Cell signaling

Cell signaling refers to '*communication between cells*.

Regulates:

- development of cells and their organization into tissues,
- growth and cell division,
- coordination of cellular functions.

Types of signaling

Endocrine (hormonal)

Cells secrete signal molecules (primarily hormones) that enter the blood and through the circulatory system to the target cell, to which receptor binds.

- Action - remote.
- Speed – in minutes.

Paracrine

Cells release chemical substances (eg growth factors) into ECT that act as local mediators and affect cells in the immediate vicinity. For example, signaling molecules that regulate inflammation at the site of infection or cell proliferation during healing wounds work in this way.

Autocrine

The secreted signaling molecule binds to the receptor of the cell that produced it.

Synaptic

This signaling is specific to the nervous system of animals. A nerve cell produces a chemical signal (neurotransmitter) that is transmitted to another nerve cell synaptic cleft.

- Speed - up to 100 m/s[1].

Methods of cellular communication

By direct contact

1. Joining complexes ensure the continuity of cells that are adjacent to each other. In animal cells using nexus (gap junctions), in plant cells using plasmodesmata.
2. Interaction of cell surface molecules.

Through signaling molecules

Signal molecules are substances that are capable of transmitting a signal. They can be divided according to their chemical nature into several groups:

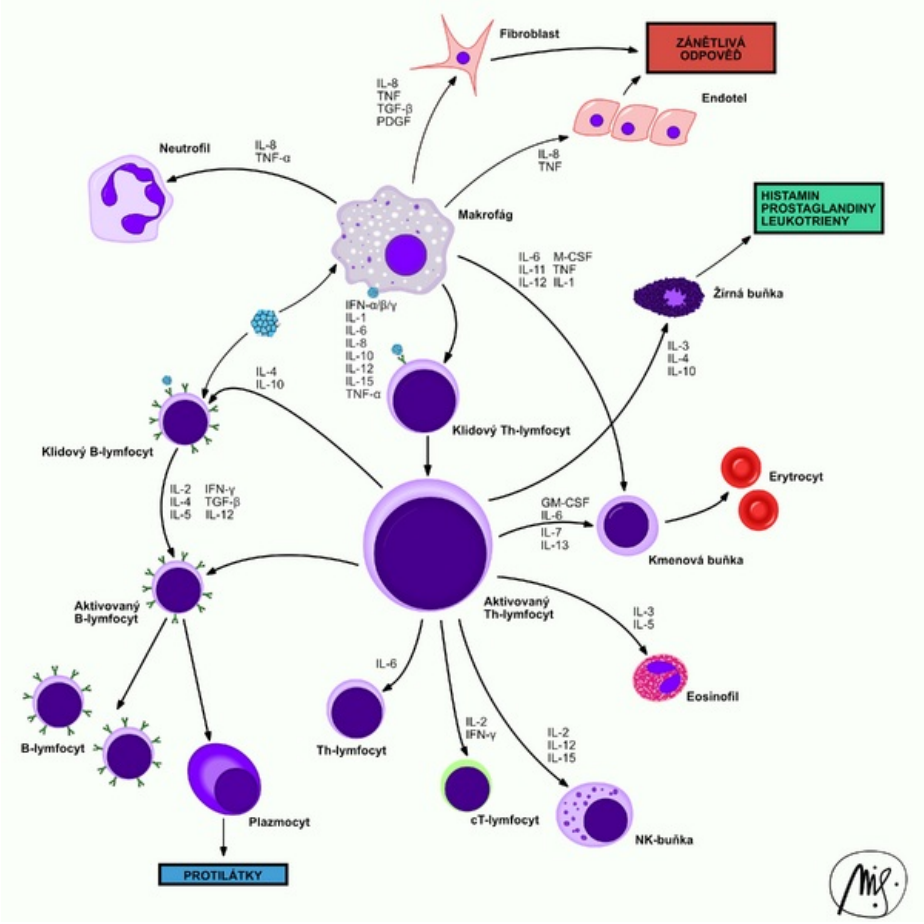
1. **Lipophilic signaling molecules**:
   - steroid hormones,
   - thyroid hormones,
   - fatty acid derivatives (eicosanoids),
   - retinoids (retinal).
2. **Peptide and protein signaling molecules**:
   - peptide hormones (e.g. liberins, statins, insulin, glucagon, vasopressin),
   - growth factors and cytokines.
3. **Amino acid derivatives**:
   - hormones (e.g. adrenaline, noradrenaline),
   - neurotransmitters (e.g. GABA, glutamate, glycine),
   - mediators (eg histamine).
4. **Small inorganic molecules and ions**:
   - NO,
   - WHAT,
   - Ca^{2+}.
5. **Nucleotides**:
   - cAMP,
   - cGMP.

