophily due to the repulsion between the negative charges of sialic acid.

Selectins

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

- N-terminal Ca-dependent lectin domain,
- an epidermal growth factor-like domain (EGF-like domain) connected to several repeating sections,
- transmembrane region,
- cytoplasmic end.

The contact between leukocytes circulating in the blood and endothelial cells of the vessel wall is mediated by specific adhesion molecules, where **P-selectin** plays an important role. It is a lectin, i.e. 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 **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 **main mediators of adhesion between cells and the extracellular matrix** (integrins "integrate" the intracellular cytoskeleton with the extracellular matrix). They 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, they are heterodimers of a- and b-subunits.

Regulation of integrin activity

The mere presence of an integrin on the cell surface is not sufficient to bind the respective ligands. It requires **activation**. An example would be platelets. Only after activation of platelets by collagen or thrombin can integrin aIIbb3 bind fibrinogen. This interaction accelerates thrombus formation. During this activation, there are **conformational changes** of the proteins of the platelet cytoskeleton, which will enable the binding of the cytoskeletal protein 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 a 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 has 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 is formed by **Ca-dependent adhesion molecules**, which primarily mediate homotypic cell-cell adhesion. They can therefore be both a ligand and a receptor. They are responsible for:

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

They are widespread in practically all tissues. There are the largest number of different types in the brain; a number of very specific contacts between cells are created here. 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 junction that holds layers of epithelial cells together. Layers of polarized epithelial cells, such as those of the intestinal mucosa or renal tubules, contain abundant E-cadherin on the lateral side of the cells.

Other adhesion molecules

CD44

A very widespread glycoprotein. It is on hematopoietic cells (B and T cells, monocytes, neutrophils), epithelial cells, fibroblasts, neuroglia. There are different variants of CD44. The standard type **binds hyaluronate**, variants include fibronectin, laminin, collagen. CD44 also show a homotypic interaction. They are important for a number of immune reactions, especially for the interaction between leukocytess and endothelial cells during the migration of leukocytes to sites of inflammationu.

VAP-1 (Vascular Adhesion Protein-1)

It is a mediator of the **binding of lymphocytes to the endothelial cell** (primarily to the endothelial cells of the venules of the peripheral lymph nodes). VAP-1 expression is induced during **chronic inflammation** in vessels tonsil, intestine, skin and synovium. It is also found in the liver sinusoids, cervix and vaginal mucosa. It is not on circulating leukocytes in the blood. It is significantly expressed in psoriasis and allergic lesions, as well as in inflammation of the colon, chronic dermatoses. An increased level is also found in liver disease.

Extravasation

Monocytess (precursors of macrophages) that absorb and digest foreign substances, neutrophils releasing antibacterial proteins and T- and B-lymphocytes participating in the immune defense mechanism must reach the affected site during an infection of the organism, where they trigger a defense reaction (inflammation). The above-mentioned cells circulating in the blood must accumulate in the affected area, penetrate the vessel wall and initiate the defense process in the interstitium. This phenomenon is called *extravasation* (**trapping on the wall and penetration**).

Sequence of marches in extravasation

Free leukocyte in the blood circulation → leukocyte rolling along the vessel wall → adhesion to the endothelium → extravasation → invasion into 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. Cytokines produced by leukocytes are called interleukins (leukocytes influence each other with them). 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,
- they control the development and function of cells of the immune system, as well as other cells,
- are important molecules that can influence proliferation, differentiation and cell migration.

Unlike hormones, cytokines are not produced in glandular formations, but by different individual cells, they mainly act locally: paracrine or autocrine, not endocrine like hormones. Cytokines have a **pleiotropic effect** (one cytokine has multiple effects); they also act **redundantly** (several cytokines have the same effect) and sometimes also **antagonistically** (one cytokine inhibits others). Their activity can be divided into five larger areas:

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

The effect of individual cytokines is rather difficult to predict. They do not perform it alone but together with other cytokines or other molecules, both synergistically and antagonistically. Cytokines usually **start a cascade of production of other cytokines** in which the next cytokine can affect the previous one. Cytokines themselves do not have antigen specificity, but cytokine receptors, which are expressed on the surface of cells that have been previously activated by the antigen, implement 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 mostly produced for a very short period of time after cell activation in an immune or inflammatory response.

