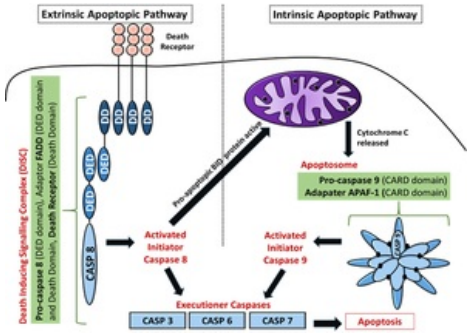
Disorders of apoptosis signaling in tumor cells

One of the functions of apoptosis is to prevent malignant tumor growth. Apoptosis is part of tissue homeostasis, maintaining the balance between cell formation and death. Excessive apoptosis leads to tissue hypotrophy (e.g., in ischemia). Decreased apoptosis (as well as increased cell replication) leads to tumor formation. All tumor cells had to suppress apoptosis during their transformation.

Apoptosis is triggered via two pathways: the extrinsic and the intrinsic pathways. In some cells, both pathways must be activated (especially the extrinsic pathway, which subsequently activates the intrinsic pathway). In other cells, the activation of the intrinsic pathway only is sufficient. Both pathways meet at the point of activation of the executioner (effector) caspases 3, 7, and 6, and then apoptosis ensues.

Extrinsic pathway

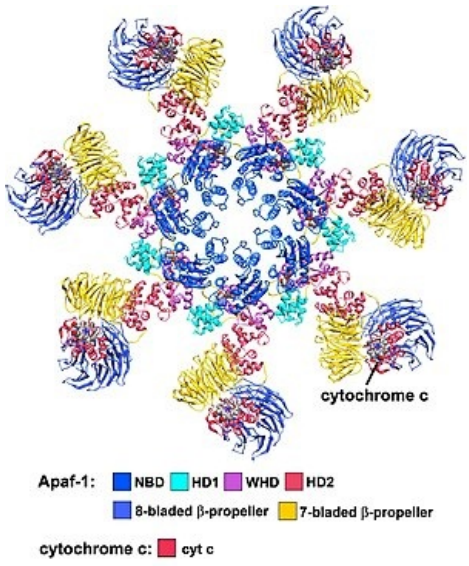
It begins with the binding of the **DR** (Death Receptor) ligand to the DR (**Fas ligand** to **Fas** receptor) and subsequent trimerization of these receptors (the ligand is either present on an apoptosis-triggering cell or is secreted in an apocrine manner). Other ligands for specific death receptors also exist. These ligands can be cytokines, growth factors, hormones, or toxins. The initiator procaspase 8 or 10 binds to these receptors via the **FADD (Fas-associated protein with death domain)** protein, which proteolytically activates the procaspases to their active form upon **DR** activation. This whole complex is called DISC (Death inducing signaling complex). The activated initiator caspases have 2 tasks: to activate executioner procaspases 3 and 7 and cleave the **Bid** protein to the **t-Bid** (its active form). Caspase 3 then activates procaspase 6.



Pathways of apoptosis activation

Intrinsic pathway

It is also known as the mitochondrial pathway. Due to the change in the permeability of the inner mitochondrial membrane, **cytochrome c** is released into the cytosol, where it binds to the inactive **APAF1** (apoptotic protease activating factor 1) protein and thus changes its conformation. After binding to **ATP,** the **APAF1-cyt c-ATP** complex associates in a pentamer capable of binding procaspase 9, which upon binding it, it is transformed to the active caspase 9. The formed complex is called the **apoptosome** and it transforms procaspases 3 and 7 to their active forms. The change in mitochondrial membrane permeability is regulated **by the Bcl family of proteins**. Proapoptotic **Bax** and **Bak** form homodimers or heterodimers, which induce an increase in the permeability of the inner mitochondrial membrane. However, it should be impermeable in a healthy cell, and therefore there are anti-apoptotic proteins. These are **Bcl-2** and **Bcl-xl**, which with **Bak** and **Bax** form **Bax/Bcl-2** heterodimers. Elevated levels of **Bcl-2** were found first in the B lymphoma (B-Cell Lymphoma). The intrinsic pathway is induced by O_2 and nutrient deficiencies, virus infections, glucocorticoids, heat, and radiation (DNA or mitochondrial damage).



Apoptosome

Signaling disorders

Losing the activation signal

DR expression can either be reduced or normal, but the synthesized receptors are non-functional, such as in the case of decoy receptors. These receptors lack the cytosolic death domain (**DD**), which prevents **FADD** binding and **DISC** formation.