Mechanism of action of signaling molecules

It depends on whether the signaling molecule is water soluble (hydrophilic) or fat soluble (hydrophobic). The cytoplasmic membrane of cells is permeable to hydrophobic (= lipophilic) signaling molecules and to small inorganic molecules such as NO. These molecules bind to **cytoplasmic or nuclear receptors'**, which mostly act as transcription factors controlled by ligands and after binding the signal molecule affect the transcription of genes. For hydrophilic signaling molecules (peptides, proteins) and amino acid derivatives, the cytoplasmic membrane is impermeable and therefore their signaling must take place via receptors located in the cytoplasmic membrane of the target cells (so-called ``membrane receptors*). After binding of a signal molecule (ligand) to a membrane receptor, signal transduction occurs, i.e. signal transmission from the receptor to the interior of the cell. This is followed by intracellular signaling, which often involves second messengers or specific protein kinases. These subsequently regulate the activity of effector proteins and the behavior of the cell will change. Effector proteins can be enzymes affecting metabolism, transcription factors, components of the cytoskeleton or ion channels.*

Signaling Stages

1. Production of a signal molecule signaling by a cell (based on superior stimulation – e.g. hormones controlled by the hypothalamo-pituitary axis, or when the concentration of certain molecules changes – e.g. glucose or ions).
2. Reception of the signal by the target cell → the signal molecule binds to the receptor.
3. Signal transmission (= signal transduction) – can be one-step or involve a cascade of changes in molecules (the so-called signaling pathway).
4. The signal triggers a specific response.
5. Degradation of the signaling molecule.



Cytokine interactions between cells of the immune system

Types of Membrane Receptors

They differ in the signal that is created inside the cell after the binding of the extracellular signal molecule to the receptor.
⚠

Enzymotropic receptors (catalytic receptors, enzyme-linked receptors or receptors with intrinsic enzymatic activity)

They are proteins that, for example,bypasses the phospholipid bilayer of the membrane only once. They consist of an extracellular part of a protein with a binding site for a signaling molecule, a transmembrane α-helix, a cytoplasmic part that either contains its own enzymatic activity or is associated with an enzyme. A receptor is either a ligand-directed enzyme or a protein that binds to the enzyme. Many receptors contain a cytoplasmic portion that functions as a tyrosine protein kinase. After binding the signal molecule, 2 receptor proteins join and a dimer is formed. This activates the tyrosine kinase parts of the receptor, which phosphorylate the tyrosines (with the help of phosphate groups from ATP) of the receptor itself. Phosphorylated tyrosines serve as binding sites for various proteins, which themselves become active after binding. Thus, for example, the signaling molecule Ras (GTP-binding protein) is activated, which subsequently activates other protein kinases and, finally, a change in gene expression occurs. Signal termination is catalyzed by protein-tyrosine-phosphatase, or activated receptors can be endocytosed and degraded in lysosomes. E.g. growth factors or insulin bind to receptors with tyrosine kinase activity, in more detail below. The group of enzymotropic receptors also includes receptors with serine/threonine kinase, guanylate cyclase or tyrosine phosphatase activity.

Receptors with tyrosine kinase activity

They are mainly receptors for most growth and differentiation factors such as EGF (epidermal growth factor), PDGF (platelet-derived growth factor), IGF-1 (insulin like growth factor) and insulin receptor. After binding of the ligand to the receptor, it is activated and the phosphate group is transferred from ATP to specific tyrosines. Either the tyrosines of the receptor proteins themselves (autophosphorylation) or the tyrosines of specific cellular proteins (intracellular protein kinases) are phosphorylated. This initiates a cascade of intracellular signal transmission.

Ras proteins are among the important intracellular signal proteins that are primarily involved in *signal transmission from a receptor with tyrosine kinase activity to the interior of the cell*, where they activate the serine/threonine phosphorylation cascade. Ras proteins are anchored in the cytoplasmic part of the plasma membrane. It belongs to the family of ``monomeric GTPases *(as opposed to G proteins - trimeric GTPases). However, the activation and function of monomeric and trimeric GTPases is similar. They are in a constant transition between an* ***active***''' ***when*** *GDP'* is bound. Ras proteins are phosphorylated (activated) by receptor tyrosine kinases, inactivated by phosphatases and GTP hydrolysis, which they themselves carry out.

