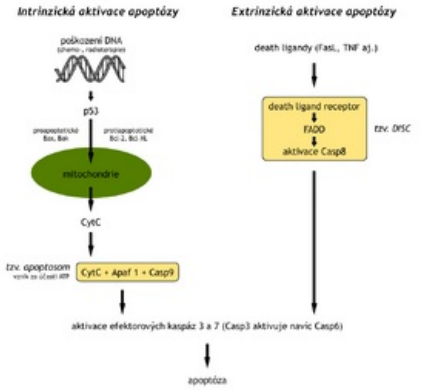
Apoptosis signaling disorders in tumor cells

One of the basic functions of apoptosis is to prevent the malignant proliferation of tissues. Apoptosis is part of tissue homeostasis – the balanced formation and destruction of cells. Excessive apoptosis leads to tissue hypotrophy (e.g. in ischemia). Reduced death (as well as increased cell replication) leads to tumor transformation. All transformed cells had to suppress apoptosis during their transformation.

Apoptosis is triggered in two ways – intrinsic and extrinsic pathways. In some cells, both must be activated (especially the outer one, which subsequently activates the inner one), in others only the inner one is sufficient. Both pathways converge by activating the executive caspases 3, 7, and 6, and then apoptosis occurs.

Outer track

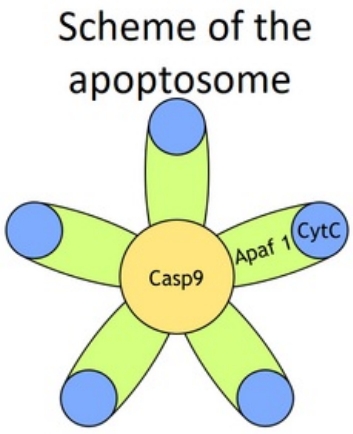
It begins with the binding of **DR L** (Death Receptor ligand) to the Death Receptor, i.e. **Fas L** to the **Fas** receptor and the subsequent trimerization of these receptors (the ligand is taken there either thanks to cell apoptosis triggering or apocrine secretion, apoptosis triggering factors also include cytokines, growth factors, hormones, toxins). Via the **FADD** protein, the initiator procaspase 8 or 10 homodimer binds to these receptors, which after **DR** activation is proteolytically activated into an active caspase homodimer. This whole complex is called DISC (Death inducing signaling complex). Caspase homodimer has 2 roles: activate executive procaspases 3, 7 and cleave **Bid** protein to **t-Bid** protein. Caspase 3 then cleaves procaspase 6. Caspases 3, 6, 7 are the executor proteases of apoptosis itself.



Ways of the apoptosis activation

Inner track

Or mitochondrial. Thanks to the change in the permeability internal mitochodnrial membrane **cytochrome c** is released into the cytosol, where it binds to the inactive **Apaf-1** protein and thus changes its conformation. After binding **ATP the Apaf-1*cyt c*ATP** complex assembles into a pentamer, which is able to bind procaspase 9, which after binding turns into active caspase 9. The whole complex complex is called an apoptosome. This apoptosome is able to convert procaspases 3, 7 into caspases 3, 7. The change in mitochondrial membrane permeability is regulated by **the Bcl family of proteins**. Proapoptotic **Bax**, **Bak** they form homodimers or heterodimers that mean the permeability of the inner mitochondrial membrane. However, this should be impermeable in a healthy cell, which is why there are anti-apoptotic proteins **Bcl-**, **Bcl-xl**, which together with **Bak** and **Bax** form **Bax/Bcl-2** heterodimers and these are impermeable. Increased levels of **Bcl-2** were first found in B-Cell Lymphoma.
The internal pathway is induced by lack of O_2 and nutrients, viral infection, gkucocorticoids, heat, radiation (damage to DNA or mitochondria).



Scheme of the apoptosis

Signaling failures

Loss of activation signal

There can be either a reduction in **DR** expression, or non-functional ones, such as so-called decoy receptors, are synthesized. These lack the cytosolic **DD** domain, so **FADD** cannot bind and **DISC** activation is thus prevented.

