***CANCER AND APOPTOSIS***

Apoptosis is a regulated energy-dependent se- quence of events by which a cell self-destructs. In this suicidal process,

1. the cell shrinks, the chromatin condenses, and the nucleus fragments.
2. The cell breaks up into membrane-enclosed apoptotic vesicles (apoptotic bodies) containing varying amounts of cytoplasm, organelles, and DNA fragments.
3. Phosphatidylserine, a lipid on the inner leaflet of the cell mem- brane, is exposed on the external surface of these apoptotic vesicles. **It is one of the phagocytic markers recognized by macrophages and other nearby phagocytic cells that engulf the apoptotic bodies.**

Apoptosis is a normal part of multiple processes in complex organisms: embryo- genesis, the maintenance of proper cell number in tissues, the removal of infected or otherwise injured cells, the maintenance of the immune system, and aging.

It can be initiated by injury, radiation, free radicals or other toxins, withdrawal of growth fac- tors or hormones, binding of proapoptotic cytokines, or interactions with cytotoxic T-cells in the immune system.

Apoptosis can protect organisms from the negative effects of mutations by destroying cells with irreparably damaged DNA before they proliferate.

***A. Normal Pathways to Apoptosis***

Apoptosis can be divided into three general phases:

1. an initiation phase,
2. a signal integration phase,
3. and an execution phase.

Apoptosis can be initiated by external signals that work through death receptors, such as tumor necrosis factor (TNF), or deprivation of growth hormones .

It can also be initiated by intracellular events that affect mitochondrial integrity (e.g., oxygen deprivation, radiation) and irreparably damaged DNA.

In the signal integration phase, these proapoptotic signals are balanced against antiapoptotic cell survival signals by several pathways including members of the Bcl-2 family of proteins.

The execution phase is carried out by proteolytic enzymes called **caspases**.

**1. CASPASES**

Caspases are cysteine proteases that cleave peptide bonds next to an aspartate residue.

They are present in the cell as procaspases that are activated by proteolytic cleavage of the inhibitory portion of their polypeptide chain.

**The different caspases are generally divided into two groups according to their function:**

1. initiator caspases, which specifically cleave other procaspases;
2. and execution caspases, which cleave other cellular proteins involved in maintaining cellular integrity.

**The initiator caspases are activated through two major signaling pathways**:

1. the death receptor pathway
2. and the mitochondrial integrity pathway.

Diagram

Description automatically generatedThey activate the execution caspases, which cleave protein kinases involved in cell adhesion, lamins that form the inner lining of the nuclear enve- lope, actin and other proteins required for cell structure, and DNA repair enzymes.

They also cleave an inhibitor protein of the endonuclease CAD (**c**aspase-**a**ctivated **D**Nase), thereby activating CAD to initiate the degradation of cellular DNA. With destruction of the nuclear envelope, additional endonucleases (Ca2􏰀- and Mg2􏰀-de- pendent) also become activated.

**2. THE DEATH RECEPTOR PATHWAY TO APOPTOSIS**

The death receptors are a subset of TNF-1 receptors, which includes Fas/CD95, TNF-receptor 1 (TNF-R1) and death receptor 3 (DR3).

These receptors form a tri- mer that binds TNF-1 or another death ligand on its external domain and binds adaptor proteins to its intracellular domain.

The activated TNF-receptor complex forms the scaffold for binding two molecules of procaspase 8 (or procas- pase 10), which autocatalytically cleave each other to form active caspase 8 (or cas- pase 10).

Caspases 8 and 10 are initiator caspases that activate execution caspases 3, 6, and 7.

Caspase 3 also cleaves a Bcl-2 protein, Bid, to a form that activates the mitochondrial integrity pathway to apoptosis.

Diagram

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Diagram

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Apoptosis is also induced by intracellular signals indicating that cell death should occur. Examples of these signals include growth factor withdrawal, cell injury, the release of certain steroids, and an inability to maintain low levels of intracellular calcium.

All of these treatments, or changes, lead to release of cytochrome c from the mitochondria.

Cytochrome c is a necessary protein component of the mitochondrial electron transport chain that is loosely bound to the outside of the inner mitochondrial membrane. Its release initiates apoptosis.

In the cytosol, cytochrome c binds Apaf (pro**a**poptotic **p**rotease-**a**ctivating **f**actor).

The Apaf–cytochrome c complex binds caspase 9, an initiator caspase, to form an active complex called the **apoptosome**.

The apoptosome, in turn, activates execution caspases (3, 6, and 7) by zymogen cleavage.

**4. INTEGRATION OF PRO- AND ANTIAPOPTOTIC SIGNALS BY THE BCL-2 FAMILY OF PROTEINS**

The Bcl-2 family members are decision makers that integrate prodeath and antideath signals to determine whether the cell should commit suicide.

Both proapoptotic and antiapoptotic members of the Bcl-2 family exist.

Bcl-2 family mem- bers contain regions of homology, known as Bcl-2 homology (BH) domains. There are four such domains.

The antiapoptotic factors contain all four domains (BH1 to BH4). The channel forming proapoptotic factors contain just three domains (BH1 to BH3), whereas the proapoptotic BH3-only family members contain just one BH domain, BH3.

The antiapoptotic Bcl-2–type proteins (including Bcl-2, Bcl-L, and Bcl-w) have at least two ways of antagonizing death signals.

They insert into the outer mitochondrial membrane to antagonize channel-forming proapoptotic factors, thereby decreasing cytochrome c release.

They may also bind cytoplasmic Apaf so that it cannot form the apoptosome complex.

These antiapoptotic Bcl-2 proteins are opposed by **proapoptotic family members that fall into two categories:** ion-channel–forming members and BH3-only mem- bers.

The prodeath ion-channel–forming members, such as Bax, are very similar to the antiapoptotic family members, except that they do not contain the binding do- main for Apaf.

They have the other structural domains, however, and when they di- merize with proapoptotic BH3-only members in the outer mitochondrial membrane, they form an ion channel that promotes cytochrome c release rather than inhibiting it.

The prodeath BH3-only proteins (e.g., Bim and Bid) contain only the structural domain that allows them to bind to other Bcl-2 family members (the BH3 domain) and not the domains for binding to the membrane, forming ion channels, or binding to Apaf.

Their binding activates the prodeath family members and inactivates the antiapoptotic members. When the cell receives a signal from a prodeath agonist, a BH3 protein such as Bid is activated (see Fig. 15.12).

The BH3 protein activates Bax (an ion-channel–forming proapoptotic channel member), which stimulates release of cytochrome c.

Normally, Bcl-2 acts as a death antagonist by binding Apaf and keeping it in an inactive state. However, at the same time that Bid is activating Bax, Bid also binds to Bcl-2, thereby disrupting the Bcl-2–Apaf complex and freeing Apaf to bind to released cytochrome c to form the apoptosome.

Diagram

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