

Signaling disorders causing tumor cell hyperproliferation

Introduction

Cell signaling represents a set of complex **cascade reactions**, which are mediated by an interconnected network of kinases, phosphatases, transcription factors, G proteins and enzymes.

A simplified scheme represents binding of a ligand to a receptor, activation of this receptor, signal transduction in the cell (or its amplification – most often by a cascade of kinases) and activation of transcription factors that regulate the expression of certain genes. The expression of a certain gene means the synthesis of a protein with a specific function for **cell proliferation, differentiation, initiation or blocking of apoptosis or the cell cycle**. Individual proteins in the cascade recognize the phosphorylated domains of the previous member of the cascade using their own -SH2 domains.

Signaling pathways in the cell are important for carcinogenesis at the molecular level. Disturbances in these cascades—usually overexpression or inhibition of a particular cascade intermediate—can induce changes in the cell that give it a proliferative advantage and thus subject the cell to clonal selection.

Signaling pathways for growth factors

- They use a wide range of signal transducers
- As an example, we can mention the cascade through **MAPK protein** and **PI3K/Akt**
- Binding of the growth factor to the receptor induces dimerization of the receptor, which activates the tyrosine kinase activity of the receptor and results in its autophosphorylation
- A cascade of phosphorylation and dephosphorylation of individual members of the signaling pathway follows

MAPK cascade (mitogen activated protein kinase)

- It consists of receptor and **Ras protein** activation and three related kinases, of which there are multiple types, depending on the primary stimulus: **MAPKKK** (mitogen activated protein kinase kinase kinase), **MAPKK** and **MAPK**
 - By phosphorylating the receptor, the signal is transmitted via the **Grb2** and **SOS** proteins to the Ras protein. Ras protein is a G protein with GTPase activity. After binding of GTP to RAS, the **Raf protein is activated**
 - The Raf protein activates other kinases in the cascade, namely MEK and Erk
 - Phosphorylated **Erk** enters the nucleus, where it activates transcription factors responsible for cell growth and differentiation
 - In addition to the above, stress and pro-inflammatory cytokines can trigger the activation of the Rac protein after activation of the Ras protein, which triggers a cascade through MEKK, MKK and SAPK/JNK, which in the nucleus activate genes responsible for growth, differentiation and apoptosis. MKK can also be activated via ASK 1, which directly responds to the action of oxidative stress
- schematic of the MAPK cascade

Pathologically, the following may occur:

- To overexpress the receptor for growth factors (EGFR family)
- To a mutation in k-ras, whereby the GTPase activity of the Ras protein is lost and it becomes permanently stimulated
- To the loss of the lipid bond that holds Ras to the membrane, causing the protein to lose its function (however, this disorder inhibits signaling, it is used therapeutically)
- To overexpress some of the kinases
- The entire MAPK signaling cascade is much more complex, and the individual pathways are interconnected, so it is difficult to clearly separate them from each other. The principle of all variants of the MAPK cascade is the same, their application depends on the type of stimulus

PI3K/Akt pathway

- **PI3K** is activated either by autophosphorylation of the receptor for growth factors (of the EGFR family) or by activation of the receptor for cytokines
- PI3K creates **PIP3** from membrane proteins, which activates **PKD1**, which subsequently phosphorylates the **Akt protein** – a kinase that has a broad spectrum of activity
 - For example, it phosphorylates IKKalpha, thereby triggering the NF kappaB signaling pathway
 - It activates glycolysis and inhibits glycogen synthesis
 - It acts on the MDM2 protein, which controls the activity of the p53 protein by inhibiting it
 - Activates the 14-3-3 protein, which phosphorylates the Bad protein, releasing it from binding to the Bcl-2 protein, which is activated by it
 - It activates the mTOR protein signaling pathway, which ultimately triggers cellular proteosynthesis

- and proliferation.
 - Inhibits cell cycle blockers
- schematic diagram of the PI3K/Akt pathway

Pathologically, it can occur:

- - To increase receptor activity (similar to the MAPK pathway)
 - A mutation in the gene for PI3K, resulting in uncontrollable activity of this kinase
 - To overexpression of the Akt protein - for example, ovarian tumors
 - To a mutation in which the PTEN phosphatase function is lost, which inhibits the formation of PIP3, a product of PI3K

JAK/STAT track

Normální funkce JAK/STAT.

- - It starts with a receptor for cytokines (also interleukins), which dimerizes after binding a substrate. It is a receptor with associated tyrosine kinase activity mediated by **JAK kinases**. By dimerizing the receptor, they activate, phosphorylate each other and, in addition, activate Grb2 and Ras, PI3K and **STAT proteins by phosphorylation**
 - Phosphorylated STAT proteins dimerize and enter the nucleus, where they function as transcription factors for the expression of c-Myc, cytokines, and other transcription factors
 - Activated transcription negatively inhibits the signaling cascade through the SOCS protein, which inhibits the activity of JAK kinases
 - diagram of the JAK/STAT track

Pathologically

- - JAK kinases are most frequently upregulated, which occurs in some lymphoproliferative and myeloproliferative diseases
 - Downregulation of the SOCS gene can also occur (e.g. by DNA hypermethylation)

NF kappaB

- - It reacts to the action of **TNF**, growth factors, cytokines.
 - Upon binding to the receptor, the TNF factor triggers a cascade that acts on **IKK**
 - IKK kinase phosphorylates the IκB complex and it breaks down into two complexes:
 - IκBα, NFκB1, p50, RelA
 - IκBβ, NFκB2, p52, RelA, p65
 - The IκB inhibitor is separated from each complex and is degraded in the proteasome. The above-mentioned proteins join the p50,RelA,p50,p52,NFκB complex, which enters the nucleus and acts there as a transcription factor
 - NFκB is responsible for cell proliferation, is involved in the inflammatory response and immune regulation. It also participates in the survival and differentiation of B lymphocytes. Disorders of this pathway can be observed in some hematological malignancies
 - The pathway is also activated after the action of pro-inflammatory cytokines
 - scheme of NFκB signaling This pathway can be **dampened by the administration of salicylates, flavonoids, glucocorticoids**

