Journal of Advances in Biology & Biotechnology

Volume 27, Issue 11, Page 241-270, 2024; Article no.JABB.124915
ISSN: 2394-1081

Cell Death Mechanisms

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/jabb/2024/v27i111609

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/124915

Original Research Article

Received: 12/08/2024
Accepted: 14/10/2024
Published: 04/11/2024

ABSTRACT

Cells and their building blocks ensure the maintenance of life by performing complex tasks such as taking in nutrients, excreting waste materials, producing energy, growth, division and reproduction. The form of intercellular communication and coordination is critical for the organism to grow, develop, and adapt to its environment optimally. The numerical balance of the cells that make up the organism is very important for it to survive in a healthy way. While new cells are being created in the living being, some of the existing cells are also eliminated through cell death, thus ensuring a stable balance. As new cells are generated within the organism, a portion of the existing cells undergoes elimination through the process of cell death, thereby maintaining a stable balance. To uphold this mechanism, various forms of cell death mechanisms are activated. Cell death occurs spontaneously, genetically or by other factors that are a part of the life of living things. It basically exists in two main forms. These are programmed and unprogrammed cell death. Cell death mechanisms are critical for the development, survival and health of living organisms. This process, which is basically divided into two main categories, is called programmed cell death (apoptosis) and unprogrammed cell death (necrosis). Programmed and unprogrammed cell death mechanisms are

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Cite as: *Seçer, Merve Nur Şahan, and Mine Dosay-Akbulut. 2024. "Cell Death Mechanisms". Journal of Advances in Biology & Biotechnology 27 (11):241-70. https://doi.org/10.9734/jabb/2024/v27i111609.*

very important for the proper functioning of biological systems and the continuation of life. While programmed cell death (apoptosis) plays very important roles in the regulation and development of tissues, homeostasis, immune response and prevention of diseases, unprogrammed cell death (necrosis) is important in the rapid repair of tissue by clearing damaged cells and the clearance of pathogens. Understanding the way death mechanisms work is very important in terms of understanding the effects that may occur on a healthy continuation of life and in developing more effective methods in the treatment of diseases that may arise as a result. For these reasons, what death mechanisms are, their types, differences and working principles have been tried to be summarized in this study.

Keywords: Cell; death mechanisms; apoptosis; necrosis.

1. INTRODUCTION

1.1 Cell

Cells are the basic building blocks that make up living organisms. Cells, the smallest unit of life, consist of one or more cells, from single-celled microorganisms to multicellular humans. Cells have various structures and organelles to fulfill the vital functions of organisms (nutrition, respiration, waste disposal and reproduction). Basic parts of the cell from outside to inside; It consists of the cell membrane surrounding the cell, the cytoplasm that carries out various vital activities, and the nucleus containing the genetic material.

The cell membrane consists of a selectively permeable structure that separates the cell from the external environment and enables its interaction, allowing the molecules in the environment to enter or leave the cell according to their properties. Cytoplasm is a semi-fluid liquid structure containing various salts, enzymes, organic molecules and organelles within the cell. The cell nucleus is the control center in eukaryotic cells that carries the cell's genetic information and regulates gene expression.

Organelles within the cell are specialized structural units that enable the cell to function properly. Ribosomes, one of the cell organelles, are located in the nuclear membrane and cytoplasm and are the units responsible for protein synthesis. The endoplasmic reticulum (ER) is the cell's cargo system. They are two types of organelles, granular and non-granular, located between the cell membrane and the nucleus in plant and animal cells, and perform functions such as protein and lipid synthesis. Mitochondria are organelles that are responsible for providing the energy required for the cell (ATP production) and meeting the cell's need for respiration. The Golgi apparatus, consisting of flat sacs, are organelles that enable the processing, packaging and transport of proteins inside or outside the cell. Lysosomes are organelles responsible for digestion in the cell that contain many degrading enzymes. In addition to breaking down the waste materials created by the cell, they are also responsible for breaking down bacteria and viruses that enter the cell. Vacuoles are organelles, consisting of fluid-filled spaces in the cytoplasm. It adjusts the osmotic pressure and pH of the cell. Vacuoles are found in various functions; as food vacuole, digestive vacuole, secretory vacuole, excretory vacuole, storage vacuole and contractile vacuole. Centrosomes are structures that enable the division and transportation of chromosomes that are responsible for cell division. Chloroplasts are organelles found in plant cells that enable the plant to produce nutrients and oxygen.

Cells and their building blocks ensure the maintenance of life by performing complex tasks such as taking in nutrients, excreting waste materials, producing energy, growth, division and reproduction. The form of intercellular communication and coordination is critical for the organism to grow, develop, and adapt to its environment optimally.

1.2 Cell Cycle

Life in both prokaryotes and eukaryotes consists of certain processes. These processes consist of birth, growth, reproduction, aging and death. In order for the organism to survive in this healthy way, the numerical balance of the cells that make up it is very important. While new cells are being created in the living being, some of the existing cells are also eliminated through cell death, thus ensuring a stable balance. In order to maintain this mechanism, it is destroyed by various cell death mechanisms such as apoptosis, which is programmed cell death, and necrosis, which is pathological cell death (Bellamy, Malcomson, Harrison, & Wyllie, 1995; Ellis, Yuan, & Horvitz, 1991).

The cell cycle is the process in which biochemical and structural changes occur from the beginning of division of one cell to the division of another cell, resulting in the formation of two cells that are genetically identical to each other (Sherr, 2000). The cell cycle is one of the basic mechanisms of living organisms that ensure the division and proliferation of cells, which form the basis of vital activities. This process, which consists of a series of stages, covers the period from when a cell begins to divide until newly formed cells divide again.

The cell cycle is generally divided into two: rest and division periods. The resting period is also called the G0 phase and is a period in which the normal vital activities of the cell continue and is longer than the division phase. It is generally examined in two main phases: interphase and mitosis phase. With the timing of DNA synthesis during mitosis [nuclear division], the cell cycle of eukaryotic cells is divided into four separate phases. The M phase of the cycle corresponds to mitosis, which is mostly followed by cytokinesis (Cooper, 2019).

Interphase phase; It is the period when the cell prepares to divide by copying the cell's DNA. The cell grows in volume and DNA replication prepares the cell for division. It is the preparation phase for mitosis, which covers most of the cell cycle (95%). It is divided into three substages: G1 (Growth 1), S (Synthesis), and G2 (Growth 2). The division period consists of G1, S, G2 phases, in which preparations are made for mitosis, and M phase, in which mitosis takes place. G1 phase is the part between the end of the cytokinesis step in the previous cell division and the beginning of the S step. It is the step in which the cell grows in

volume and the decision is made whether the cell will divide again or not (Wenzel & Singh, 2018). In the interphase phase, the cell grows in the G1 phase, which is the preliminary phase to double the genetic material, in the S (Synthesis) phase, the genetic material is doubled by DNA replication, and in the last phase, the G2 (Growth 2) phase, the cell completes its preparations for division by making its final checks before division. In S phase, each chromosome is replicated only once. G2 phase is the preparation step for mitosis. Duplication of centromeres occurs in this phase (Feldman, 2012).

