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REVIEW ARTICLE

Life of the cell: is it important how cells die?

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Summary

Cell death emerges during embryonic development, and is preserved after the birth as an important process for maintaining homeostasis by removing damaged or aged cells. Two forms of cell deaths exist: accidental and regulated cell death. Necrosis is an accidental, unregulated, passive form of cell death that occurs due to the collapse of cellular homeostatic mechanisms under extreme non-physiological conditions. Regulated cell death is an active, energy-dependent process that functions as a physiological mechanism for maintaining homeostasis and in numerous pathological conditions when it provides selective elimination of potentially dangerous or infected cells. There are many types of regulated cell death: intrinsic and extrinsic types of apoptosis, autophagy dependent cell death, necroptosis, pyroptosis, ferroptosis, parthanatos, mitochondrial permeability transition-driven necrosis, lysosome-dependent cell death, immunogenic cell death, entosis and NET-osis. Different types of cell death are interconnected. Abnormal activation of the different forms of cell death can cause diseases. Dysregulation of the apoptotic program can lead to hyperplasia, autoimmune diseases and tumorigenesis, pyroptosis is associated with bacterial infection and necroptosis with human inflammatory skin diseases and carcinogenesis. Understanding the regulatory mechanisms of apoptosis led to the discovery of BH3 mimetics, drugs used for treatment of some types of B cell malignancies. Drugs that target necroptosis, pyroptosis and autophagy are under investigation and could be potentially used in future as therapies for various diseases, including cancer. The aim of this review is to summarize new knowledge about the processes of cell death, and to emphasize the importance of newly discovered molecular pathways regulating various types of cell death, enhancing our comprehension of health and disease.

Key words: cell death, necrosis, apoptosis, autophagy

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INTRODUCTION

The life of a cell, like the life of an organism, ultimately ends in death (1). Cell death emerges during embryonic development, playing a crucial role in morphogenesis and is preserved postnatally as an important process for maintaining homeostasis by removing damaged or aged cells (1). Cell death can occur as a component of physiological processes at the end of the cell's lifecycle, or due to the action of pathological factors that irreversibly damage cells (2). Therefore, there are two forms of cell deaths: regulated cell death and accidental cell death (1).

Accidental cell death was initially observed by Karl Vogt in 1842, but the concept of cell death and the terms necrosis and necrobiosis were introduced for the first time by Rudolf Virchow, in 1858 (3). Regulated cell death, or apoptosis, was morphologically described in 1885 by Walter Fleming and originally named chromatolysis, while the concept of programmed cell death was introduced later in 1950s, and named apoptosis by Kerr, Willy and Curie, in 1972 (3,5,6). Research on cell death started at the Institute of Histology and Embryology, Faculty of Medicine in Belgrade when its founder Aleksandar Dj. Kostić described cells with morphological characteristics of apoptosis in his doctoral dissertation, in 1921, and continued in 1980s (4). In 1990s, it was hypothesized that autophagy, the process of degradation of cellular components inside lysosomes, first observed in 1960s by electron microscopy, can also lead to cell death and Klionsky and Yoshinori began detailed research into the mechanisms of this process which later led to Nobel Prize-winning discoveries (7, 8,9).

In the beginning of the 21-century, cell death was classified according to its morphological characteristics into apoptosis, autophagy, necrosis and mitotic catastrophe (10), while in 2018, the current classification of cell death into accidental and regulated cell death (RCD) was postulated. Necrosis is an accidental, unregulated, passive form of cell death that occurs due to the collapse of cellular homeostatic mechanisms under extreme non-physiological conditions (2). RCD, or programmed cell death is an active, energy-dependent process (11). It occurs as a physiological process, during the development and maintenance of homeostasis and in numerous pathological conditions when it provides for selective elimination of potentially dangerous or infected cells (2). There are many types of regulated cell death, like apoptosis, necroptosis, pyroptosis, cell death dependent on autophagy, etc. **(Figure 1)** (2). Morphologically, all forms of cell death still may exhibit different combinations of microscopic features of apoptosis, autophagic cell death and necrosis (2). Even though various types of cell death

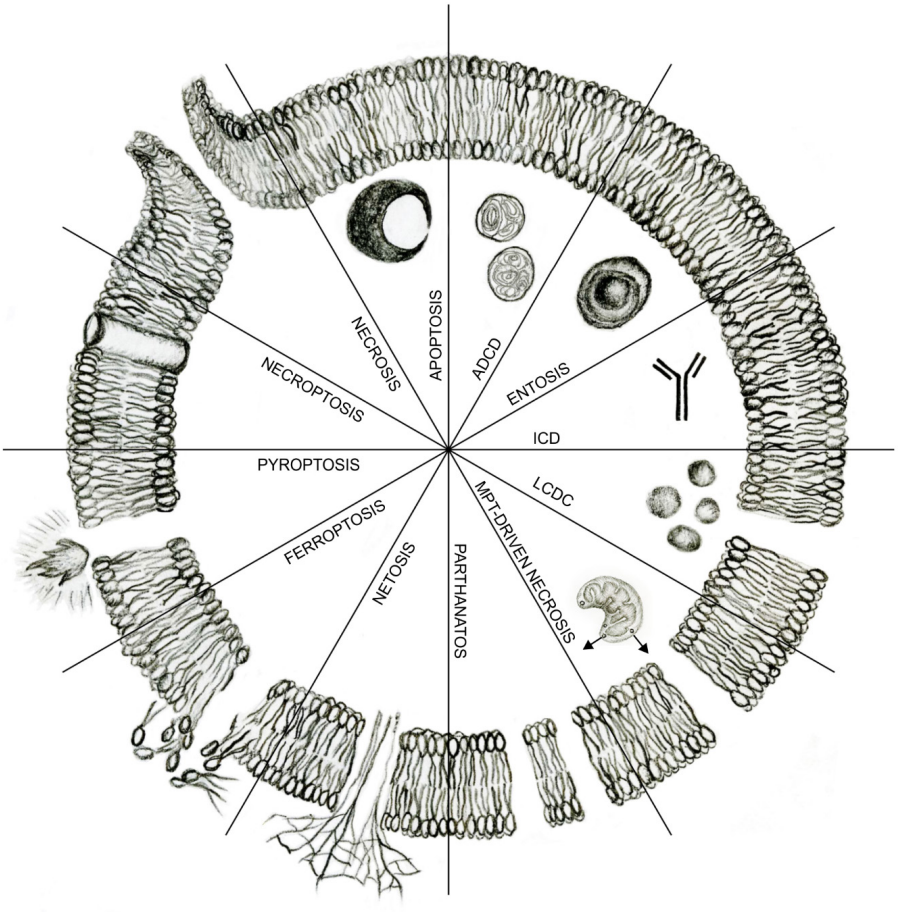

Figure 1. Classification of cell death. Types of cell death: apoptosis, ADCD (autophagy-dependent cell death), entosis, ICD (immunogenic cell death), LCDC (lysosome dependent cell death), MPT (mitochondrial permeability transition)-driven necrosis, parthanatos, NETosis, ferroptosis, pyroptosis, necroptosis, necrosis