The tyrosine phosphorylation of Ras proteins, which is carried out by receptor tyrosine kinases on the cytoplasmic side of the plasma membrane, is quickly terminated by dephosphorylation by specific tyrosine phosphatases. Activated Ras proteins also inactivate themselves by hydrolysis of bound **GTP** to **GDP**. Stimulating cells to proliferate and differentiate, however, requires long-term signaling. Further signal transmission is ensured by ``phosphorylation of serines and threonines by MAP-protein kinases (mitogen-activated protein kinases)*. Serine and threonine phosphorylation has a longer duration than Ras protein tyrosine phosphorylation.*

The active Ras/GTP complex binds to Raf-kinase (MAP-kinase 1) and activates it by phosphorylating serines and threonines.

Other protein kinases are also involved in the regulation of Raf-kinase activity:

1. activation of Raf-protein kinase increases Src-protein kinase by tyrosine phosphorylation;
2. protein kinase C by serine phosphorylation;
3. phosphorylation of serines by protein kinase A has an inhibitory effect

Active Raf-kinase activates by phosphorylation MAP-kinase 2, which activates MAP-kinase 3, which enters the nucleus. Here, a regulatory protein is activated, which stimulates the activity of genes involved mainly in the regulation of cell proliferation.

Activated Ras proteins phosphorylate and thereby activate a cascade of three types of MAP-kinase. Binding of the first MAP-kinase (referred to as Raf) to the activated Ras protein results in its phosphorylation and thus activation. This then catalyzes the serine/threonine phosphorylation of another MAP-kinase and this enzyme activates another (third) MAP-kinase Activation of the last MAP-kinase in the cascade by MAP-kinase phosphorylation requires phosphorylation of both "threonine" and "tyrosine" *. After entering the nucleus, the activated MAP-kinase first phosphorylates the regulatory protein, which is bound to a short DNA sequence in the regulatory region of the early response genes - the myc, jun and fos genes. This results in their transcription.*

Late response gene products are involved in the regulation of cell proliferation. These include, for example, the main components of the cell cycle control system – '*cyclins and cyclin-dependent protein kinases.*

Receptors with tyrosine phosphatase activity

The specific activity of these enzymes ensures that the phosphorylation of tyrosines takes **velmi for a short time**, and that only a **small**''''''*amount* of tyrosines are phosphorylated in resting cells. An example of a receptor with tyrosine phosphatase activity is the membrane glycoprotein CD45, which is found on the surface of white blood cells. It participates in the activation of T and B lymphocytes after encountering foreign antigens.

Receptors with guanylate cyclase activity

It is, for example, a receptor binding **atrial**''''''*natriuretic*''''''**peptides *(ANPs), which is a group of peptide hormones. They are found in kidney cells and in the cells of*** *smooth muscle of blood vessels''*. Atrial natriuretic peptides are secreted by atrial muscle cells when blood pressure rises. They stimulate the kidneys to excrete Na+ and water and induce relaxation of muscle cells in the walls of blood vessels. Both of these effects lead to a reduction in blood pressure.

The receptors have an extracellular region for binding ANPs and an intracellular guanylate cyclase catalytic domain. Binding of the ligand to the receptor activates the cyclase to produce cyclic 3',5'-GMP (cGMP). cGMP binds to cGMP-dependent protein kinase and thus activates it to phosphorylate the serines and threonines of specific proteins, which are involved in further signal transmission and realization of the final expression.

Receptors with attached tyrosine kinase activity

It differs from receptors with tyrosine kinase activity in that the tyrosine kinase in this case is encoded by another separate gene (e.g. proto-oncogene src) and is non-covalently attached to the cytoplasmic part of the receptor polypeptide chain. These receptors form a large heterogeneous group. They are, for example, receptors for most of the *cytokines* that regulate the proliferation and differentiation of cells of the hematopoietic system; antigen-specific receptors on T and B lymphocytes; hormone receptors (eg growth hormone, prolactin) and others.

The antigen is presented by **MHC** molecules and recognized by T lymphocyte receptors (TCR); The TCR is activated and transmits a signal via signaling molecules to the nucleus. Subsequently, **cytokine expression** occurs.

The secreted cytokine binds to and activates the membrane receptor of the B lymphocyte with associated '*tyrosine kinase activity*. The tyrosine kinase is encoded by the **proto-oncogene**'''*src*.