In summary, the production of RNA and proteins to be used in DNA replication is carried out in the G1 phase. In S phase, the regions where DNA replication will begin are marked and the DNA is made diploid. In the G2 phase, final preparations for mitosis are made. Finally, in M phase, mitosis occurs in which the cell completely becomes two daughter cells (Rieter, 2004).

In the mitosis phase, two new cells are formed including the cell nucleus and the cytoplasm. Mitosis phase consists of four sub-steps: prophase, metaphase, anaphase and telophase, which include the phases in which the paired chromosomes are aligned on the cell axis and pulled to different poles, where sister chromatids are separated from each other and the cell is divided into two. The cell cycle is a chain of events that includes the division of the cytoplasm and organelles in order to send the DNA replication of the cell to the daughter cells that will be formed (Mura, Feillet, Bertolusso, Delaunay, & Kimmel, 2019).

The events that occur during the cell cycle, when chromosomes are replicated and transferred to daughter cells, are common to all cell cycles. Because, with some exceptions, the newly divided cell must have a complete genome in order to survive (Nurse, 2000). In S. cerevisiae, unlike in typical eukaryotic cells, the nuclear membrane remains intact during mitosis, which is referred to as closed mitosis. The structure responsible for centromere function in this organism is known as the Spindle Pole Body (SPD) and is located within the nuclear membrane. Additionally, S. cerevisiae does not possess lysosomes; instead, the vacuole takes on lysosomal functions (Feldman, 2012). The restriction checkpoint in the G1 phase in mammalian cells is the control element that regulates the growth and division cycle in the cell (Cooper, 2003). Before reaching the restriction point, the cell cycle may be arrested due to a number of cellular and external factors and they may enter a non-proliferative phase called G0 or latent phase. This situation is fundamentally different from other cell cycle exits, such as aging or terminal differentiation. When cellular conditions or environmental effects return to normal conditions, the cell cycle continues by transitioning from G0 to G1 phase (Grant & Cook, 2017). Factors controlling the cell cycle; cyclins (Cln), cyclin-dependent protein kinases (Cdk) and cyclin-dependent kinase inhibitors (Cki), which are Cdk inhibitors (Hartwell, 1973).

In the cell cycle, Cdks function as kinases that coordinate cellular activities specific to the cycle

phase (Morgan, 1997). They become active by forming a complex with cyclins (Cln). Cln-Cdk complex activity is controlled by cyclin-dependent kinase inhibitors (CKI) factors depending on extracellular and intracellular signals. Checkpoints in the cell cycle are phylogenetically preserved signaling cascades that are activated in response to errors that may occur in steps such as DNA replication, DNA damage or chromosome segregation (Bartek & Lukas, 2001; Bartek & Lukas, 2003). Regulatory checkpoints; They include G1/S (restriction checkpoint), G2/M (DNA replication checkpoint) and metaphase/anaphase (mitotic apparatus checkpoint). The restriction checkpoint is first affected by growth factors, cell size, cell nutrition and damage to DNA. The DNA replication checkpoint is affected by inappropriate DNA replication and damage (Wenzel & Singh, 2018).

Regulation of the cell cycle is provided by various control mechanisms and proteins. Checkpoints are essential for detecting and repairing errors and DNA damage that may occur at any stage in the cell cycle. When malfunctions occur, which may not occur frequently, the errors are quickly corrected with other proteins and the system runs smoothly. The synthesis of these proteins responsible for control is regulated by tumor suppressor genes (TSG; tumor suppressor gene) called proto-oncogenes. Under normal conditions, the activities of proto- oncogenes and tumor suppressor genes are in balance. Disturbances that may occur in this balance, that is, disruptions in proto-oncogenes, may lead to a decrease in the synthesis of some proteins that prevent cancer formation, and as a result, cancer formation. It is thought that this balance is disrupted by various mutations and damage to the DNA chain caused by various factors. Additionally, silencing tumor suppressor genes through various epigenetic modifications can disrupt this balance (Park & Vogelstein, 2003). Cells have signal transduction mechanisms that detect external signals with special receptors and provide the most appropriate cellular response (Kurnaz, 2013). Although they have a very complex structure and contain many branches, the working principle of all signal transmission pathways is similar to each other. Signaling mechanisms are activated by the presence of an external stimulus (primary message). It shows its final effects by activating or inhibiting structural and metabolic events such as intracellular enzymes, ion channels, transcription factors, regulation of gene expression, and membrane permeability.

After the cell gives the appropriate response to the primary message, the signaling mechanism stops working. The loss of function of the systems that terminate this signal transmission causes the signal flow to be continuous and, therefore, many diseases to occur when the signal cannot be stopped (Berg, Tymoczko, & Stryer, 2012). Signal transduction pathways have four basic features: specificity, duplication, desensitization, and integration, which enable cellular communication and information flow to continue in a healthy way (Kurnaz, 2013). When a signal molecule binds to its receptor, a number of intracellular responses occur for the vital activities of the cell such as proliferation, metabolism, movement, differentiation and cellular behavior. The mechanism of action of intracellular signaling molecules is affected by the localization of signal receptors. The main pathways of intracellular signal transduction involve target enzymes that are stimulated to transmit or enhance a signal. The increased signal may stimulate the nucleus to respond to the stimulus.

Basic intracellular signaling pathways; cAMP and cGMP pathways include the phospholipase C-Ca+2 pathway, NF-kB transcription pathway, Ca+2-calmodulin, MAP kinase pathway, and JAK-STAT pathway (Kierszenbaum, 2007). These cellular signaling pathways are very important for the cell to continue its life in a healthy way. Genetic or epigenetic changes in these pathways may cause clinically important diseases.

2. SIGNALING MOLECULES

Intercellular information transfer and communication are provided by various signaling molecules in multicellular organisms. These signal molecules are produced by the cell that wants to create a warning. The desired effect is achieved by binding to proteins called receptors located on the membrane, nuclear membrane or cytoplasm of the target cell. Signal molecules can also carry signals to places far from the region where they are secreted and to neighboring cells. Some signals generated may cause changes in the activity of one or more enzymes already present in the target cell. This ensures that the cell response is rapid. The majority of the stimulation molecules that cause such rapid changes are water-soluble. They bind to special receptors located on the cell membrane.

Stimulation molecules that are not water-soluble stimulate gene expression. Mostly, these types of signaling molecules are fat-soluble. They cause a slower but longer-lasting response in the target cell than water-soluble stimulation molecules. Such long-term interactions have a very important place in cell growth and differentiation (Güneş, 2003). There may be more than one receptor in a cell. Different cell types may also have different receptors for the same signaling molecule, each leading to a different response. In such a case, different cells respond to the same signal molecule in different ways (Kurnaz, 2013; Güneş, 2003).