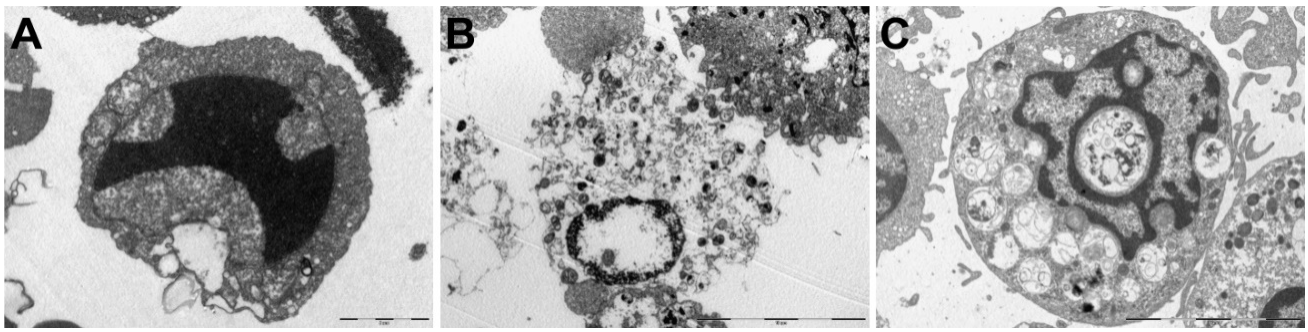

Figure 2. Transmission electron microscopy images of different types of cell death: lymphocyte apoptosis (A), necrosis of the B16 cell (B), autophagy in lymphocytes (C). Magnification 8900x (A, C) and 3500x (B)

have been discovered, including recently described cuproptosis and paraptosis, in this review we discussed only the types of cells death included in the latest classification of cell death (2).

The aim of this review is to summarize new knowledge about the processes of cell death, and to emphasize the importance of newly discovered molecular pathways regulating various types of cell death, enhancing our comprehension of health and disease.

NECROSIS

Necrosis is an unregulated form of cell death induced by external injury, independent of any signaling pathways or cellular energy expenditure, and is morphologically characterized by edema (swelling) of membrane organelles as well as swelling of the entire cell (oncosis) (11). The morphological hallmark of necrosis is the disruption of cell membrane integrity accompanied by the leakage of cellular contents into the extracellular space that always triggers an inflammatory response and local damage to neighboring cells **(Figure 2b)** (11).

Necrosis that occurs after apoptosis or autophagic cell death, when ATP is depleted, is called secondary necrosis (11). In addition to energy-independent passive necrosis, there are also regulated forms of necrosis that do require energy (11).

APOPTOSIS

Apoptosis or "cellular suicide" is a genetically regulated process, in which cell undergoes a characteristic sequence of morphological changes, including condensation of chromatin, typically resembling a crescent moon, organelle compaction, cytoplasmic condensation, cell shrinkage, and finally, fragmentation of the cell into apoptotic bodies by cell blebbing (6). The morphological characteristics of apoptosis, including chromatin and cytoplasmic condensation while the organelles remain intact, can be observed with transmission electron microscopy that is still considered to be golden standard for apoptosis identification **(Figure 2a)** (7). During apoptosis, membranes remain intact, preventing the release of cellular contents into the extracellular environment; therefore, there is an absence of inflammatory response or tissue damage (1, 11). Phosphatidylserine is displayed on the cell surface of apoptotic cells and apoptotic bodies as an "eat me" signal for surrounding cells and macrophages that rapidly remove dying apoptotic cells and apoptotic bodies from extracellular space by the process of efferocytosis (1, 2, 11).

The key players in the process of apoptosis are the family of cysteine proteases, called caspases, which are found in healthy cells in the form of inactive zymogens with low-to-absent protease activity (1). Their cascade activation leads to the execution of the apoptotic program (1). Initiator caspases (caspase-2, -8, -9, -10) are normally monomeric with a long prodomain that serves as a docking site for assembly into a self-activating complex, built around homomeric interactions between death (DD), death effector (DED), and caspase activation and recruitment (CARD) domains. Downstream or executioner caspases (caspase-3, -6, -7) exist as preformed dimers that become activated when the cleavage of a connector between subunits forms an open active site. In the extrinsic pathway of apoptosis, signals for caspase activation come from surrounding cells or molecules that bind to membrane receptors, so-called death receptors (tumor necrosis factor receptor 1 (TNFR1), Fas/CD95, TNFRSF10A, and TNFRSF10B), leading to the activation of initiator caspases (Figure 3) (1). In the intrinsic pathway of apoptosis, signals for caspase activation originate from within the cell due to various damages of organelles such as nucleus, endoplasmic reticulum or Golgi apparatus (1). Although activation of apoptosis by intrinsic pathway in the damaged cell can be mediated both by cytosolic and mitochondrial pathways, mitochondria have a central place in this type of cell death (1). Mitochondrial outer membrane permeabilization (MOMP) leads to increased permeability to small molecules, including cytochrome c, and the formation of the apoptosome which is specialized for activating effector caspases (1). Active caspases target many proteins essential for cellular viability, hence triggering apoptotic cell death (1). Among more than 1500 identified caspase substrates there is endonuclease, an enzyme that breaks down DNA, leading to the characteristic condensation of chromatin in the nucleus (1).