TGF

- - TGF acts on its TGF receptors, which activate the **Smad2** protein
 - Phosphorylation of Smad2 activates Smad4, which acts in the nucleus as a transcription factor and is responsible for cell activation, cell growth, increased cell motility and migratory potential
 - TGF plays a role in angiogenesis and the formation of metastases, where it potentiates cell migration while disrupting the consistency of the ECM matrix and increasing vascular permeability
 - Its production is stimulated, for example, by the activation of the hypoxia-sensitive HIF protein in the tumor cell, which triggers the synthesis of ECM proteases, growth factors and cytokines, which are needed in angiogenesis
 - scheme of TGFβ signaling
 - application of TGF in angiogenesis

Wnt/Beta catenin

- - It is a pathway mediating signal transduction through Beta catenin (a protein involved in intercellular adhesion junctions), which is activated by the binding of the Wnt protein to its receptor
 - Beta-catenin subsequently acts in the nucleus as a transcription factor
 - Deregulation of this pathway leads in some cases to the development of a malignant disease
 - the Wnt/beta catenin signaling pathway

Notch track

- - This signaling pathway mediates juxtacrine (ligands are membrane proteins of the neighboring cell that sends the signal) communication between neighboring cells in very close contact with each other

- It is used in the development of the nervous, cardiovascular and endocrine systems
- Activation of the receptor triggers a cascade by modifying the receptor protein, which in the resulting modification acts as a transcription factor in the nucleus
- Mutations in Notch receptors are involved in the development of some types of T leukemia
- In the cascade, the enzyme **gamma secretase** is also used, which is a possible therapeutic target of the so-called targeted therapy
- scheme of Notch signaling

Cell cycle regulation

- It is regulated at two main checkpoints, where DNA integrity and quality are assessed before replication, and then regulatory and repair mechanisms monitor whether errors have occurred after DNA replication and whether the DNA has been replicated in its entirety.
- The role of regulation is mainly played by two proteins, products of tumor suppressor genes, the disorders of which can cause uncontrolled hyperproliferation of cells.

pRB

- it is normally bound to the transcription factor **E2F** and blocks the synthesis of cyclin E. In the case of activation of the cyclin D/CDK4,6 complex, pRb is phosphorylated, thereby releasing it from binding to E2F and synthesizing cyclin E (crossing the G1/G0 checkpoint), which will enable the synthesis of cyclin A and entry into the S phase.
- Synthesis of cyclin D is inhibited by proteins p15, p16 and p27 inhibits Cdk2, which is required for entry into the S phase of the cycle. These inhibitory proteins are deactivated upon mitogenic stimulation by growth factors (e.g. TGF) or cell cycle regulating proteins (e.g. c-Myc products)

p53

- Is a protein responsible for controlling the integrity of the genome ("guardian of the genome")
- It induces the production of proteins that inhibit cell cycle progression until the DNA is checked or the cell is stimulated.
- Its level is kept at a low level thanks to the mdm2 protein, which ensures ubiquitinylation of p53 (after ubiquitinylation, p53 travels to the proteasome, where it is degraded).
- However, DNA damage activates the **ATM/ATR** kinase, which phosphorylates p53, and phosphorylated p53 cannot interact with mdm2.
- This subsequently induces GADD45 (DNA repair) proteins, BRCA1 tumor suppressor, p21, which blocks Cdk and thus stops the cell cycle, and last but not least, Bax protein, which triggers the internal pathway of apoptosis. At the same time, the Bcl2 protein is inhibited.
- cell cycle- G1/S checkpoint
- cell cycle- G2/M checkpoint

List of abbreviations [[edit](#) | [edit source](#)]

Akt - protein kinase B
 ASK - apoptosis signal-regulating kinase 1
 ATM/ATR - ataxia telangiectasia mutated protein kinase/ATM and Rad3 related protein kinase
 Bad - a member of the Bcl-2 family of pro-apoptotic proteins
 Bax - pro-apoptotic factor
 c-Myc - oncogene, transcription factor of signaling pathways for mitosis
 Erk - extracellular signal-regulated protein kinase
 Grb2 - growth factor receptor adapter protein 2
 HIF - hypoxia-inducible factor
 IKK - I κ B kinase
 I κ B - inhibitor of NF κ B
 JAK - Janus activator tyrosine kinase pathway for cytokines and growth factors
 MAPK - mitogen-activated protein kinase
 MDM2 - mouse double minute 2
 MEK (MKK) - MAPK/ERK kinase
 MEKK - a kinase that activates Erk through MEK
 mTOR - mammalian rapamycin
 PDK1 - phosphatidyl dependent kinase
 PI3K - phosphatidyl-inositol-3-kinase
 PIP3 - phosphatidyl-inositol-3,4,5,-triphosphate
 Rac - cytosolic Ras
 Raf - cytoplasmic serine/threonine kinase activated by Ras
 Ras - GDP/GTP binding protein
 SAPK - stress-activated protein kinases
 Smad - Smad and Mad related proteins
 SOCS - suppressor of cytokine signaling
 SOS - son of sevenless
 STAT - signal transducer and transcription activator

Links

References

- - MASOPUST, Jaroslav, et al. *Pathobiochemistry of the cell*. 1st edition. Prague: Charles University, 2nd Faculty of Medicine, 2003. 344 pp. ISBN 80-239-1011-6 .
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External links

- - www.cellsignal.com

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