Apoptosis and clinical consequences of its dysregulation

Apoptosis is a **physiological process** in which **energy is consumed**. **It does not cause an inflammatory reaction** (unlike necrosis). It is important for embryonic development, in hormone-dependent cycles (endometrium, mammary gland, prostate) and for cell renewal (intestinal epithelium, etc.). Disturbances in the regulation of apoptosis can lead to cancer, organ hypotrophy (e.g. kidney) or congenital developmental defects (e.g. syndactyly).

Stages of apoptosis

1. The signal for apoptosis - the decision to die,
2. The execution of apoptosis,
3. Degradation of apoptotic bodies by phagocytosis.

Signal for apoptosis

- It can come externally or internally,
- **external pathway** - growth factor deficiency, cytotoxic cytokines (**FasL**, TNF), morphogens, glucocorticoids, etc.,
- **internal pathway** - signals mainly from mitochondria, controlled by the Bcl-2 gene family (bax and bcl-2 gene).

Signals for survival

- Growth factors, cytokines, hormones, viral protein p53.

Signal for apoptosis

- Morphogens, viruses, glucocorticoids, genotoxic effects, cytotoxic cytokines (TNF, FasL), T-lymphocytes and NK-cells (granzyme B, perforins).

Genes - suppressors of apoptosis

- Bcl-2, bag, Rb.

Genes - inducers of apoptosis

- bax, bak, bad, TP53.

Execution of apoptosis

- Signals for apoptosis cascade to activate **ICE (caspases)**, which triggers the actual execution of apoptosis,
- chromatin condensation and aggregation in the periphery of the nucleus, DNA cleavage between nucleosomes (fragments are 180 to 200 bp long),
- the ER enlarges, forms pockets and fuses with the cytoplasmic membrane,
- forming vacuoles and aggregating filaments,
- mitochondria burst and release **cytochrome C**,
- and finally, **apoptotic bodies form**.

Phagocytosis of apoptotic bodies

- Uptake by macrophages and surrounding cells.

Genes and proteins related to apoptosis

The Rb gene produces the p105 protein, which is phosphorylated at least 10 sites in the G1 checkpoint by cyclin/cdk complexes (cyclin D/cdk 4, 6 and cyclin E/ ckd2), altering its ability to associate with the E2F protein, which forms heterodimeric complexes with DP1. E2F and DP1 are transcription factors that induce the expression of genes required for S-phase development (e.g. DNA polymerase, thymidine kinases, dihydrofolate reductases, c-myc, c-myb and cdc2). This means that the Rb gene is essential for S-phase development and suppresses apoptosis. Mutations in the Rb gene cause retinoblastoma, bone, breast, lung, prostate or bladder tumours.

The TP53 gene is a tumor suppressor gene whose key role also lies in the regulation of the G1 checkpoint. The product of the TP53 gene, p53 protein, is a transcription factor that activates the expression of genes for factors that inhibit cell proliferation. One of these is the p21 protein, which stops the development of the cell division cycle so that DNA repair can occur. If the DNA damage is unrepairable, p53 is involved in the induction of apoptosis. TP53 mutations are present in 50% of cancers, and congenital mutation of this gene leads to Li Fraumeni syndrome.

Bcl-2 and **bax** are genes whose products form both homodimers and heterodimers together. Bcl-2 suppresses apoptosis, bax induces apoptosis. Bcl-2-bax heterodimers do nothing. Depending on whether the amount of bax-bax or bcl2-bcl-2 homodimers predominates, apoptosis will or will not occur.

The p35 protein is encoded by some viruses. It inhibits apoptosis so that the virus can continue to live and spread in the host cell. The p35 protein is cleaved by caspases instead of their other substrates, thus preventing them from effectively inducing apoptosis.

Cells also need stimulation by **survival factors** (hormones, cytokines, growth factors) to survive. If they are not stimulated, this leads to apoptosis. These include PDGF, FGF, HGF, IGF, etc.

Fas receptor is a transmembrane receptor that belongs to the TNF family. Signal transduction from it is via caspases. FasL is a transmembrane protein, but can be alternatively cleaved from the membrane. FasL is expressed by T-lymphocytes, macrophages and NK cells. Fas-induced apoptosis results from contact between the Fas receptor and FasL (ligand). This type of apoptosis is involved in the selection of T-lymphocytes in the peripheral blood, the cytotoxic effect of T-cells and NK-cells, and the termination of the immune response (death of immune cell clones).

Caspases are **proteases** involved in various pathways of apoptosis induction. So far, 11 of them have been described. They are synthesised as precursors and can be activated e.g. via Fas receptors or TNF receptors etc. Once activated, caspases are cascaded (similar to e.g. the haemocoagulation reaction) leading to the execution of apoptosis.

Links

Související články

- Apoptosis
- Caspases
- Defects in apoptosis signalling in cancer cells

Literature

- KAPRAS, Jan a Milada KOHOUTOVÁ. *Kapitoly z lékařské genetiky III.*. 1. vydání. Praha : Karolinum, 2009. sv. 1. ISBN 80-246-0001-3