Signal reshuffle

TRADD (Tumor necrosis factor Receptor Associated Death Domain) does not bind the required **FADD** (Fas Associated Death Domain), which is able to bind procaspase 8. Instead, **TRADD** binds to **TRAF** (TNF Receptor Associated Factor), which through a cascade of several kinases expresses the transcription factor **NFkB** . The effect of **NFkB** consists in the activation of antiapoptotic factors **XIAP**, **FLIP** and **Bcl-2**. There are assumptions that it negatively affects the course of apoptosis itself.

Inactivation of the DISC by FLIP proteins

The **FLIP** protein has a very similar structure to procaspase 8, it contains a **DED** domain , which binds to the **FADD** protein and takes the place of one or two procaspase 8 in the **DISC**. Thus, homodimers cannot form or be proteolytically activated. This inhibition is directly proportional to the **FLIP** protein concentration. There is no need

to despair right away, even with insufficient activation of caspase 8, it can at least cleave proteins around the **DISC**, e.g. protein **Bid**. This then, as **tBID**, eliminates the **Bcl-2** protein and thereby causes cytochrome to escape from the mitochondria.

Inhibitory Caspases

IAPs (Inhibitors of Apoptosis Proteins) prevent their activation to caspases by directly binding to the active sites of procaspase. They are, for example, **HIAP, XIAP, SURVIVIN, LIVIN**. Increased expression of SURVIVIN has been demonstrated in many tumor types.

Mitochondrial signaling disorders associated with the tumor suppressor p53

When DNA is damaged, transcription of the **TP53** gene occurs , the product of which is the transcription factor **p53**. The **p53** protein has a key role in suppressing tumor processes. Firstly, by expressing **p21, GADD45** builds the cell cycle, secondly, by increasing the expression of **Bax, PUMA** and suppressing **Bcl-2**, it significantly helps to release cytochrome ca and other pro-apoptotic factors from mitochondria. (Altering the Bax/Bcl-2 ratio.) Another pro-apoptotic effect is the upregulation of **FAS**, **DR5** or **Apaf 1**.

Functions of pro-apoptotic factors released from mitochondria	
factor	**function**
Cytochrom c	activation of the apoptosome (see above)
SMAC/DIABLO	It represents another link between the extrinsic and intrinsic pathways by inactivating XIAP, which would like to inhibit caspase 3. This interaction is of great importance, as caspase 3 further cleaves XIAP through positive feedback.
Endonuclease G	cleaves DNA in caspase-independent apoptosis
HtrA2	is the main IAP antagonist, preventing the inactivation of caspases
AIF	Apoptosis Inducing Factor acts during caspase-independent apoptosis, after release from mitochondria it induces chromatinu and fragmentation of the DNA.

Other possibilities of influencing apoptosis

Point mutation of the **Ras** gene can lead to excessive activation of **Akt** kinase (via MAP kinases). This is generally associated with cell survival. It weakens the internal activation of apoptosis by phosphorylating caspase 9, phosphorylating **Bad** (phosphorylation of these proteins means inactivation). It also inactivates **Fas L**. It also positively affects **NFkB** through the **IKK** kinase.

Apoptosis signaling is a very complicated process regulated by many proteins. Fortunately, there are many "safeguards" that can jump in if the first one fails, whether it is internal and external activation and their interconnection or caspase-independent apoptosis. The tumor process is multiple and **a single mutation is certainly not enough to suppress apoptosis**. Nevertheless, one must keep in mind p53 and the Bcl family of proteins whose defects can be fatal from the point of view of oncogenesis.

Links

Related articles

- Apoptosis
- Apoptosis and clinical consequences of disorders of its regulation
- Caspases

Source

- VERMACH, Petr. *Vypracované otázky ke zkoušce z patobiochemie.* 2010.

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- Wikipedia. *Apoptosis* [online]. [cit. 2010-11-21]. <https://en.wikipedia.org/w/index.php?title=Apoptosis&oldid=391050559>.

External links

- E-learningový materiál (https://el.lf1.cuni.cz/p45782335/) (pouze členové akademické obce 1. LF UK)