For example, acetylcholine receptors are found in striated muscle, cardiac muscle, and on the surfaces of pancreatic ecinar cells. Acetylcholine released from the neighboring neuron initiates contraction in striated muscle cells, relaxation in cardiac muscle cells, and excitosis of secretory granules containing digestive enzymes in pancreatic ecinar cells. In some cells, different receptor-hormone complexes may cause the same cellular response. For example, binding of glucagon or epinephrine to receptors in liver cells stimulates the breakdown of glycogen and the release of glucose into the blood (Güneş, 2003).

In the receptor-ligand complex, the ligand binds to the receptor and changes the properties of the receptor, providing the necessary stimulus to the cell. The ligand has no enzymatic properties, is not metabolized into any harmful or beneficial products, and does not take part in any cellular activity. Once the necessary stimulus has been generated, target cells usually modify the ligand or cause its degradation. In this way, the response to the warning is terminated or changed (Güneş, 2003).

3. SECONDARY MESSENGERS

Secondary messengers are molecules that play an important role in intracellular signal transmission. They trigger biochemical reactions within the cell by carrying signals from outside of the cell into the cell. Briefly, primary messengers (hormones or neurotransmitters) bind to receptors on the surface of the target cell from outside the cell, causing secondary messengers to make changes within the cell. This process is an important step in the cellular response because a single primary messenger molecule can trigger the production of multiple secondary messenger molecules.

Examples of secondary messengers include cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), inositol triphosphate (IP3), diacylglycerol (DAG) and calcium ions (Ca2+). Each of these messengers regulates various functions of the cell by affecting different pathways and targets in the cell. Secondary messengers are very important for understanding the responses of cells to their environment. Therefore, the regulation and functions of secondary messengers are very important for understanding the mechanisms underlying many diseases. Through studies on the functions and mechanisms of secondary messengers; By targeting the development of new therapeutic strategies and the production of smart drugs directed at target proteins with specific secondary messengers, it has become possible to take important steps towards the treatment of diseases.

cAMP is often involved in triggering protein kinase A (PKA) activation. Thus, they enable phosphorylation of proteins and therefore alteration of the cell's metabolic activity, gene expression and cell division. Diacyl Glycerol, Inositol Triphosphate (IP3), cAMP (cyclic adenosine monophosphate), cGMP (guanosine monophosphate), calcium ions (Ca2+) are known as secondary messengers that play fundamental roles in intracellular signal transmission.

A hormone that functions through the secondary message mechanism binds to its receptor on the plasma membrane, and the receptor-hormone complex activates the catalysis of GDP to GTP on the G protein Gq to which it is attached, and also activates the G protein. Activated Gq travels in the plasma and stimulates Phospholipase C (PLC). Activated PLC breaks down phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol.

Inositol triphosphate also diffuses into the ER and thus binds to its specific receptor (IP3- gated Ca2+). It causes calcium ions trapped here to attack the cytosol. Diacylglycerol and calcium ions activate protein kinase (Güneş, 2003; Sümer-Turanlıgil & Uyanıkgil, 2010). This process increases the intracellular Ca2+ concentration and triggers various cellular responses. On the other hand, DAG (diacylglycerol) is involved in protein kinase C (PKC) activation, which regulates various functions of the cell.

cAMP and cGMP are called cyclic nucleotides and are produced from ATP and GTP by the enzymes adenylyl cyclase and guanylyl cyclase, respectively. These molecules play important roles in intracellular signal transduction by activating kinases such as protein kinase A (PKA) and protein kinase G (PKG). cAMP is especially effective in regulating cellular responses of hormones and neurotransmitters, while cGMP is generally effective in processes such as smooth muscle relaxation and neurotransmission. Calcium ions (Ca2+), when released inside the cell or taken in from outside of the cell, have a wide range of effects by regulating enzyme activities, gene expression and various functions of the cell. Through these secondary messengers, cells can respond to external signals in a rapid and coordinated manner, which plays an important role in maintaining the overall homeostasis of the organism.

Any mutation or damage in the genes involved in the activation mechanism of Protein Kinase causes the protein kinase to be constantly active and the signal transmission to be uninterrupted. Although the cell only uses phosphatase and GTPase activity to terminate this signal, it is insufficient. This situation causes uncontrolled cell division, that is, tumor formation, with the signal stimulating cell division (Güneş, 2003; Sümer-Turanlıgil & Uyanıkgil, 2010).
When an enzymatic protein associated with the signal receptor becomes active, this active protein catalyzes and activates a large number of molecules of a second enzyme. These active molecules activate many molecules of a third enzyme, creating chain events very quickly. This situation is called replication by enzyme cascades. Additionally, the continued presence of a signal can cause 'desensitization' of the receptor system. When this arousal drops below a certain threshold, it becomes sensitive again (Kurnaz, 2013). When multiple signals occur, these signals are integrated into a single response in line with the needs of the organism. When different signals bind to their specific receptors and cause signal transmission that will have opposite effects to each other, the cellular response presents this as integrated input (Kurnaz, 2013; Güneş, 2003).

4. CELL SIGNALING PROTEINS

Cell signaling proteins play a critical role in the healthy survival of the organism and in intercellular communication by enabling cells to respond to changes in their environment. Cell signaling proteins are of great importance in regulating biological processes. Cells are exposed to many physical and chemical stimuli. The response to these stimuli is provided by perceiving the signal with specific receptors (Küçükkaya & Afrasyap, 2013). The response to endocrine signals plays a very important role in the cellular response. Cell signaling proteins take signal molecules, called ligands, from outside the cell and carry them to targets within the cell. This is called signal transduction. First, the ligand binds to the receptor protein on the cell surface. With the change in the receptor resulting from this binding, certain mechanisms within the cell are activated or inhibited. A highly specialized and regular control is provided in various functions of the cell. When a signal molecule binds to its receptor, localization of the receptors is very important. For example, the receptor for steroid hormones synthesized from cholesterol is found within the cell. They contain estrogen, testosterone, progesterone and corticosteroids, and steroid receptors function similarly to transcription factors.

Another group of signaling molecules act by binding to cell surface receptors. Examples of these include peptide hormones, growth factors, neurotransmitters, neuropeptides, eicosanoids and leukotrienes (Sümer-Turanlıgil & Uyanıkgil, 2010). Intercellular signals are provided by chemical messengers called hormones. Communication within the cell is provided by unique proteins and enzymes that activate each other along the signaling pathway and cause a cellular response (Voet & Voet, 2004).

5. HETEROTRIMERIC G PROTEINS

Heterotrimeric G proteins are a family of proteins activated by receptors on the cell surface, consisting of 3 subunits that are very important in intracellular signal transmission. These subunits; They are called α, β and γ. The Gα subunit of G proteins is the component that binds GDP and GTP nucleotides (Lobingier & von Zastrow, 2019; Voet & Voet, 2004; Milligan & Kostenis, 2006).