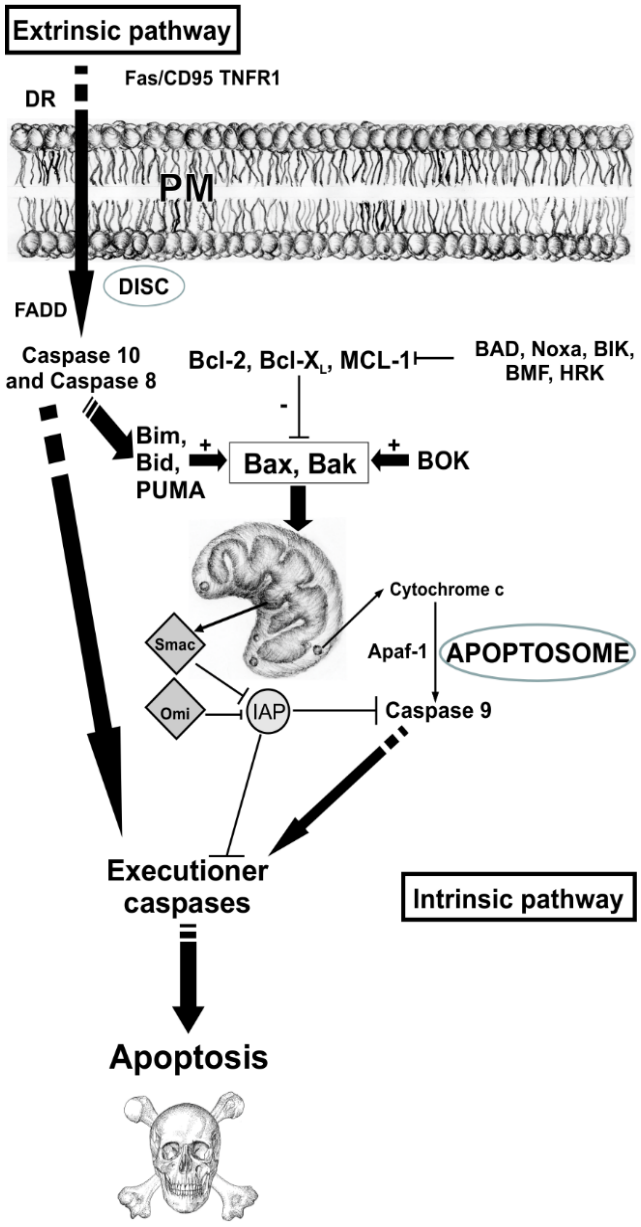

Figure 3. Extrinsic and intrinsic pathways of apoptosis. In extrinsic pathway ligand binding to death receptor Fas/CD95 makes conformational changes that help binding of its DD (death domain) with DD of FADD (Fas-associated death domain protein). A second domain in FADD, a DED, binds to DED domain in initiator caspases (caspase-8, and -10), leading to caspase dimerization. Caspase-activating assembly made of the death receptor, FADD, and caspase complex is called DISC (death-inducing signaling complex). In the intrinsic pathway, cytochrome c released from mitochondria binds to APAF-1 (apoptotic protease activating factor 1) and enables its oligomerization in heptameric wheel and exposure of its CARD domain. Interaction of CARD domain of APAF-1 with CARD in initiator caspase (caspase-9) helps docking of caspase-9 and is necessary for its proteolytic activity. This caspase-activating assembly platform, the apoptosome, is specialized for activating caspase-9 and -7, which have CARD-type prodomains. Interaction of Bcl-2 proteins (BAX, BAD, Bcl-2, BclXL, Mcl/1, BAD, Noxa, BIK, BMF, HRK, BOK, Bim, Bid, PUMA) regulate MOMP and cytochrome c release from the mitochondria. Cytochrome c release may be induced after Bid truncation by active caspase-8, linking the "extrinsic" and "intrinsic" pathways. Both pathways unite at the site of activation of executioner caspase-3 by upstream caspase-8, -9, or -10.

A number of regulatory proteins modulate the process of apoptosis. An important modulatory effect is exerted by proteins from the Bcl-2 (B-cell lymphoma-2) family of proteins **(Figure 3)** (1).

Various anti- and pro-apoptotic members of Bcl-2 family perform their actions at intracellular membranes (mitochondrial outer membrane, endoplasmic reticulum and nuclear membranes) and form a network of interactions that control MOMP (11). Their ability to selectively bind to each other is essential to their function in regulating MOMP and apoptosis (11). Bcl-2 family proteins selectively bind to each other via Bcl-2 homology domains (BH). The majority of proapoptotic and antiapoptotic Bcl-2 proteins are "multidomain" proteins that share sequence homology within 3–4 BH domains (12). A subset of proapoptotic Bcl-2 proteins show sequence homology with others only within the BH3 domain, death domain required for binding to "multidomain" Bcl-2 family members (12). These "BH3-only" molecules are: BID (BH3 interacting domain death agonist), BIM (Bcl-2 interacting mediator of cell death), BAD (Bcl-2 antagonist of cell death), Noxa, BIK (Bcl-2 interacting killer), BMF (Bcl-2 modifying factor), HRK (harakiri) and PUMA (p53 upregulated modulator of apoptosis) (12). Bcl-2 family interactions regulate mitochondrial intramembranous oligomerization of BAX (Bcl-2-associated X protein)/BAK (cl-2 antagonist killer 1), which is the key mechanism of MOMP (12). Antiapoptotic proteins, Bcl-2, BclXL (B-cell lymphoma extra-large) and Mcl-1 (myeloid cell leukemia sequence 1), inhibit apoptosis either by inhibiting BAX/BAK oligomerization or by engaging activator BH3-only proteins (12). "BH3-only" proteins activate apoptosis by both activating BAX/BAK oligomerization and by suppressing antiapoptotic proteins on the mitochondria and endoplasmic reticulum (12). BIM, BID and PUMA are "BH3-only" proteins known as "activators" that directly bind and trigger BAX/BAK oligomerization and bind and inhibit antiapoptotic Bcl-2 proteins (12). BAD, Noxa, BIK, BMF, HRK are BH3-only proteins known as "sensitizers" that bind and inhibit antiapoptotic Bcl-2 proteins (12). Disorders in the regulation of apoptosis are involved in the pathophysiology of a whole range of diseases (13, 14, 15). Overexpression of antiapoptotic molecules or downregulation of proapoptotic molecules was found in malignant cells resistant to apoptosis. High levels of Bcl-2 were first found in human follicular lymphomas and later in chronic lymphocytic leukemia cells (13). Abnormal expression of bcl2 family members, like Mcl-1 and BclXL is frequently found in many malignant tumors, like breast, gastric, prostate and hepatocellular carcinoma (14). Research data demonstrates that together with irregularities of pro-apoptotic BCL2 proteins and anti-apoptotic BCL2 proteins, aberrations of the components of the apoptosome and effector caspases also contribute to the pathogenesis of many cardiovas-

cular, hepatic, neurological, renal, autoimmune, inflammatory, infectious, and oncological diseases (14).