Receptors associated with ion channels (ionotropic receptors)

File:Ligand-gated ion channel receptor.jpg

Some receptor proteins regulate the activity of ion channels by binding a signaling molecule. Their opening and closing is its own signaling response. After the binding of the nerve mediator, the conformation of the receptor changes and the ion channel closes or, conversely, opens for specific ions that move along their electrochemical gradient and the membrane potential changes. This type of cellular signaling occurs in so-called excitable tissues - the nervous system and muscles.

G-protein-coupled receptors (GPCR = G-protein–coupled receptor)

File:Functions of G-protein coupled receptors.jpg

A receptor is a polypeptide chain that crosses the membrane seven times. In the resting state, the G-protein probably does not even touch the receptor. It consists of three subunits α, β, γ. GDP is bound to the α subunit at rest. After ligand binding, the receptor couples to a G-protein and GDP is replaced by GTP. Termination of the signal is accompanied by the hydrolysis of GTP back to GDP (the α subunit has ``GTPase activity*). The target of action of the activated G-protein (its dissociated α subunit or βγ complex) can be ion channels or enzymes in the membrane.* **Adenylate cyclase** *(production of cAMP) and '**phospholipase C*** (production of IP_3 and DAG) are most often activated.

General diagram of signal path

Hormone → membrane receptor → G-protein → adenylate cyclase → cAMP → protein kinase A →

1. phosphorylation of enzymes affecting metabolism (quick effects);
2. phosphorylation of gene regulatory proteins → influencing gene transcription (slow effects).

Second messengers and their functions

Second messengers are small, non-protein, in water soluble molecules. They are called second, because the first messenger is a signal molecule, which binds to the receptor protein. They are involved in transfering the signal in pathways starting by G-protein receptors as well as in pathways starting by an enzyme-linked receptors. They are made from easily accesible substrates and have a short half life. Second messengers include **cAMP, kalcium cations, cGMP, inositol-1,4,5-trisphosphate, diacylglycerol, phosphatidylinositol-3,4,5-trisphosphate** and more. Except for calcium cations, second messengers are produced by specific enzymes after stimulation of membrane receptors. Afterwards seccond messengers activate proteinkinases, which phosphorylate aminoacids serine or threonine in various intracellular proteins. Phosphorylation changes activity of these proteins in terms of activation or inhibition. Activity of second messengers is limited and they are degradated by different enzymes.

Second messenger	Substrate	Enzyme	Efector	Degradation
cAMP	ATP	adenylate cyclase (AC)	proteinkinase A (PKA)	fosfodiesterases (PDE)
cGMP	GTP	guanylate cyclase (GC)	proteinkinase G (PKG)	fosfodiesterases (PDE)
Calcium cations (Ca^{2+})	–	release from ER after stimulation IP_3	calmodulin	re-resorption to ER with help of Ca^{2+} ATP-ase
inositol-1,4,5-trisphosphate (IP_3)	phosphatidylinositol-4,5-bisphosphate (PIP_2)	phospholipase C (PLC)	proteinkinase C (PKC)	phosphatases – defosforylation to inositol
diacylglycerol (DAG)	phosfatidylinositol-4,5-bisphosphate (PIP_2)	phospholipase C (PLC)	proteinkinase C (PKC)	lipases – formation of glycerol and free fatty acids
phosphatidylinositol-3,4,5-trisphosphate (PIP_3)	phosfatidylinositol-4,5-bisphosphate (PIP_2)	phosphatidylinositol-3-kinase (PI3K)	proteinkinase B (PKB)	phosphatase PTEN – cleavage of phosphate in position 3

Cyclic adenosinmonophosphate (cAMP)

Cyclic AMP is made from ATP by enzyme adenylate cyclase, which is binded to the cytoplasmatic membrane and activated through G-protein after binding of signal molecule to it's membrane receptor. cAMP then transfers the signal from cytoplasmatic membrane to the metabolic pathways in cytoplasm. Transfer molecule following the cAMP is usually **proteinkinase A (cAMP-dependent proteinkinase)**, which phosphorylates other proteins. PKA-regulated proteins are involved for example in regulation of glycid and lipid metabolism, transport of water and ions in kideys and more. cAMP doesn't stay in cell for long and is soon transformed by *fosfodiesterase to* AMP (adenosinmonophosphate).