While G proteins are inactive, the α subunit βγ complex and GDP are bound together. The G protein does not interact with the extracellular receptor or intracellular effector systems. A signal molecule binds to the appropriate G protein-coupled receptor, stimulating the receptor, thereby causing the release of GDP

from the guanine nucleotide binding site of the α subunit and binding of GTP instead. As a result of GTP binding, the GTP-bound α subunit and βγ dimer separate from each other. Its activity is regulated by stimuli such as the activated G protein and βγ complex ion channels/enzymes (Lobingier & von Zastrow, 2019; Sümer-Turanlıgil & Uyanıkgil, 2010; Küçükkaya & Afrasyap, 2013; Milligan & Kostenis, 2006). The G protein βγ complex enables the activation of a wide range of signaling proteins, including specific ion channels [Na+, K+ and Ca2+], various protein tyrosine kinases and phospholipase C (Voet & Voet, 2004). These interactions with G proteins result in the regulation of various systems such as hormonal activity, sensory perception, cell growth and differentiation, and neuronal activity.

5.1 G Protein Coupled Receptors (GPCR)

These proteins, which show their effects with G Proteins, act on nucleosides, nucleotides, dopamine and other biogenic amines [histamine, serotonin, prostaglandins, thromboxanes, leukotrienes, Ca+2, catecholamines (epinephrine, norepinephrine), 20-carbon fatty acids, arachidonic acid derivatives and similar excesses. They play a role in many critical physiological events. GPCRs, which have important sensory functions, constitute smell and taste receptors in mammals. They are found in the formation of light-sensing proteins called rhodopsin in the eye retina. They are also used as important target structures for pharmaceutical substances (Voet & Voet, 2004).

Gα, which is in the GTP-bound active form, attaches to the adenylyl cyclase molecule in the plasma plane with its palmitol group. Adenylyl Cyclase becomes active and stimulates cAMP synthesis from ATP. The increase in cAMP in the cytosol causes activation of cAMP- dependent protein kinases. Activated protein kinases cause the cellular response to be shaped by stimulating other protein kinases that have very important roles in signal transmission (Karagül, Altıntaş, Fidancı, & Sel, 2000).

5.2 Protein Kinases

Protein kinases play important roles in cellular signaling processes. They activate or deactivate proteins by adding phosphate groups to proteins through phosphorylation in cells. They control various biological processes such as growth, cell division, movement and metabolism. Additionally, diseases such as cancer, diabetes, and inflammation can occur due to damaged protein kinases. When Protein Kinase A (PKA) is inactive, it forms a tetramer (D2K2) complex with two identical catalytic (K) and two regulatory (D) subunits. It does not have catalytic properties. The autorepressor domain of D subunits utilizes the substrate- binding cleft of K subunits.

Protein Kinase D (PKD) is a serine/threonine kinase belonging to the Protein Kinase C (PKC) family, which is involved in processes such as cellular growth, migration, and differentiation. Its activation occurs mostly by diacylglycerol (DAG) and phosphatidylinositol-4,5- bisphosphate (PIP2). The K subunit determines the properties and functions of different isoforms of Protein Kinase D. There are three main isoforms: PKD1, PKD2 and PKD3. Each of the isoforms is involved in various cellular processes and tissues. The PKD1 isoform is especially involved in cellular growth and differentiation, the PKD2 isoform is mostly involved in cell migration and metastasis, and PKD3 is involved in energy metabolism and cell survival mechanisms. Activation or inactivation of Protein Kinase D (PKD) is controlled by various mechanisms such as phosphorylation, protein-protein interactions and intracellular localization (Storz, 2012).

When cyclic adenosine monophosphate (cAMP) binds to the D subunit, it causes changes that activate Protein Kinase A (PKA) by removing the autorepressive sites in the D subunit from the catalytic site of K.

Although Protein Kinase A is involved in signal transduction by phosphorylation in many cell types, its catalytic subunit enters the nucleus and phosphorylates the cAMP response element binding protein (STEB), which changes gene expression regulated by Cyclic adenosine monophosphate (cAMP) (Kurnaz, 2013; Küçükkaya & Afrasyap, 2013).

5.3 Adapter Proteins

They are proteins that are responsible for connecting two or more proteins together in signal transmission or in intracellular signals or protein complexes. They take part in activating specific signaling pathways in the cell by regulating many protein-protein interactions.

Adapter proteins essentially help other proteins transmit signals quickly and accurately within the cell. They take part in many cellular processes,

including cell growth and differentiation, apoptosis and the regulation of immune responses.

A Kinase Anchoring Proteins (AKAP), an adapter protein, plays an important role in cellular signal transduction. AKAPs keep various enzymes in certain cellular regions such as the cell membrane, cytosol or cell nucleus, ensuring that the enzymes are activated at the right time and in the right place. Thus, cellular processes are regulated and cell functions function properly.

A Kinase Anchoring Proteins play a role in keeping Protein Kinase A (PKA) in specific cellular regions, where PKA phosphorylates its substrates. One part binds to the D subunit of PKA, the other part binds to other structures such as ion channels, microtubules, actin filaments, mitochondria or the nucleus. In this way, Kinase A Anchoring Proteins keep Protein Kinase A in the desired regions.

Since each different cell contains different A Kinase Anchoring Proteins, cAMP stimulates mitochondrial cells in one cell and phosphorylates actin filaments in another cell. This allows adapter proteins to control many different signals with a single secondary messenger (Kurnaz, 2013).

Phosphorylation mechanism; It plays an important role in vital activities such as cellular metabolism, gene expression and muscle contraction. Dysfunction or abnormal expression of these proteins can cause uncontrolled cellular growth and proliferation in some types of cancer, heart and neurodegenerative diseases, and metabolic disorders.

5.4 Calmodulin

They are messenger proteins that enable calcium to bind within the cell. They function as a complementary subunit of Ca2+/calmodulin-dependent protein kinases (KaM kinase). It is an acidic protein with four Ca2+ binding sites. When the Ca2+ level increases in the cell, Ca2+ binds to calmodulin and causes a conformational change in the protein. They take part in regulating the activity of various proteins (KaM kinase, phosphorylase b). Phosphorylase b, which becomes active in the muscles, activates glycogen breakdown by triggering their contractions with calcium ions. In this way, the fuel required for ATP synthesis is provided (Tandoğan & Ulusu, 2005).

It undergoes a structural change by binding calcium ions with four specific binding sites. Thus, it interacts with other proteins. Calmodulin plays a role in regulating calcium-mediated signaling pathways. When the calcium level inside the cell increases, it binds calcium ions and activates them. Activated calmodulin regulates other cellular functions by binding to various target proteins such as protein kinases and phosphatases. Through this regulatory mechanism, calmodulin enables cells to play a vital role in maintaining intracellular balance in response to environmental stimuli. A defect in calmodulin can cause many diseases and pathological conditions such as heart disease, cancer, and neurological disorders.

6. RECEPTOR TYROSINE KINASE PATHWAY

Receptor tyrosine kinases (RTKs) are one of the main signal transduction pathways that regulate the vital functions of cells such as growth, division and differentiation. They are located on the cell surface and are protein receptors responsible for transmitting signals from outside the cell into the cell. These receptors; It becomes active when a ligand binds to a receptor on the cell surface. Once activated, the tyrosine residues of RTKs are autophosphorylated, initiating signal transduction.