If a cell starts apoptosis and displays the nuclear morphology characteristic for apoptosis, but does not have enough energy to complete the initiated process of apoptosis, it may progress to secondary necrosis (16). Secondary necrosis is controlled by caspase-3 that cuts DFNA5 (deafness-associated tumor suppressor), into a necrosis-promoting DFNA5-N fragment that inserts into the plasma membrane, creating large pores that facilitate the release of inflammatory molecules into the extracellular space (16).

AUTOPHAGY-DEPENDENT CELL DEATH (ADCD)

Autophagy is an intracellular catabolic process responsible for the breakdown of damaged and/or non-functional cytoplasmic components and organelles, with the participation of lysosomal enzymes (17). Depending on the way material for degradation reaches a lysosomal lumen, three different types of autophagy are being described: chaperone mediated autophagy (CMA), microautophagy and macroautophagy (17).

In CMA, certain cytosolic proteins are first unfolded with a help of cytosolic chaperone proteins, after which they pass through a lysosomal membrane protein complex containing Lysosome-associated membrane protein 2A (LAMP2A) forming a distinct channel, thus reaching a lysosomal lumen where they are degraded (18).

In microautophagy, peculiar membrane invaginations of the lysosomal membrane are formed, projecting towards lysosomal lumen (19). After these invaginations are pinched off the lysosomal membrane, vacuoles that are formed, together with their cytosol-derived content, are degraded by lysosomal enzymes (19). In mammals, the process also takes place in endosomes (19), and in lysosomes it may include flap-like lysosomal membrane extensions, as sequestration mechanism (20).

Macroautophagy (hereafter referred to only as autophagy) relies on the formation of double membrane structures termed autophagosomes, which subsequently fuse with lysosomes (7). Autophagosomes are formed after a closure of cytoplasmic cisternal structures termed isolation membranes or phagophores, which sequester parts of the cytoplasm, including organelles, destined for degradation **(Figure 2c)** (7).

In mammalian cells, autophagy is regulated by two kinases: mTOR (Mammalian target of rapamycin) and AMPK (AMP-activated protein kinase) (Figure 4) (17, 21). In the presence of growth factors, autophagy is inhibited by mTOR which phosphorylates and inactivates another kinase ULK1 (Unc-51-like kinase 1) (17). On the other hand, AMPK acts as a cellular energy sensor **(Figure 4)** (22). When intracellular ATP/ADP ratio decreases, AMPK activates autophagy by phosphorylating and activating ULK1 and other proteins that regulate autophagy (23).

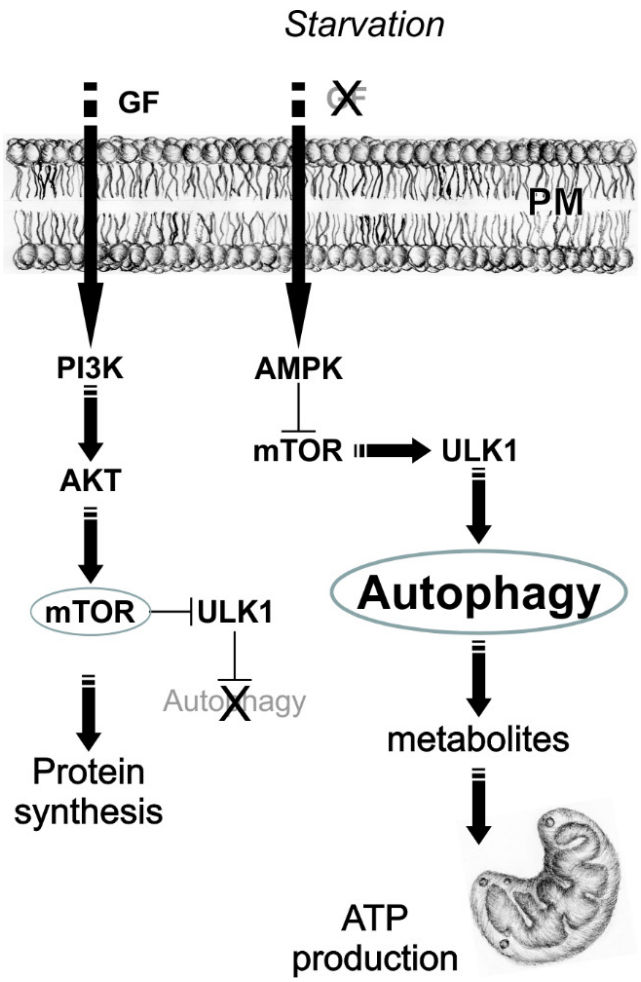

Figure 4. Activation of autophagy. Ligand binding to GF (growth factor) receptor leads to the activation of PI3K (phosphatidylinositol 3-kinase), AKT (protein kinase B) and mTOR that stimulates protein synthesis and inhibits autophagy through inactivation of ULK1. During nutrient starvation, AMPK, activates autophagy by inhibiting mTOR leading to ULK1 activation. Breakdown of organelles and proteins in autophagosomes produces metabolites that can be used for production of ATP in mitochondria.

Because it participates in the degradation of non-essential cytoplasmic components, recycling of their constituent molecules (e.g. during starvation) and removing of damaged and/or nonfunctional organelles and macromolecules, autophagy is generally considered to be cytoprotective (2). Blocking autophagy by artificial means generally leads to the acceleration of cellular destruction (rather than preventing cell death) (2, 24, 25). However, there are certain biological conditions where it is clear that excessive activation of autophagy may lead to cell death (2). Since the inhibition of autophagy in these circumstances rescues the cells, this type of cell death is being called autophagy-dependent cell death (2, 26).

