

## APOPTOSIS: PROGRAMMED CELL DEATH AND ITS CLINICAL IMPLICATIONS

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**Summary.** The fact that cell death is not ultimately a bad thing came as a surprise to many researchers. Physiological cell death has been observed in various multicellular organisms. Apoptosis or programmed cell death is the predominant form of physiological cell death by which the organism eliminates unnecessary or damaged single cells. It is a major component of normal development and disease. Apoptosis is characterized by membrane blebbing, shrinkage of the cell, nuclear fragmentation and chromatin condensation. Organelles are preserved almost intact. Cell surface molecules change to assure that apoptotic cells will be immediately recognized and engulfed by neighboring cells or phagocytes leading to little or no inflammation. A wide variety of physiological and pathological stimuli can initiate apoptosis. They act via receptor mechanisms, through biochemical agents, or cause DNA and cell membrane damage. Death receptors that initiate apoptosis include the Fas receptor and the TNF receptor systems. After an appropriate stimulus, the first stage of apoptosis or "decision phase" is the genetic control point of cell death. This is followed by the second stage or "execution phase", which is responsible for the morphological change in apoptosis. The third stage is engulfment of the dying cell followed by degradation of the engulfed cell DNA. There are two overlapping signaling pathways leading to apoptosis, termed the intrinsic and extrinsic pathways. In the intrinsic, various stimuli, such as oxidative stress, lead to mitochondrial dysfunction and the release of pro-apoptotic factors. Ligand binding to cell surface death receptors, such as Fas, activates the extrinsic pathway. During the last decades the molecular mechanisms involved in disordered apoptosis were unraveled, suggesting that cancer, chronic disease, and fetal developmental abnormalities can occur as a result of disordered apoptosis.

**Key words:** Apoptosis, cell death, death receptors, caspases

### Introduction

The fact that cell death is not ultimately a bad thing came as a surprise to many researchers. Physiological cell death has been observed in various multicellular organisms for more than one century (1, 2). Although biological rationale for physiological cell death is not clear for single cell organisms, there is growing evidence that some form of it does exist in unicellular organisms like *Trypanosoma cruzi* and perhaps even in bacteria (3, 4).

### Definition

Apoptosis is energy-dependent, innate, genetically controlled process by which the organism eliminates unnecessary or damaged single cells (5, 6, 7). It is the most predominant form of physiological cell death, or cell suicide, first described by Kerr *et al.* in 1972 (8). They coined the term "apoptosis", based on an ancient Greek word used to describe the "falling off" of leaves from trees or petals from flowers (7). The term apoptosis is often used synonymously with programmed cell

death, and it is a major component of normal development and disease (9). In the mid-1980's Ellis and Horvitz reported programmed cell death during the development of the nematode *Caenorhabditis elegans* and cloned the *C. elegans* death genes (ced genes) responsible (10). During the development of the nematode *Caenorhabditis elegans*, 131 cells die to leave a final total of 959 in the adult.

### Mechanism of Cell Death – Apoptosis and Necrosis

Cell death may be described by either of two well-characterized mechanisms, apoptosis or necrosis. In some circumstances cells may die by apoptosis, as well as by necrosis. The mode of cell death – whether it be apoptotic, necrotic, or indeterminate – depends upon the injurious stimuli and the amount of cellular energy. Unlike necrosis, apoptosis does require energy for its occurrence. The stimuli that induce apoptosis in the presence of energy lead to necrosis in the absence of it. Thus, cells injured by stressful stimuli may enter ap-

optotic programs, but undergo necrosis secondarily when energy levels within cells decline (7, 11). Prominent features of necrosis are swelling of cells, disruption of membranes, and lysis of the nuclear chromatin. Because cellular contents are lost into the extracellular space, necrotic tissue evokes inflammatory response. Apoptosis is distinguished from necrosis by a characteristic set of features including membrane blebbing, shrinkage of the cell, nuclear fragmentation and chromatin condensation. The cell shrinks and detaches from neighboring cells with a loss of microvilli and junctional complexes or desmosomes (12). Nuclear membrane becomes convoluted, whilst the nucleolus becomes enlarged and abnormally granular. Chromatin condenses and forms aggregates near the nuclear membrane. Endonucleases cleave the DNA into fragments (13, 14). Organelles are preserved almost intact. Dilation of the endoplasmic reticulum and swelling of the mitochondria have been observed. Nucleus undergoes a characteristic condensation of chromatin often extending to cap-like, densely heterochromatic regions (15).