Receptor Tyrosine Kinases, unlike G Protein Coupled Receptors (GPCR), enable the transmission of extracellular signals. RTKs have intrinsic protein kinase (Tyr) activity. It consists of the ligand binding site on the outer surface of the cell membrane, the enzyme active site on the cytoplasmic surface, and an intramembrane compartment that connects these two. Receptor tyrosine kinases phosphorylate cytoplasmic region-specific target proteins from endogenous protein kinase residues (Kurnaz, 2013).

In summary, RTKs are activated by ligand binding, and this activation triggers the autophosphorylation of tyrosine residues. Phosphorylated tyrosine residues function as the binding point of various signaling proteins. This causes a series of biochemical reactions to begin within the cell.

Insulin hormone regulates blood sugar levels and plays important roles in energy metabolism. In order for this hormone to be effective, it must bind to the insulin receptor, which belongs to the RTK family, on the cell surface. When this binding occurs, it carries out autophosphorylation

with tyrosine kinase activity. These phosphorylated tyrosine residues activate many signaling pathways that increase glucose uptake in the cell and promote glycogen synthesis (Lipsick, 2019). The interaction between Receptor Tyrosine Kinases and the insulin hormone is very important, especially for metabolic disorders such as diabetes. Defects in the insulin receptor may cause insulin resistance by reducing the sensitivity of cells to glucose.

6.1 Free Radicals

Free radicals are atoms or molecules that possess one or more unpaired electrons, resulting in a high degree of reactivity. This characteristic leads free radicals to engage in rapid and typically harmful interactions with other molecules. Among the most common free radicals are superoxide [O_2•−], hydrogen peroxide [H_2O_2], and hydroxyl radical [•OH]. These radicals can occur as a natural consequence of cellular metabolism; however, external factors and environmental elements can also significantly contribute to the formation of free radicals (Bast, Haenen, & Goelmen, 1991; Halliwell & Gutteridge, 1985; Nawar, 1996). Free radicals are reactive and short-lived entities. They can be produced as a result of various chemical reactions necessary for maintaining normal metabolism or energy production within cells. The formation of free radicals is generally explained by three fundamental mechanisms:

1. **Homolytic Cleavage**: The homolytic cleavage of a covalently bonded normal molecule occurs when one of the shared electrons remains with one atom. This can be represented as $X : Y \rightarrow X\bullet + Y\bullet$.
2. **Electron Loss**: The formation of a free radical occurs when a normal molecule loses an electron. This process can be described as $A - e^- \rightarrow A^+ + e^-$.
3. **Electron Addition**: The addition of a single electron to a normal molecule results in the formation of a free radical. This can be expressed as $A + e^- \rightarrow A\bullet$ (Kılınç & Kılınç, 2002; Widmaier, Raff, & Strang, 2014; Cadenas & Sies, 1985).

Free oxygen radicals arise from both endogenous and exogenous reactions. Among the endogenous sources, their formation is a natural consequence of oxygen utilization in all organisms that carry out aerobic metabolism. This process encompasses biochemical events such as mitochondrial electron transport, various synthesis and degradation reactions, as well as oxidative phagocytosis (e.g., during the immune response). In this context, free oxygen radicals play significant roles in biological systems (Saltman, 1989; McCord & Wong, 1978; Grisham & Granger, 1989).

Exogenous sources are external factors that increase the formation of free oxygen radicals. These sources include toxins such as chemicals, tobacco, and alcohol, as well as air pollution, solar radiation, and ionizing radiation such as X-rays. These factors can induce oxidative stress at the cellular level, leading to various biological effects (Grisham & Granger, 1989; Nazlıkul, 2013).

Superoxide radicals, hydroxyl, peroxyl, alkoxyl, nitrogen oxide, and nitrogen trioxide are commonly found free radicals in organisms. These radicals have a very short lifespan and exhibit high reactivity, tending to interact rapidly with other molecules. This can lead to significant effects in cellular processes and trigger damage associated with oxidative stress.

The effects of free radicals are dose-dependent. At low doses, these radicals can have stimulatory effects in detoxification reactions, immune functions, and intracellular signaling processes. However, at high doses, they can cause harmful effects on lipids, proteins, and DNA, disrupting cellular functions and leading to cell death (necrosis or apoptosis). Free oxygen radicals (SOR) constitute a significant source of oxidative stress and contribute to the aging process. These radicals interact with lipids, proteins, and DNA in tissues, rendering them incapable of performing their normal functions (Nazlıkul, 2013; Videla & Fernandez, 1988).

Free radicals are generated through various mechanisms as a result of interactions within the cell and with environmental factors. These processes include the reduction of oxygen in the mitochondrial electron transport chain during cellular respiration, the breaking of molecular bonds by ionizing radiation to produce reactive particles, and the effects of environmental pollutants, heavy metals, and certain toxic substances. These factors increase the production of free radicals, thereby elevating the risk of oxidative stress and cellular damage.

Low levels of free radicals have positive effects on cellular functions. In particular, they play a significant role in cellular signal transduction, necessitating the contribution of reactive

oxygen species (ROS) at specific levels for the activation of processes such as cell growth and differentiation. Additionally, immune system cells produce ROS as part of their defense mechanisms against pathogens; these radicals play a critical role in the destruction of infected cells and the initiation of inflammatory responses.

However, excessive amounts of free radicals can lead to various negative effects within cells and are closely related to mechanisms of cell death. Primarily, these radicals act as triggers for oxidative stress, causing damage to cellular components (DNA, proteins, lipids). Oxidative stress can lead to the impairment of cellular functions, resulting in the activation of apoptotic (programmed cell death) or necrotic (uncontrolled cell death) processes. Furthermore, free radicals can cause oxidative damage to DNA molecules, laying the groundwork for mutations and the development of cancer. Unsaturated fatty acids in cell membranes are oxidized by free radicals, leading to lipid peroxidation; this condition can compromise the integrity of the cell membrane, resulting in cell death. Finally, free radicals oxidize cellular proteins, leading to structural and functional changes that adversely affect enzyme activities and cellular functions (Hancock, Desikan, & Neill, 2001; Cheeseman & Slater, 1993).

7. REACTIVE OXYGEN SPECIES (ROS)

Oxygen present in the atmosphere is referred to as molecular oxygen (O_2) or dioxygen. Only a limited portion of normal oxygen is reduced during metabolic processes that occur in cellular components, primarily in mitochondria, resulting in the formation of reactive oxygen species.