This is different from previous cell death classifications (10), from the time when the cytoprotective role of autophagy was not properly acknowledged by the scientific community. Latest advances in the understanding of biological roles of autophagy enabled us to understand that a sheer presence of a large number of autophagy-related structures in dying cells is not enough to declare that

cells are dying by autophagy (2). Previously called autophagic cell death, it is now recognized that for the process of autophagy-dependent cell death to be demonstrated, it is not enough to notice that cells are dying "with" autophagy (27). Instead, it is necessary to prove that excessive autophagy is effectively killing the cells, by demonstrating that autophagy inhibition rescues them (2, 27).

In autophagy dependent cell death, cells actively participate, and the process is genetically regulated (2). This is a way some neurons die in rodent models of neonatal hypoxia-ischemia, and it also may occur in certain other pathological conditions (2, 28). In non-pathological conditions, autophagy-dependent cell death is also necessary as a mechanism of cell death in Drosophila metamorphosis (2).

OTHER FORMS OF CELL DEATHS

Necroptosis

Necroptosis is a type of RCD initiated by signals from the extracellular or intracellular microenvironment detected by death receptors (FAS, TNFR etc.) or pattern recognition receptors (PRRs) (2, 29). As the name suggests, necroptosis shares features with necrosis (early membrane disruption and cell and organelle swelling) and apoptosis (which is tightly regulated via genetics, signaling molecules, or toxins). In contrast to apoptosis, necroptosis is not only caspase-independent, but also induced by inhibition of caspase-8 (29, 30). The molecular markers of necroptosis are phosphorylated RIPK3 (receptor-interacting serine/threonine protein kinase 3) and phosphorylated MLKL (mixed lineage kinase domain like pseudokinase) **(Figure 5)** (1).

Necroptosis has been mostly investigated as the response to microbial infection. In cancer, necroptosis is beneficial for the antitumor immune response, not only because of MLKL-dependent cell lysis and uncontrolled release of cellular contents, but also because of tightly regulated activation of RIPK1/RIPK3/NFκB proinflammatory signaling, which leads to the synthesis of proinflammatory cytokines prior to cell disintegration (29).

As our understanding of the molecular mechanisms of necroptosis continues to evolve, it holds the potential to lead to innovative therapies and interventions in diverse fields of research, as it has been shown to play an important role not only in infections and systemic inflammatory response syndrome but in chronic pulmonary disease, acute kidney failure and fibrosis, liver disease, cardiovascular, neurodegenerative diseases and cancer (31).

Pyroptosis

Pyroptosis represents a unique form of RCD, primarily associated with the innate immune response to infections and inflammatory disorders. The term "pyroptosis"

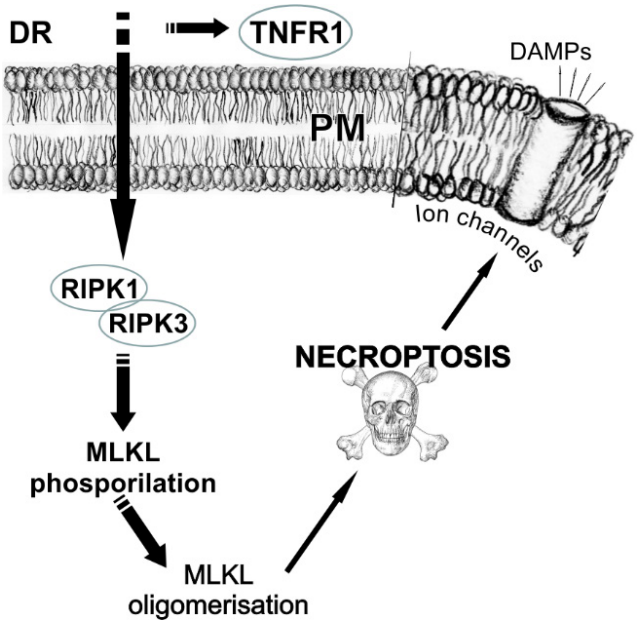

Figure 5. Molecular pathways of necroptosis. After ligation of TNFR-1, RIPK1 associates with RIPK3. RIPK3 phosphorylates the MLKL that oligomerizes after phosphorylation and promotes plasma membrane permeabilization. There are at least two pathways leading to the loss of cell integrity in necroptosis: MLKL could form a platform at the plasma membrane for the opening of calcium and sodium ion channels, enabling the influx of ions in the cell, cell swelling and rupture and/or MLKL itself could form pores in the plasma membranes.

was coined by D'Souza et al. in 2001, from Greek words pyro (fire or fever) and ptosis (falling), to emphasize the inflammatory nature of this type of cell death (32). For decades it was misconceived as a special form of apoptosis in monocytes, since it shared some features with apoptosis, like involvement of caspase-1 (33). Caspase-1, recognized as inflammatory caspase, is required for the cleavage of precursor pro-IL-1β into active IL-1β, also known as leukocytic pyrogen (34). Later, in 2002, the inflammasome was proposed to be a molecular platform for the activation of caspase-1 **(Figure 6)** (35).

Furthermore, it was demonstrated that pyroptosis could be induced in caspase-1 independent manner, by the activation of other caspases, specifically caspase-4, 5 and 11 (33). In 2015 it was discovered that both caspase-1 and caspase-4/5/11 share gasdermin D (GSDMD) as a key substrate in induction of pyroptosis, and since then, pyroptosis is commonly defined as gasdermin-mediated programmed cell death (33). The N-terminal domain of GSDMD can oligomerize to form pores in the cell membrane, causing cell swelling and lysis (33).

Although pyroptosis shares some features with apoptosis, like DNA fragmentation and intact nucleus, there are many differences between them, including the loss of membrane integrity, cellular swelling, the rupture of cell membrane and consequent inflammation (36).