Several cell surface molecules change to assure that apoptotic cells will be immediately recognized and engulfed by neighbouring cells or phagocytes leading to little or no inflammation. The nuclear fragments and organelles are packaged in membrane-bound vesicles ingested by surrounding cells (15, 16, 17, 18) (Fig. 1).

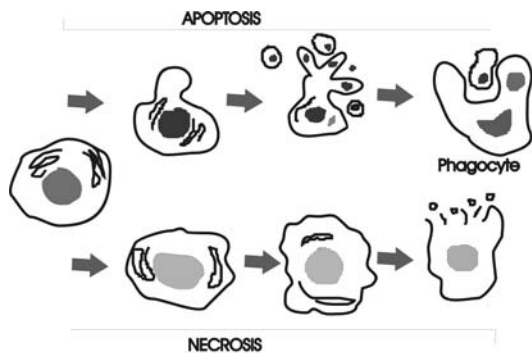


Fig. 1. Cell death - necrosis and apoptosis. Necrotic cells are swollen. There is early loss of plasma membrane integrity and leakage of cytosol into extracellular space. Apoptotic cells are shrunken and develop blebs. Membrane integrity is not lost until late. Nuclear chromatin undergoes condensation and fragmentation. The cytoplasm becomes divided to form apoptotic bodies containing organelles and/or nuclear debris.

**Pathogenesis of apoptosis**

A wide variety of physiological and pathological stimuli can initiate apoptosis. They act via receptor mechanisms, through biochemical agents that enhance the downstream components of the apoptotic pathway, or cause DNA and cell membrane damage (5). The signal that initiates apoptosis may result from the binding of cell-surface 'death' receptors (Fas receptor and the TNF receptor system) or from damage to the genome.

Death receptors that initiate apoptosis include the Fas receptor and the TNF receptor systems (19) (Fig. 2).

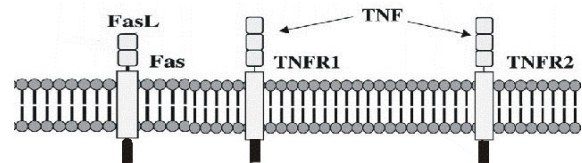


Fig. 2. The signal that initiates apoptosis may result from the binding of a cell-surface 'death' receptors: the Fas, tumour necrosis factor receptor type 1 (TNFR1) and tumour necrosis factor receptor type 2 (TNFR2) with ligands: Fas ligand (FasL) to Fas and TNF to TNFR1 and TNFR2.

The Fas receptor, initially known as CD95 or APO-1, is a transmembrane glycoprotein death receptor that is activated by the binding of an appropriate extracellular ligand, (Fas ligand) to cell membranes. It promotes trimerization of the receptor and facilitates binding of intracellular signaling molecules such as the FADD (Fas-associated death domain). Following the binding of the TNF receptor, intracellular molecules called "death domains" are produced. A TNF receptor associated death domain (TRADD) has been identified too (6, 19).

After an appropriate stimulus, the first stage of apoptosis or "decision phase" is the genetic control point of cell death. This is followed by the second stage or "execution phase", which is responsible for the morphological change in apoptosis. The third stage is engulfment of the dying cell followed by degradation of the engulfed cell DNA. In *Caenorhabditis elegans*, the protein products of the three genes are involved in cell death. Two of these, *ced-3* and *ced-4* are required for cell death (10). The third one, *ced-9*, antagonizes the killing activity of *ced-3* and *-4*. The killer gene *ced-3* encodes the CED-3 protein, a member of a class of cysteine proteases that cleave after aspartate residues, hence their name 'caspase' (cysteine aspartyl protease) (20). The first mammalian homologue of CED-3 identified in 1993 was ICE (interleukin-1L converting enzyme), now called caspase-1. The CED-4 protein interacts with both CED-3 and CED-9 proteins (21, 22). A mammalian homologue of CED-4 has been identified as Apaf-1 (apoptotic protease activating factor), a large protein implicated in regulating caspase activity through mediating cytochrome c-dependent activation of caspase-9 (23). The mammalian homologues of CED-9 are the Bcl-2 proteins – key regulators of cell survival (24, 25).