Important reactive oxygen species include superoxide radical (O_2•−), hydroxyl radical (•OH), and hydrogen peroxide (H_2O_2). The first two of these radicals are classified as free radicals, while hydrogen peroxide is considered a prooxidant substance (Navarro & Boveris, 2004). An increase in the intracellular levels of reactive oxygen species (ROS) or a decrease in antioxidants due to pathological processes leads to a disruption of oxidative balance. This disruption causes harmful effects on cellular structures, resulting in the emergence of oxidative stress. Oxidative stress can contribute to the development of various diseases by causing damage to DNA, lipids, and proteins. An increase in ROS levels can lead to damage in cell membranes, structural and functional alterations of intracellular proteins, and structural damage to DNA, resulting in cellular injuries. Among the effects of oxidative stress, the oxidation of polyunsaturated fatty acids (PUFA) present in biological membranes by reactive oxygen species and the subsequent triggering of lipid peroxidation play a significant role (Sies, 1991; Gupta et al., 2014).

The main reactive oxygen species (ROS) include superoxide (O_2•−), hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), and singlet oxygen ($^1O_2$). Superoxide is an oxygen molecule that has undergone electron loss and typically occurs during mitochondrial processes. Hydrogen peroxide is a relatively stable structure that is not a free radical; however, it can convert into more reactive species upon interaction with metal ions. The hydroxyl radical is an extremely reactive free radical that can rapidly react with biomolecules, causing significant cellular damage. Singlet oxygen is a form of oxygen that differs in its electronic structure and is primarily produced during photochemical reactions in biological systems (Halliwell, 1991).

While free radicals are defined as molecules with high reactivity due to an unpaired electron, reactive oxygen species (ROS) encompass a broader classification that includes both these free radicals (such as superoxide and hydroxyl radical) and non-free radical components (such as hydrogen peroxide).

List 1. Free Radicals and Reactive Oxygen Species (ROS)

Free Radicals	Reactive Oxygen Species (ROS)
Possess an unpaired electron and have high reactivity.	Reactive molecules containing oxygen atoms (some are less reactive).
Examples: Superoxide (O_2•−), hydroxyl radical (•OH)	Examples: Superoxide, hydroxyl radical, hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$)
Arise from metabolic processes, environmental toxins, and UV radiation.	Can originate from endogenous (aerobic metabolism) and exogenous (air pollution, toxins) sources.
Can lead to cellular damage, oxidative stress, and cell death.	Reactive oxygen species play a significant role in oxidative stress, cellular damage, and immune response, exhibiting both beneficial and detrimental effects.
A subset of reactive oxygen species.	Includes not only free radicals but also other reactive oxygen components.

8. PROGRAMMED AND UNPROGRAMMED CELL DEATH MECHANISMS

Cell death occurs spontaneously, genetically or by other factors that are a part of the life of living things. It basically exists in two main forms. These are programmed and unprogrammed cell death (Gao et al., 2022). Cell death mechanisms are critical for the development, survival and health of living organisms. Through this process, it activates a series of complex mechanisms necessary for the controlled elimination of damaged, dysfunctional and unnecessary cells.

This process, which is basically divided into two main categories, is called programmed cell death (apoptosis) and unprogrammed cell death (necrosis). These mechanisms ensure the controlled destruction of cells. Cell death mechanisms are mechanisms formed to ensure the internal protection of the cell. Both types of cell death play an important role in the health of the cells and therefore the organism. It plays a critical role in maintaining the general homeostasis of the organism, responses to infections, and prevention of diseases such as cancer.

8.1 Programmed Cell Death

Cell death involves a series of events with some morphological and molecular markers, such as losing the integrity of the plasma membrane, dividing into pieces, including the nucleus, and being phagocytosed by surrounding cells (Pardee, 1974). Controlled cell death is a mechanism that has been preserved throughout evolution in multicellular organisms. It is involved in multiple essential functions, including morphogenesis, tissue homeostasis, and defense against pathogens. Two types of cell death were described for the first time in 1972 by Kerr, Wyllie and Currie.

They defined apoptosis as a genetically controllable form of cell death, and necrosis as uncontrolled and random cell death. Three new types of cell death were identified with the studies conducted by Clarke in 1990 (Gözuacik & Kimchi, 2007). Clarke made this classification according to the morphology of cell deaths during embryonic development and as a result of his studies with toxins, and pointed out that there are at least 8 types of programmed cell death. Autophagy is one of the basic death mechanisms that is thought to be an additional or alternative to apoptosis, based on studies conducted at the morphological and molecular level. Unlike apoptosis, autophagy occurs by the recycling mechanism of intracellular molecules in the absence of nutrients or in case of cellular stress (Galluzzi et al., 2012; Anding & Baehrecke, 2015).

8.2 Apoptosis

Apoptosis is the controlled death of cells. Apoptosis stops the growth and division of a cell, destroying the cell's internal components without damaging them and without damaging neighboring cells around them. Thus, harmful contents within the cell are prevented from leaking out and the risk of inflammation is minimized. The presence of these mechanisms in both prokaryotes and eukaryotes also proves that programmed cell death is evolutionarily conserved. It is an essential mechanism for the mitotic cycle and tissue regeneration during the embryological process and after birth. They play a critical role in apoptosis through caspase-dependent basic regulatory mechanisms during the development of embryonic cells (Kaiser et al., 2014). Apoptotic cell death can be triggered by cellular stress situations, damage to the cell's DNA, or the destruction of unnecessary cells formed during cellular development.

Apoptotic cell death involves a genetically programmed process and allows cells to die in a controlled manner. Thus, the normal development of the organism and the destruction of damaged and diseased cells are ensured. Apoptosis is the most well-known form of programmed cell death. However, there are also non-apoptotic programmed cell death mechanisms. Regulated cell death or programmed cell death exists in various forms: such as apoptosis, necroptosis and ferroptosis. These pathways are activated in response to internal and external signals of the cell and ensure the orderly destruction of the cell. Damaged, infected or toxic cells are destroyed by a mechanism called "Regulated Cell Death" (RCD). These mechanisms, seen especially in some fungal and bacterial species, appear to exist in both prokaryotes and eukaryotes (Cornillon et al., 1994; Olie et al., 1998; Cornillon et al., 1998; Madeo et al., 1997; Eisenberg et al., 2007; Buttner et al., 2006).

8.3 Apoptosis Mechanism

The mechanism of apoptosis first manifests itself with cytoplasmic shrinkage in the cell.

Pyknosis, also called chromosome clustering, and Karyorrex, also known as nuclear fragmentation, are among these types of cell deaths. In this process, the core material also condenses, shrinks and finally disintegrates. This phenomenon is called chromosome clustering and Pyknosis. During karyorrhex, after pyknosis, the nucleus begins to disintegrate. Thus, the nucleus is divided into multiple parts. As a result of this breakdown, the cell becomes completely dysfunctional and dies. Understanding and elucidating karyorrhex and pyknosis is of vital importance in the treatment of various diseases and controlling cell death.

These two types of cell death processes are important for understanding, elucidating and developing treatment methods for various pathologies, especially cancer, neurodegenerative diseases and heart diseases.