The main role of pyroptosis, as an important player in the innate immunity, is defense against intracellular pathogens. However, numerous studies have pointed to a much

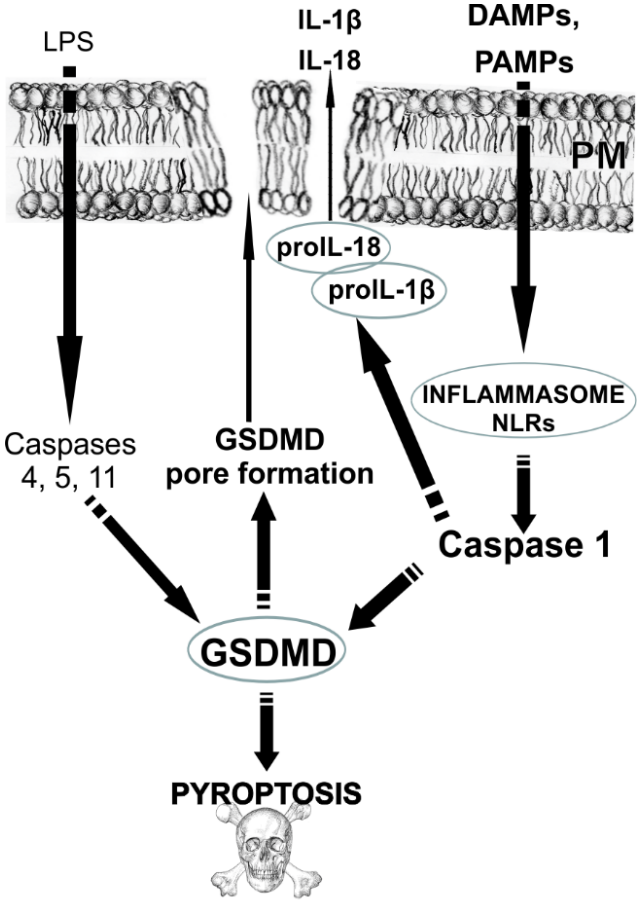

Figure 6. The mechanisms of pyroptosis. In canonical inflammatory pathways, PAMPs and DAMPs are detected by inflammasome, cytosolic multiprotein complex involving NLR (nucleotide-binding oligomerization domain (Nod)-like receptors) proteins which activate caspase-1. Caspase 1 performs cleavage of inflammatory cytokines IL-1β and IL-18 into mature forms, and cleavage of GSDMD that leads to formation of GSDMD pore and pyroptosis. In noncanonical inflammatory pathways, binding of LPS (lipopolysaccharides) leads to the cleavage of GSDMD, formation of GSDMD pore and pyroptosis.

broader aspect of pyroptosis as a type of RCD involved in inflammatory diseases and sepsis, cardiovascular, metabolic diseases, neurodegeneration and cancer (36).

Ferroptosis

Ferroptosis is a distinctive form of RCD, induced by iron-dependent, lipid peroxidation-mediated membrane damage. Although the term "ferroptosis" was coined not that long ago, in 2012, and ferroptosis-like cell death was described in 2001 as a cell death induced by oxidative stress ("oxytosis") (37), pioneering research was made back in the 1950s and 1960s, when the researchers observed cell death induced by cysteine-deprivation (38).

The primary system regulating ferroptosis is the cellular antioxidant system cysteine-glutathione (GSH)-glutathione peroxidase 4 (GPX4) (39). GPX4 is an antioxidant enzyme which catalyzes the reduction of lipid-hydrogen peroxides, cholesterol- and phospholipid hydrogen peroxides (PLOOHs), from cellular membranes and protects cells from the oxidative stress (40). Two compounds widely used for induction of ferroptosis, erastin and RSL3, act by interfering with GPX4-pathway that leads to the accumulation of PLOOHs in the cell and ferroptosis (39).

Potent inducers of ferroptosis include enzymes that directly oxygenate polyunsaturated fatty acids present in cellular membranes, such as lipoxygenases (LOXs), cytochrome P450 oxidoreductase (POR), and two membrane-remodeling enzymes, acyl-CoA synthetase long chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3). The importance of mitochondrial tricarboxylic acid cycle in lipogenesis, together with mitochondrial roles in beta-oxidation of fatty acids and oxidative metabolism, strongly links mitochondria with ferroptosis (39).

As the name suggests, iron has a central role in induction and regulation of ferroptosis. Iron is required as catalyst in numerous metabolic enzymes involved in reactive oxygen species (ROS) generation and lipid peroxidation, including LOXs and POR. Furthermore, intracellular iron ions can catalyze Fenton reaction, generating highly reactive hydroxyl radicals that initiate a chain reaction that culminates in lipid peroxidation and massive PLOOH production. Cellular processes that regulate iron homeostasis within cells (iron uptake, storage, utilization and efflux) therefore affect ferroptosis (41).

Cells undergoing ferroptosis exhibit swelling, with increased cell membrane density and membrane rupture. The distinctive feature of ferroptosis is the atrophy or condensation of mitochondria, disappearance of cristae and rupture of outer mitochondrial membrane (41).

A growing body of research indicates a potentially important role of ferroptosis in tumor suppression, ischemia-reperfusion injuries (also, associated with organ transplantation), immune surveillance, neurodegeneration and lung and liver fibrosis (39, 41).

Parthanatos

Parthanatos is a caspase-independent form of cell death which leads to DNA fragmentation (42). The term „parthanatos" is coined from „par", referring to poly(ADP)ribose (PAR), one of the key participants in this type of cell death, and „Thanatos", personification of death in Greek mythology. Parthanatos is a precisely regulated, multistep process resulting in large-scale DNA fragmentation and chromatin condensation (42).

One of the mechanisms for ensuring genome stability includes a nucleic enzyme called poly (ADP-ribose) polymerase 1 (PARP1). This DNA base-excision repair system facilitates DNA damage repair through the synthesis of PAR polymer (43). However, in instances of excessive DNA damage, such as ROS, inflammation, ischemia, hypoxia, etc., PARP1 becomes hyperactivated. Hyperactivation of PARP1 is the initial step in parthanatos, resulting in the production of long-chained, branched PAR polymers (42).

PARP1 overactivation causes cellular energy depletion. Namely, PARP1 hyperactivation requires nicotinamide adenine dinucleotide (NAD^+) as a cofactor, which is an important cofactor in cellular metabolism, including ATP synthesis. On the other hand, resynthesis of NAD^+ requires many ATP molecules. Additionally, accumulation of PAR polymers causes translocation of apoptosis-inducing factor (AIF) from mitochondria to nucleus (44). AIF may be considered as a parthanatos "executor", leading to massive DNA fragmentation, chromatin condensation, membrane rupture and cell death.

Parthanatos as a form of cell death is found in many diseases, while PARP inhibitors are extensively explored for the pharmacological treatment of breast, ovarian, and colorectal cancer (45).