Cyclic guanosinmonophosphate (cGMP)

Is formed similiarly to cAMP, meaning it's formed by enzyme ***guanylate cyclase*** from GTP. Guanylate cyclase is activated for example by atrial natriuretic peptid (ANP)[2]. cGMP activates **proteinkinase G (cGMP-dependent proteinkinase)**, which phosphorylates target proteins. Signal transduction including cGMP use for example rods in eye retina or smooth muscle cells in cavernous bodies of penis.

Second messengers derived from phosphatidylinositol-4,5-bisphosphate

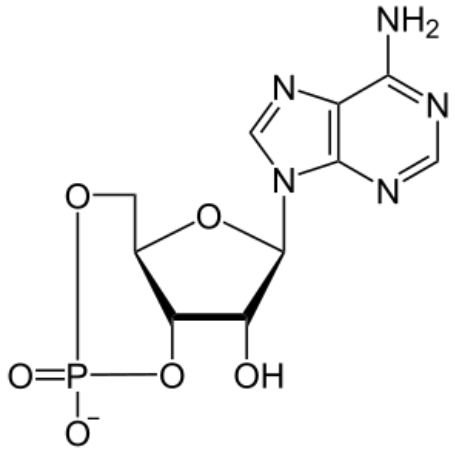
Phosphatidylinositol-4,5-bisphosphate (PIP_2, also $PtdIns(4,5)P_2$) is a phospholipid found in cytoplasmatic membrane. From phosphatidylinositol-4,5-bisfosfate can be synthesised second messengers, which can affect two different proteinkinases.

Phosphatidylinositol-3,4,5-trisphoshate

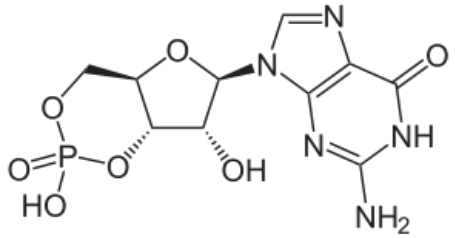
Phosphatidylinositol-3,4,5-trisphosphate (PIP_3, aslo $PtdIns(3,4,5)P_3$) is synthesised by phosphorylation of PIP_2 by enzyme ***phosfatidylinositol-3-kinase*** (PI3K). It stays binded in the inner layer of cytoplasmatic membrane and here activates *phosphatidylinositol-dependent kinase 1* (PDK1), which phosphorylates (and by that activates) **proteinkinase B**. Proteinkinase B (PKB, also called AKT) phosphorylates proteins that regulate proliferation, cell cycle and apoptosis.

Diacylglycerol a inositol-1,4,5-trisphosphate

Signal molecule binds to a receptor, which leads to an activation of enzyme phospholipase C, which splits phosphatidylinositol-4,5-bisphosphate to 1,2-diacylglycerol (DAG) a inositol-1,4,5-trisphosphate (IP_3, also $Ins(1,4,5)P_3$). Both are second messengers. IP_3 diffuses through cytosol, and binds to a calcium channel in endoplasmatic reticulum and opens it. Calcium cations are releases from endoplasmatic reticulum and therefore raise the Ca^{2+} level in cytosol. DAG stays immersed in cytoplasmatic membrane. DAG and calcium cations together activate **proteinkinase C**, which then phosphorylates proteins associated with cytoskeleton and by that affect contraction, migration and secretion in cells.



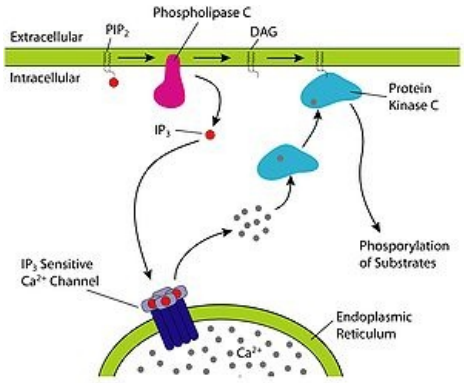
cAMP



cGMP

Calcium cations

Ca^{2+} is more regular second messenger than cAMP. Rise of Ca^{2+} concentration causes contraction of muscle cells or secretion of certain substances. Cells always contain certain level of Ca^{2+}, but extracelular level is much higher than intracellular. Intracellular level is raised by opening of calcium channels in endoplasmatic reticulum, which is caused by binding of IP_3 onto this channels. Calcium cations could be accounted for as third messegers. Calcium cations activate other proteins directly or with a help of **calmodulin**, protein binding Ca^{2+}. Calmodulin with binded calcium cations activates CaM-kinases, which phosphorylate other proteins.



PIP2 cleavage to IP3 and DAG

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