Chromosome clustering refers to the collection of chromosomes in a certain order during various stages of the cell cycle, especially during mitosis and meiosis. Thus, the genetic material of the cell is transferred equally and regularly to two daughter cells, ensuring that the new cells formed are healthy. Again, during pyknosis, chromatin in the cell nucleus condenses and shortens, so the nucleus appears dark and dense. This process is a step on the path to the programmed death of the cell (apoptosis) and often causes the cell to lose its functionality. Pyknosis is a phenomenon that also occurs in the cell nucleus during cell death (apoptosis). It is an important phenomenon seen especially in cell death processes. Pyknosis occurs as part of the programmed death process of the cell. It usually begins as a result of the cell losing its function or being damaged. The occurrence of pyknosis is important in elucidating cell death and can help in the diagnosis of many diseases.

Both processes are critical to the development, growth and health of living things. While chromosome clustering ensures that genetic information is transferred correctly; With pyknosis, damaged or unwanted cells are cleared from the body. Both of these processes are a natural part of the life cycle of cells and are vital for cells to perform their normal functions.

Controlled cell death; It is divided into two groups: apoptotic (intrinsic and extrinsic apoptosis) and non-apoptotic (autophagy, entosis, mitoptosis, ferroptosis, pyroptosis and necroptosis) (Galluzzi et al., 2018; Yan, Elbadawi, & Efferth, 2020). Apoptosis plays a very important role in the immune system against infections by destroying DNA damaged cells. It is a very effective mechanism against cancer as it destroys damaged cells that may cause metastasis, but when this mechanism does not occur properly, it can cause cancer and other genetic and immunological diseases. During apoptosis, the membrane forms an outward bubble, the cytoplasm shrinks, and organelles and DNA are broken into pieces. Apoptosis can occur with an intrinsic mechanism, that is, a mitochondria-centered mechanism, or an extrinsic mechanism, that is, a mechanism that affects the cell from the outside (Elmore, 2007).

Intrinsic apoptosis is called mitochondrial apoptosis. Extrinsic apoptosis is called the death receptor pathway (D'Arcy, 2019). The most important causes of intrinsic apoptosis include the proliferation of ROS (reactive oxygen species) within the cell, stress and damage to DNA replication, undesirable defects in mitosis, and changes in the ER and microtubules (Brumatti, Salmanidis, & Ekert, 2010; Czabotar, Lessene, Strasser, & Adams, 2014).

Triggering of intrinsic apoptosis occurs by the release of mitochondrial proteins and HtrA serine peptidase 2 and the activation of the initiator caspase 9 (Chipuk, Bouchier-Hayes, & Green, 2006). Meanwhile, the permeability of the mitochondrial outer membrane is lost. The permeability of the outer membrane of mitochondria is controlled by the Bcl2 group of proteins (BAX, BAK, which induces apoptosis, and Bclxl, Bcl2l, which prevents apoptosis) (Singh, Letai, & Sarosiek, 2019). The breakdown of intracellular structures occurs with an important role of Caspase 3, 6 and 7 (McIlwain, Berger, & Mak, 2015). Bax and Bak proteins are called apoptosis-inducing proteins because they form pores in the outer membrane of mammalian mitochondria (Moldoveanu, Follis, Kriwacki, & Green, 2014). Therefore, the number of Bax proteins affects the size of the pores formed in the mitochondrial membrane (Gillies et al., 2015). Bclxl and Bad proteins belonging to the Bcl2 family play a role in binding to Bax and Bak proteins in the mitochondrial membrane, changing their structure, and thus preventing the formation of pores required for intrinsic apoptosis (Llambi et al., 2011). During reticular stress, Bak and Bax proteins activate Ca2+ ion transfer between the ER and mitochondria by activating ER membrane permeability. Thus,

mitochondria-derived intrinsic apoptosis becomes active (Bassoy et al., 2017). The membrane permeability of mitochondria indirectly allows proteins that regulate electron transfer in mitochondrial respiration, such as cytochrome c, to pass into the cytosol. When cytochrome c passes into the cytosol, it binds to apoptotic peptidase activating factor (APAF1) and procaspase 9 and forms the apoptosome, which will activate Caspase 9 (Li et al., 2000). Activated caspase 9; It enables intrinsic apoptosis to occur by activating caspase 3 and caspase 7 (Julien & Wells, 2017). FAS and TNF membrane receptors, called death receptors, and caspase 8 and caspase 10, which are initiator caspases, play critical roles in extrinsic apoptosis (Schulze-Osthoff et al., 1998). When the receptors on the plasma membrane detect a problem outside the cell, they lead the cell to programmed death through extrinsic apoptosis induced by caspase 8 and activated by caspase 3. When cell damage is detected, precursor caspases activate inactive procaspases. When the death ligands produced by macrophages bind to death receptors on target cell membranes, caspase 8 is activated, causing extrinsic apoptosis to begin. Activation of executioner caspases causes activation of endonucleases, DNA fragmentation, deformation of nuclear proteins and cell membrane, cross-linking of proteins, expression of ligands for phagocytic cells and formation of apoptotic bodies (D'Arcy, 2019).

9. NON-APOPTOTIC PROGRAMMED CELL DEATH MECHANISMS

Controlled cell death involves a series of interconnected signal transduction mechanisms. In this death system, if there is a condition of caspase dependence while membrane integrity is preserved, it can be called apoptotic cell death. If the cell membrane is disrupted and there is no dependence on caspases, these situations are called non-apoptotic controlled cell death. With non-apoptotic cell death, cells lose their functions and die, but it consists of a series of mechanisms that do not have typical morphological features such as apoptosis. These mechanisms are known as autophagy, entosis, mitoptosis, ferroptosis, pyroptosis, necroptosis, cuproptosis, anoikis and parthenatosis.

9.1 Autophagy

Autophagy; It consists of the words "auto = self" and "phagy = eating". Autophagy, also known as self-eating, is a death mechanism that has been preserved throughout the evolutionary process. It is a mechanism that occurs when intracellular macromolecules and organelles are engulfed by a double-membrane vesicle called Autophagosome and broken down by lysosomes. Autophagy death mechanism is a mechanism that occurs in response to cellular stress and to control the healthy internal balance of the cell. In the first studies on autophagy, it was seen that autophagy helps the response to cellular stress and ensures cellular internal balance by recycling intracellular molecules in cases of nutrient deprivation (Ohsumi, 2001). In recent studies, it has been shown that autophagy plays important roles in the regulation of metabolism, cell differentiation, aging, morphogenesis, cell death and degradation of intracellular pathogens (Mizushima, Levine, Cuervo, & Klionsky, 2008; Shintani & Klionsky, 2004). In addition to all these studies, it has been understood that abnormalities in autophagy cause the development of infectious diseases, cancer and neurodegenerative diseases (Yang & Klionsky, 2010).

Autophagy; It occurs through three different main mechanisms: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA). Macroautophagy, which occurs at the basal level in most cells, is responsible for the breakdown of protein fragments and damaged organelles. Microautophagy involves the direct ingestion of the cytoplasm by the lysosome and the degradation of cytoplasmic contents. Chaperone-mediated autophagy also ensures the selective transport of KFERQ motif proteins (Lysine, Phenylalanine, Glutamate, Arginine, Glutamine) to the lysosome membrane. With chaperone-mediated autophagy, cytosolic proteins that are misfolded or formed as a result of errors are reduced (Xie & Klionsky, 2007).