Mitochondrial permeability transition-driven necrosis

Mitochondrial permeability transition (MPT)-driven necrosis is a form of cell death caused by a sudden increase in the inner mitochondrial membrane (IMM) permeability to small molecules. This type of cell death is initiated by the increase in Ca^{2+} and ROS in the mitochondrial matrix (46). The crucial event in MPT-driven necrosis is the formation of mitochondrial permeability transition pore (mPTP) in the IMM. The formation of mPTP enables permeability of IMM for molecules up to 1.5 kDa in size. The sustained opening of the mPTP causes abrupt change in mitochondrial permeability leading to the loss of mitochondrial membrane potential, mitochondrial swelling, rupture of the outer mitochondrial membrane (OMM), disruption of cellular energy metabolism and finally, necrotic death. Opposite to sustained mPTP opening, transient mPTP opening is not associated with cell death. Such reversible mPTPs are permeable to small molecules up to 300 Da and play a role in the mitochondrial homeostasis of Ca^{2+} (47).

It was long considered that the main structural components of mPTP are voltage-dependent anion channel (VDAC) in the OMM, adenine nucleotide translocase (ANT) in the IMM, and cyclophilin D (Cyp-D) in the mitochondrial matrix. Numerous experiments confirmed that neither VDAC nor ANT are required for the induction of mPTP (48). However, Cyp-D was recognized as an important regulator of the mPTP opening. Cyp-D is not a structural pore component of mPTP; it is a Ca^{2+}-sensitive isomerase present in the mitochondrial matrix which translocate to the IMM and mediates mPTP opening.

MPT-driven necrosis has been implicated in the pathogenesis of ischemic heart and brain disease, and many degenerative diseases which is why targeting its molecular steps might translate into novel therapeutic approaches (49).

Lysosome-dependent cell death

Lysosome-dependent cell death (LDCD) represents a form of RCD which is characterized by primary lysosomal membrane permeabilization (LMP), a phenomenon that leads to cell death (2). LMP is characterized by the release of lysosomal contents, including proteolytic enzymes of the cathepsin family, into the cytosol where they act in various ways as executors of cell death (50). LMP may occur downstream of MOMP and represent an epiphenomenon of intrinsic apoptosis (51). Alternatively, lysosomes can be permeabilized prior to mitochondria, which may involve the recruitment of BAX to the lysosomal membrane and formation of pores (52). Additional triggers of LPM may include lysosomotropic agents (e.g., sphingosine), calpains, reactive oxygen species (ROS), STAT3 etc. (53).

Cathepsins can catalyze proteolytic activation or inactivation of BID, BAX, anti-apoptotic BCL2 family members and XIAP, and therefore lead to LCDC with the involvement of MOMP and caspases (54). However, MOMP and caspases are not necessarily involved in LDCD so this type of RCD does not always exhibit apoptotic morphology (55).

LDCD is involved in different pathological and physiological conditions, such as intracellular pathogen response, inflammation, neurodegeneration, cardiovascular disorders, aging and tissue remodeling during involution of mammary gland after lactation (2, 50).

Immunogenic cell death

Immunogenic cell death (ICD) represents a form of RCD that is capable of initiating adaptive immune response in an immunocompetent host (2). This adaptive immune response is specific for endogenous (cellular) or exogenous (viral) antigens that are expressed by dying cells (2).

Various stimuli can initiate ICD, including viral infection, specific forms of radiation therapy, some FDA-approved chemotherapeutics and hypericin-based photodynamic therapy (2). These agents initiate release of damage-associated molecular patterns (DAMPs), such as calreticulin, ATP, type I IFN, cancer cell-derived nucleic acids, high-mobility group box 1 (HMGB1) and annexin A1 (ANXA1) by dying cells. DAMPs are being recognized by PRRs on immune system cells leading to the activation of an immune response with the formation of immunological memory (2, 56). Calreticulin relocates from the endoplasmic reticulum to the outer leaflet of plasma membrane where it functions as an "eat me" signal for DCs, macrophages and neutrophils and acts as a trigger for Th17 cell priming (57). ATP has a role as a "find-me" signal for dendritic cell precursors and macrophages and activates inflammasome (58). Cancer cells which are going to die by ICD release nucleic acids which can be taken up by DCs, macrophages and neutrophils and this results with the activation of type I IFN immune response (59).

Entosis

Entotic cell death, also known as entosis or cellular cannibalism, is a type of cell death in which a cell invades a living neighboring cell and eventually dies after being engulfed. This is a characteristic type of non-apoptotic cell death, which is recognizable by its cell-in-cell phenomenon, and which occurs in human tumors and non-tumor tissues, such as epithelial cell cultures (60). Entosis has several interesting features that distinguish it from other types of cell death, mainly that the entrapped cell can survive and even divide in the host cell, or it can leave the invaded cell without any sign of degradation (61). Although present in both physiological and pathological conditions, the exact role of entosis remains unclear with literature data suggesting both pro- and anti-tumorigenic effects. It is believed that entosis allows cancers to be removed by their healthy neighbors, as the tumorigenic cells have lost their cell-cell connections, and on the other hand, allows surrounding cells to survive by promoting cell competition (62). Entosis has also been associated with the process of embryo implantation (63), the elimination of spermatozoa by the Sertoli cells (64), but also in the pathophysiology of non-cancerous conditions such as diabetic cardiomyopathy (65). Several studies have shown that different drugs can induce entosis in various cancer cell lines. Methylselenoesters, novel synthesized selenium compounds, have caused entosis by cell detachment in pancreatic cancer cells (66). Recently published papers have shown that known and well-studied cytotoxic drugs, such as nintedanib and doxorubicin in combination with calcifediol, can induce entosis in prostate and breast cancer cells (67). These data highlight the possible therapeutic implications of entosis in cancer management.