**"Decision phase"**

Two genes are important for control of apoptosis, Bcl-2 and p53. A family of mammalian proteins similar to Bcl-2 promotes or inhibits apoptosis (26, 27). Proteins such as Bcl-2 and Bcl-xL prevent apoptosis, whereas Bcl-2 associated x proteins (Bax) such as Bax, Bad, Bak and Bcl-xS promote apoptosis (28, 29, 30). The gene p53 is a 53-kDa nuclear phosphoprotein that

binds to DNA to act as a transcription factor, and controls cell proliferation and DNA repair (31). The gene *c-myc* is a proto-oncogene that encodes a sequence-specific DNA-binding protein that acts as a transcription factor and induces apoptosis in the presence of p53.

### "Execution phase"

The central event in apoptosis is proteolytic cleavage of cellular substrates. Cellular disruption results from activation of caspases (12, 32). Caspases cleave DNA and cytoskeletal proteins and cause a loss of cell adhesion. There is no leakage of lysosomal enzymes that can damage nearby cells or elicit immune responses (33).

Caspases are synthesized as zymogens and upstream signals convert these precursors into mature proteases. Initiator caspases (caspase-1, -2, -4, -5, -8, -9, -10 and -14) are activated via oligomerization-induced auto-processing, while effector caspases (caspase-3, -6 and -7) are activated by other proteases, including initiator caspases and granzyme B (34-39).

There are two overlapping signaling pathways leading to apoptosis, termed the intrinsic and extrinsic pathways. In the intrinsic, various stimuli, such as oxidative stress, lead to mitochondrial dysfunction and the release of pro-apoptotic factors. Ligand binding to cell surface death receptors, such as Fas, activates the extrinsic pathway (40).

The intrinsic pathway is characterized by mitochondrial dysfunction or possibly by endoplasmic reticulum stress (41). Various stimuli, particularly oxidative stress, can lead to damage of the mitochondrial inner membrane, resulting in the opening of the mitochondrial membrane transition pore (mitochondrial permeability transition-MPT) and, subsequently, in the release of cytochrome *c* and apoptosis-inducing factor (AIF) from the mitochondria. In the cytosol, cytochrome *c* complexes with Apaf-1 to activate procaspase 9, which in turn activates downstream effector caspases, such as caspase 3, 6 and 7. Mitochondrial permeability transition also leads to the release of endo G, which cleaves chromosomal DNA independently of caspase activation. Eventually, the MPT is regulated by relative proportions of anti-apoptotic (e.g. *bcl-2*, *bcl-xl*) and pro-apoptotic (e.g. *bax*, *bad*) *bcl-2* family members within a cell.

The extrinsic pathway is mediated either by cell surface receptors, including Fas receptor and the TNF receptor system, or by perforin and granzyme B released from activated, cytotoxic lymphocytes. Upon activation by their respective ligands (FasL and TNF- $\alpha$ ), both Fas and TNF1 build a complex with adapter proteins and procaspase 8. The aggregation of this complex initiates cleavage of procaspase 8 into its active form, which subsequently activates downstream effector caspases such as caspase 3. Cytotoxic lymphocytes express FasL and release granules containing granzyme B and perforin, which allows granzyme B to enter target cells. Granzyme B then directly cleaves critical cellular proteins and activates procaspases. The activation of procaspase 8 can also lead indirectly to cytochrome *c* re-

lease from the mitochondria, thereby linking the extrinsic and intrinsic pathways (Fig. 3).