Signal shift

TRADD (Tumor necrosis factor Receptor Associated Death Domain) is a membrane protein that mediates **DISC** formation by binding **FADD** after binding the **DR tumor necrosis factor receptor** (**TNFR**). Instead, **TRADD** can bind **TRAF** (TNF Receptor Associated Factor), which leads to the expression of the transcription factor **NFkB** via a cascade of several kinases. The effect of **NFkB** is to active the anti-apoptotic factors **XIAP**, **FLIP**, and **Bcl-2**, inhibiting apoptosis.

Inactivation of DISC by the FLIP protein

The **FLIP** protein has a very similar structure to procaspase 8. It contains a death effector domain (**DED**) that binds to the **FADD** protein. It functions as an anti-apoptotic protein as it can displace one or two procaspases 8 in the **DISC**. Thus, homodimers cannot be formed or proteolytically activated. This inhibition directly correlates to the concentration of the **FLIP** protein. However, even with insufficient activation of caspase 8, the **Bid** protein can still be cleaved and the intrinsic pathway can be triggered.

Caspase inhibitors

IAP (Inhibitors of Apoptosis Proteins) act by directly binding to the procaspase active sites, preventing their activation and transformation to caspases. These include **HIAP**, **XIAP**, **SURVIVIN**, and **LIVIN**. Increased expression of **SURVIVIN** has been demonstrated in many types of tumors.

Disorders of mitochondrial signaling associated with the tumor suppressor p53

When DNA is damaged, there is increased expression of the **TP53 gene**, the product of which is the transcription factor **p53**. The **p53** protein plays a key role in suppressing tumor processes. Firstly, it acts by increasing the expression of **GADD45**, which acts via **p21** to arrest the cell cycle. Secondly, it increases the expression of **Bax** and **PUMA** and suppresses the expression of **Bcl-2**. This helps initiate apoptosis by the alteration of the Bax/Bcl-2 ratio, which leads to increased inner mitochondrial membrane permeability and the release of proapoptotic factors from the mitochondria. Another proapoptotic effect is the upregulation of **FAS**, **DR5**, or **APAF1**.

The function of proapoptotic factors released from mitochondria	
factor	**function**
Cytochrome c	apoptosome activation (see above)
SMAC/DIABLO	It further links the extrinsic and intrinsic pathways by inactivating XIAP, which inhibits caspase 3. This interaction is of great importance, as caspase 3 further cleaves XIAP as a part of a positive feedback loop.
Endonuclease G	It cleaves DNA in caspase-independent apoptosis.
HtrA2	It is a major IAP antagonist that caspase inactivation.
AIF	Apoptosis-inducing factor (AIF) acts on caspase-independent apoptosis, induces chromatin condensation, and DNA fragmentation upon release from mitochondria.

Other possibilities of influencing apoptosis

Point mutation of the **Ras** gene can lead to overly active **Akt** kinase (via MAP kinases). This is associated with prolonged cell survival. It weakens the internal activation of apoptosis by phosphorylating caspase 9 and **Bad**, which inactivates them. It also inactivates **Fas L** and increases the expression of **NFkB** via **IKK** kinase.

Apoptosis signaling is a very complicated process regulated by many proteins. This is advantageous as there are many ways to achieve apoptosis in the case of the failure of a particular protein. The process by which tumors arise is complex and requires multiple mutations. In other words, a **single mutation is certainly not enough to suppress apoptosis.** However, there are some exceptions such as mutations of p53 and Bcl family of proteins, whose defects can be fatal in terms of oncogenesis.

Links

Related articles

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

Source

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

Literature

- KALOUSOVÁ, Marta. *Patobiochemie ve schématech.* 1. edition. Praha : GRADA, 2006. 200 pp. ISBN 978-80-247-3069-1.
- DVORSKÁ, M – DRIÁK, D – ŠVANDOVÁ, I. *Apoptóza v gynekologii a porodnictví : Část I, patofyziologie apoptózy* [online]. Časopis ženských lékařů Gynekolog, ©2008. [cit. 2011-01-12]. <https://www.mf.cz/produkty/gynekolog-casopis-zenskych-lekaru/clanky/2008/408cl1.htm>.
- FULDA, Simone – KLAUS-MICHAEL, Debatin. *Caspase Activation in Cancer Therapy : Pathways of Caspase Activation* [online]. ©2010. [cit. 2011-01-12]. <https://www.ncbi.nlm.nih.gov/books/NBK6027/>.
- 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)