NETosis

One of the mechanisms through which neutrophils destroy microbes is the formation of Neutrophil Extracellular Traps (NETs), which represent web-like structures made from modified chromatin and antimicrobial proteins, both originating from granules and nucleus of neutrophilic granulocytes (68). These formations bind, entrap, and finally destroy microorganisms in the extracellular space, without the need for intracellular phagocytosis. However, releasing these neutrophilic molecules/enzymes and pathogen destruction elicits neighboring tissue destruction and inflammation (69). During this process, neutrophils die, which is why this atypical type of cell death is termed NETosis. Unlike apoptosis, NETosis is characterized by the disintegration of nuclear and cytoplasmic membranes, followed by the leaking of genetic material in the extracellular space which immobilizes microorganisms (70). Though NETosis is a defensive reaction of the body, the release of intracellular granule components in the extracellular space causes proinflammatory reactions that can exacerbate existing inflammation in patients with different forms of autoimmune diseases (71). The role of NETosis in cancer progressions and metastasis is now also known, as NETosis can cause a wide range of changes needed for further development and dissemination of cancerous cells (72). NETosis can induce epithelial-mesenchymal transition in different cancers, create an optimal microenvironment for tumor development (73), and play a role in different cancer-related complications, such as venous thromboembolism (74).

CONCLUSION

Why is it important how a cell dies? In some types of cell death damaged cells do not have a preserved cell membrane and release DAMPs, therefore they are pro-inflammatory and lead to the activation of macrophages and dendritic cells (11). In contrast, apoptosis is an immunologically silent cell death, during which there is no spillage of cell contents into the environment due to the preserved cell membrane and the formation of apoptotic bodies, as well as due to the activation of caspases that inactivate DAMPs (11). Necrosis and pyroptosis are proinflammatory cell deaths during which proinflammatory cytokines are secreted, cell membrane bursts and cellular contents spill into the extracellular space leading to the damage of surrounding cells (11).

It may seem that apoptosis is a favorable form of cell death and that any pro-inflammatory form of cell death is always unfavorable and probably a result of an error in the activation of apoptosis. Nevertheless, pro-inflammatory forms of cell death may have evolved in order to remove multiple cells at the same time. Cells dying from pyroptosis, prevent the spread of infection by killing groups of cells that release DAMPs and recruit immune cells to the site of infection (75). Damaged or malignant cells dying from necroptosis attract immune cells that result in the death of malignant cell population and prevention of metastases (11). Therefore, the presence of regulated, proinflammatory cell death is in some circumstances important for the protection of surrounding cells and the organism.

Different types of cell death are interconnected. Apoptosis may inhibit the process of autophagy by caspase cleavage of Beclin and ATG (1). Furthermore, autophagy can inhibit apoptosis by increasing BCL-XL expression (1). The inactivation of autophagy during starvation leads to apoptosis, unless apoptosis is inactivated (e.g., BAX/BAK deficiency), in which case cell death occurs through necrosis (1). Inhibition of autophagy can either lead to mitochondrial dysfunction and apoptosis or to stabilization of RIPK1 and necroptosis (24, 25).

Abnormal activation of the different forms of cell death can cause diseases. Dysregulation of apoptotic pro-

gram can lead to hyperplasia, autoimmune diseases and tumorigenesis (76). Pyroptosis has a crucial place in the initiation of inflammatory response and achieving elimination of intracellular microorganism during bacterial infection, but uncontrolled pyroptosis can lead to organ failure and sepsis (77). Necroptosis has been associated with carcinogenesis related to non-alcoholic fatty liver disease and with human inflammatory skin diseases (78).

Understanding how cells dye and the knowledge about regulation mechanisms of different types of cell death, especially apoptosis, resulted in discovery of drugs that act as BH3 mimetics, ABT-737 and its oral derivative, Navitoclax, for the treatment of B cell malignancies that overexpress anti-apoptotic BCL-2 proteins (79). Drugs that target necroptosis, pyroptosis and autophagy are currently being researched and may serve as future therapeutic options for various diseases, including cancer.

Conflicts of interest

None to declare.

Author contributions

VB, TKS, MCM, TM made the design of the manuscript, review and editing of the text. The following sections of the manuscript were written by: TKS – abstracts, introduction and conclusion, TM – necrosis and apoptosis, DC – ACDC, SD – necroptosis, pyroptosis and ferroptosis, JR – parthanatos and (MPT)-driven necrosis, IP – LCDC and ICD, IZ – entosis and NETosis; MCM designed and made all figures. All authors have read and agreed to the published version of the manuscript.

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ŽIVOT ĆELIJE: DA LI JE VAŽNO KAKO ĆELIJE UMIRU?

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Sažetak

Ćelijska smrt je prisutna tokom embrionalnog razvoja, i posle rođenja kao važan proces, neophodan za održavanje homeostaze, kojim se uklanjaju ostarele i oštećene ćelije. Postoje dva tipa ćelijske smrti: akcidentalna i regulisana ćelijska smrt. Nekroza je akcidentalna, neregulisana, pasivna forma ćelijske smrti koja nastaje usled kolapsa homeostatskih mehanizama u ekstremnim nefiziološkim uslovima. Regulisana ćelijska smrt je aktivan, energetski zavistan proces, koji nastaje u fiziološkim uslovima, tokom održavanja homeostaze organizma i u brojnim patološkim stanjima kada obezbeđuje selektivnu eliminaciju potencijalno opasnih ili inficiranih ćelija. Brojni su tipovi regulisane ćelijske smrti: unutrašnji i spoljašnji tip apoptoze, ćelijska smrt zavisna od autofagije, nekroptoza, piroptoza, feroptoza, partanatos i MPT nekroza, ćelijska smrt zavisna od lizozoma, imunogena ćelijska smrt, entoza i NET-oza. Različiti tipovi ćelijske smrti su međusobno povezani. Abnormalna aktivnost različitih formi ćelijske smrti može dovesti do razvoja brojnih bolesti. Poremećaj regulacije apoptoze može dovesti do hiperplazije, razvoja autoimunskih oboljenja i tumora. Poznavanje regulacionih mehanizama apoptoze dovelo je do otkrića BH3 mimetika, lekova koji se koriste u terapiji nekih tipova malignih tumora B limfocita. U savremenim naučnim istraživanjima ispituju se lekovi koji utiču na nekroptozu, piroptozu i autofagiju koji mogu u budućnosti biti terapija za različite bolesti, uključujući i maligne tumore. Cilj ovog revijskog rada je da rezimira nova saznanja u vezi sa procesima ćelijske smrti i ukaže na značaj novootkrivenih molekularnih puteva regulacije različitih tipova ćelijske smrti u cilju boljeg razumevanja zdravlja i bolesti.

Ključne reči: ćelijska smrt, nekroza, apoptoza, autofagija

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