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

- 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 suppress the production of antibodies from activated B-lymphocytes, and can also activate macrophages, NK-cells and T-lymphocytes. They also have direct antiproliferative activity and are cytostatic or cytotoxic against various types of tumor cells.
- Chemokines – act in chemotaxis or inflammation (e.g. IL-8). They are multipotent cytokines that localize or promote an inflammatory reaction by inducing chemotaxis (attracting inflammatory cells to the site of affection) and above all by activating inflammatory cells in the affected area. They are also necessary mediators for the normal migration of leukocytes.
- **Colony stimulating factors (CSFs)** - affect the growth and proliferation of certain types of progenitor cells. E.g. G-CSF is a colony-stimulating factor of granulocyte progenitor cells to proliferate and differentiate. M-CSF affects the proliferation and differentiation of stem cells into macrophages, especially differentiation into monocytes. GM-CSF is responsible for the growth and development of progenitors of both granulocytes and macrophages.
- **Tumor-necrotizing factors (TNF)** - they are derived from macrophages, they have anti-tumor activity. The TNF family consists of two molecular individuals, TNFa and TNFb. TNFα induces the expression of other autocrine growth factors, increases the response of cells to growth factors, and induces signaling 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 induce terminal differentiation in others. Induction of TNFb results in an increase in IL-2 and antigen interaction with receptors on T-cells.

According to the main effect, cytokines can be classified into 4 large groups:

Pro-inflammatory cytokines

These include **TNF, IL-1, IL-6**. They are the main molecules that induce and enhance any inflammatory response. They are secreted by most cells already in the initial phase of inflammation. Their effect consists in changes in the affected area:

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

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

Chemokines

IL-8 is a prototype, it has a chemoattractive 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 create a kind of 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 inflammatory cells from progenitors in the bone marrow. Some cytokines also induce specific differentiation from hematopoietic stem cells.

Immunomodulatory cytokines

These mainly include **IL-2, IL-4, IL-5, IFNg** and others. They are particularly important for the development of T- and B-cells after stimulation. They induce both activation as well as determine the type of immune response.

Cytokines secreted by TH-lymphocytes (CD4+)

Effect of Type 1 Cytokines

- **IL-2** - after the initial stimulation of TH-lymphocytes (helper T-lymphocytes) by antigen-presenting cells, IL-2 is secreted, which activates the cells as an antigen and as a mitogen of mature resting T-lymphocytes. By interacting with its high-affinity receptor, IL-2 promotes the clonal expansion of effector T-cells, initially activated by the antigen.
- **IL-12'** directly induces the initial development of Th1 cells and the formation of Th1 cells secreting IFNg. IL-12 is also thought to be a suppressor of IL-4-induced IgE production. IFNg controls the class of antibodies formed by B-cells, reduces the expression of MHC I and II antigen complex. classes and increases the efficiency of the destruction of intracellular parasites by macrophages.

Effect of Type 2 Cytokines

- **IL-4** by Th2-cells induces **selective production of immunoglobulin isotypes** IgG, IgA and IgE within the humoral response. IL-4 regulates the expression of surface antigens on B-cells, resulting in the promotion of the 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 has 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 wide spectrum of activity on a number of cells with both immunosuppressive and immunostimulating effects. IL-10 produced by Th2-cells inhibits the production of cytokines, mainly IFNg, formed in Th1-cells after antigen activation. It is also a potent regulator suppressing the cell-mediated immune response, which causes its strong anti-inflammatory effect.
- **IL-13** is a pleiotropic cytokine produced by activated Th2 cells. It probably has an effect on the morphology and the emergence of phenotypes in monocytes by the induced expression of IgE-receptors and suppression of the expression of the MHC II complex. classes. It also participates in the switch between IgE and IL-4-dependent IgG4 production and IgE synthesis in the presence of T-cells.

Cytokine receptors

The effect of cytokines, by which they influence the growth and differentiation of cells, is dependent on their recognition and binding to specific receptors. These receptors located on the cell membrane transfer the relevant signal to the interior of the cell, where they trigger a signaling cascade. Binding with the respective ligand will give rise to an active multicomponent complex, which often consists of oligomerization of 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-3Rα,b, IL-4Rα, IL-5Rα, IL-6Rα, IL-7a, IL-9R, IL- 11R(gp130), IL-12Rb1,b2, IL-13R, IL-15R, GM-CSF-Ra,b,

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

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

Links

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