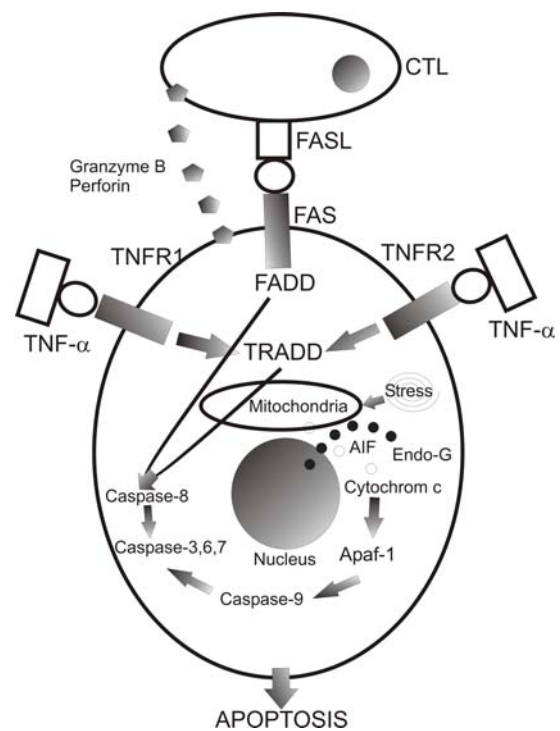


Fig. 3. The two signaling pathways for apoptosis (intrinsic and the extrinsic). The intrinsic pathway is mediated by mitochondria dysfunction resulting in the release of pro-apoptotic factors (cytochrome *c*, endo G, AIF). Cytochrome *c* complexes with Apaf-1 to activate procaspase 9. The extrinsic pathway is receptor-mediated or perforin/granzyme B-mediated. Activation by Fas ligand (FasL) or TNF- $\alpha$ , is followed by trimerization of the receptor and binding of intracellular signaling molecules such as the FADD (Fas-associated death domain), and TNF receptor associated death domain (TRADD), which activate procaspase 8. Both caspase 9 and caspase 8 activate effector caspases. Activated cytotoxic T lymphocytes (CTL) and NK cells release perforin and granzyme B, which can activate apoptosis.

The entire process of apoptosis may take only 15 minutes, and therefore may be undetectable on tissue sections (42).

### Pathways that mainly use the initiator caspase-9

Cessation of survival stimuli is thought to generate apoptotic signals that lead to translocation of pro-apoptotic proteins such as Bax to the outer mitochondrial membrane. Transcription, in some cases mediated by p53, may be required to induce proteins such as Bax. Leakage of cytochrome *c* from mitochondria into cytosol follows. Formation of a ternary complex of cytochrome *c*, the adapter protein Apaf-1, and the initiator caspase-9 results in the activation of caspase-9 followed by sequential activation of effector caspases such as caspase-3 and others. The action of caspases, endonucleases, and other enzymes leads to cellular disintegration.

### Pathways that mainly use the initiator caspase-8

Following the binding of peptides such as TNF- $\alpha$  or Fas ligand (Fas-L), their receptors oligomerize and recruit adapter proteins Fas associated death domain (FADD) and TNF receptor associated death domain (TRADD) to form death-inducing signaling complexes (DISC), causing the activation of the initiator caspase-8, which sequentially activates effector caspases.

### Clinical implications

During the last decades the mechanisms involved in disordered apoptosis were unravelled, suggesting that alterations in control of cell death or survival is implicated in pathogenesis of a variety of human diseases including cancer and many other chronic diseases (43). Deficient apoptosis is associated with cancer, autoimmune disorders and viral infections, while excessive apoptosis is associated with ischaemic injury (myocardial infarction, stroke, AIDS, neurodegenerative disease, sepsis and multiple organ dysfunction syndrome (2, 11, 44, 45). Apoptosis is responsible for cell death in development, tissue homeostasis, atrophy induced by endocrine and other stimuli, negative selection in the immune system, and substantial proportion of T-cell killing. Many cancer therapeutic agents exert their effects through initiation of apoptosis, and even the process of carcinogenesis itself sometimes depends on a critical failure of apoptosis that permits the survival of cells after mutagenic DNA damage (46).

### Apoptosis and oxidative stress

Reactive oxygen-species (ROS) such as a superoxide-anion, hydrogen peroxide, organic peroxides and radicals are generated by cells as by-products of normal metabolism (47). Oxidative stress may play the major role in carcinogenesis (48, 49). This has stimulated the interest in the possible role of antioxidants in preventing the development of cancer. Dietary antioxidants are

presumed to decrease the oxidative damage to DNA and the cancer risk. Possible cancer preventive potential of antioxidants has stimulated the consuming of antioxidant supplements among healthy population (50, 51). Reactive oxygen-species are important physiological effectors of apoptosis too (47). The observation that antioxidants by inhibiting apoptosis may interfere with the elimination of precancerous and cancerous cells and thereby promote cancer could be of great clinical importance (52). A recent meta-analysis indicated that consuming antioxidant supplements may have unwanted consequences to our health (53).

### Apoptosis and development

Two processes are responsible for organ development: organogenesis, a process of specific induction and differentiation of cells, and maturation, a process during which an organ achieves complete functional maturity (7). Organogenesis involves many cellular processes, such as cell proliferation, cell adhesion, apoptosis, cell differentiation, change in cell shape or polarity, and cell migration (55). Apoptosis plays an important role in sculpting the shape and organisation of organs during development by eliminating specific populations of cells at different stages of embryogenesis (56).

### Apoptosis and gastrointestinal tract

There is physiological and pathological occurrence of apoptosis in the gastrointestinal tract. Apoptosis is essential for maintaining the normal gut epithelial function. Dysregulated apoptosis is seen in a number of pathological conditions of the gastrointestinal tract, like inflammatory bowel disease, ischaemia-reperfusion, autoimmune liver disease, chronic viral hepatitis, alcohol liver disease, primary biliary cirrhosis, and liver cancer.

A better understanding of the mechanism of apoptosis may have important consequences for attempts to treat diseases associated with dysregulated programmed cell death.

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**APOPTOZA: PROGRAMIRANA ČELIJSKA SMRT I NJEJE KLINIČKE IMPLIKACIJE**

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Kratak sadržaj: Činjenica da ćelijska smrt nije uvek loša stvar je bila iznenađenje za mnoge istraživače. Fiziološka ćelijska smrt je zabeležena kod različitih višćelijskih organizama. Apoptoza, ili programirana ćelijska smrt je predominantna forma fiziološke ćelijske smrti, putem koje organizam eliminiše nepotrebne ili oštećene ćelije. Ona je glavna komponenta normalnog razvoja i bolesti. Apoptoza se karakteriše izbočenjem ćelijske membrane, skupljanjem ćelije, fragmentacijom jedra i kondenzacijom hromatina. Organele su skoro intaktne. Dolazi do promene ćelijskih površinskih molekula što osigurava da će apoptotična ćelija biti odmah prepoznata i fagocitovana od susednih ćelija, ne dovodeći do zapaljenja. Različiti fiziološki i patološki stimuli mogu inicirati apoptozu. Oni deluju preko receptora, biohemijskih ageransa, ili dovode do oštećenja DNA i ćelijske membrane. Receptori 'smrti' koji iniciraju apoptozu obuhvataju Fas receptore i TNF receptor sistem. Posle odgovarajućeg stimulusa nastupa prva faza ili 'faza odluke' koja predstavlja genetsku kontrolnu tačku ćelijske smrti. Nakon toga sledi druga faza ili 'faza egzekucije', koja je odgovorna za morfološke promene u apoptozu. Treći stadijum je fagocitoza i razgrdnja DNA ćelije koja umire. Postoje dva puta prenošenja signala koji vode apoptozu i koji se preklapaju, unutrašnji i spoljašnji. U unutrašnjem različiti stimuli kao oksidativni stres, dovode do poremećaja funkcije mitohondrija i oslobadjanja pro-apoptotičkih faktora. Vezivanje liganda za receptore 'smrti' na ćelijskoj površini, kao što su Fas, aktivira spoljašnji put. Tokom poslednje dekade otkriveni su molekularni mehanizmi uključeni u poremećaje apoptoze, sugerirajući da su kancer, mnoga hronična oboljenja, kao i poremećaji nastali tokom fetalnog razvoja, posledica poremećene apoptoze.

Ključne reči: Apoptoza, ćelijska smrt, receptori smrti, kaspaze