In addition to these three main autophagy mechanisms; Allophagy, defined as the process in which paternal mitochondria are eliminated during the formation of the embryo (Gyllenstein et al., 1991), and Axanophagy (neuronal autophagy), which ensures the selective disintegration of axons under pathological conditions (Rubinsztein et al., 2005).

Chromatophagy occurs when the leakage of DNA, histones and other chromatin-related proteins from the nucleus is captured by autophagosomes, with excessive induction of autophagy (Changou et al., 2014). Ciliaphagy, autophagy, which is involved in the regulation of ciliary proteins (Orhon et al., 2015). Crinophagy is the storage of more hormones than necessary

and their breakdown by lysosomes; (Sandberg & Borg, 2006). Exophagy is the direct sending of proteins out of the cell, other than the usual ways of transporting proteins within the cell. Glycophagy is the reduction of excess glycogen by lysosomes; (Abrahamsen & Stenmark, 2010). Lipophagy is the reduction of lipid droplets by autophagy. Lysophagy causes the degradation of proteins and macromolecules because lysosomes contain acidic hydrolases; (Singh & Cuervo, 2012). Mitophagy is the destruction of damaged mitochondria as a result of damage or error in mitochondrial function; (Mercer et al., 2011). Nucleophagy is the destruction of cell nucleus parts as a result of genotoxic stress without killing the cell; (Erenpreisa et al., 2012). Pexophagy refers to the preferential autophagy of non-functional peroxisomes; (Deosaran et al., 2013). Reticulophagy is the degradation of endoplasmic reticulum parts; (Bakowska-Zywicka, Tyczewska, & Twardowski, 2006). Ribophagy is the selective degradation of ribosomes; (Cebollero, Reggiori, & Kraft, 2012). Xenophagy protects the cell against infection by preventing the triggering of the immune response in case of invasion by pathogenic microorganisms; (Dupont, Temime-Smaali, & Lafont, 2010) The mechanism that occurs by using zymogens as special autophagic cargo content is called Zymophagy (Grasso et al., 2011; Vaccaro, 2012).

Stopping the autophagy mechanism by various methods often accelerates the death of stress-responsive cells rather than slowing them down. This causes permanent or non-permanent endogenic defects in autophagy [embryonic deaths and developmental defects, cancer, cardiovascular and neurodegenerative disorders] (Menzies, Fleming, & Rubinsztein, 2015; Galluzzi et al., 2017). Basal autophagy is rapidly activated in situations that cause cellular stress, such as removing damaged organelles, long-lived proteins and protein aggregates, and nutrient and growth factor deficiency (Anding & Baehrecke, 2015). Additionally, autophagy can be triggered by cellular stress such as pathogen infection, hypoxia, nutrient deprivation, or reactive oxygen species (ROS). Cancer, early dementia, some hereditary diseases, Alzheimer's and infections may occur as a result of impaired control of autophagic mechanisms (Galluzzi et al., 2012).

9.2 Entose

It was first described as cellular cannibalism in the lymphoblasts of Huntington's patients. Entosis, which can be defined as a cell within a cell, is triggered by integrin.

The cell is engulfed in the phagosome by the neighboring cell, called the entotic cell or host cell (Mormone et al., 2006). By interacting with the connection interfaces, the entotic cell directs the formation of entosis with actin and myosin accumulated in the cell cortex opposite the connection interface. This situation causes unbalanced contractile force (Ishikawa, Ushida, Mori, & Shibanuma, 2015). In entosis, actin polymerization and myosin II, Rho and Rho kinase ROCK activity must occur in the engulfed cell (Yuan & Kroemer, 2010). Entosis can be inhibited by Bcl-2 and z-VAD-fmk. The engulfed cell appears visually normal but then disappears. This situation most likely occurs through lysosomal degradation. In rare cases, engulfed cells may divide within the engulfing cell and be released again (Overholtzer et al., 2007). In order for the entotic death mechanism to occur, both cells must be of the same type and establish the same type of connection (Doukoumetzidis & Hengartner, 2008).

9.3 Mitoptosis

Mitoptosis, which is a combination of the words "mito" related to mitochondria and "ptosis" meaning disintegration, involves the breakdown and recycling of these organelles, which are the energy centers in the cell. Mitochondria serve as the main source of chemical energy that produces ATP (adenosine triphosphate), which is necessary for the functioning of cells. Mitochondria are very sensitive to damages such as reactive oxygen species (ROS), mutations in mitochondrial DNA and stress caused by physical or chemical agents. These damages prevent the healthy functioning of the mitochondria and cause various diseases and cell death. Mitoptosis is known as mitochondrial suicide and is different from mitophagy, which is the autophagic degradation of mitochondria. It involves a programmed process of fission and fusion of mitochondria that occurs with the simultaneous degradation of the ATP source. It may be associated with mitoptosis, apoptosis and autophagy (Jangamreddy & Los, 2012). Degraded mitochondria become autophagosomes or mitoptotic bodies that are extruded from the cell. This shows that mitoptosis is solely a mitochondrial death pathway. Extensive mitochondrial fragmentation indirectly causes cell death. It has been suggested that mitoptosis is a mechanism that

Table 1. Apoptosis

Extrinsic Path				Intrinsic Path					Caspases		DNA Fragmentation	
Death Receptors	DISC Formation	Caspase Activation	Executive caspases	Mitochondrial Pathway	Cytochrome c Release	Apoptosome Complex	Caspase-9 Activation	Executive Caspases	Initiator Caspases	Executive Caspases	Apoptotic signals cause DNA fragmentation in the cell nucleus	Apoptotic bodies (apoptotic blebs) are formed and these bodies are destroyed by phagocytes.
Activation of cell surface deathreceptors such as Fas (CD95) and TNF receptors	Formation of death-inducing signaling complex (DISC)	Activates initiator caspases such as DISC and caspase-8	Initiator caspases activate executioner caspases, leading to cell apoptosis.	Cellular stress - increased permeability of Bcl-2 family proteins and mitochondrial membrane as a result of DNA damage	Release of cytochrome c from mitochondria	Cytochrome c combines with APAF-1 to form the apoptosome complex	Apoptosome activates caspase-9	Activates executive caspases such as caspase -9 and caspase-3	Caspases such as caspase -8, caspase -9 initiate apoptosis signaling	Caspases such as caspase- 3, caspase- 6, caspase-7 break down cellular components and cause the cell to die by apoptosis.		

works to rid the cell of organelles that are malfunctioning and, for example, overproducing reactive oxygen species (ROS) (Skulachev, 2006). The steps of mitoptosis are briefly as follows: It is a cellular response in which mitochondrial damage is identified, then isolated and finally fragmented.

9.4 Ferroptosis

Ferroptosis is briefly defined as "iron-dependent regulated cell death (RCD)". Ferroptosis is a newly defined form of cell death that differs in its mechanism from other regulated death pathways such as apoptosis, autophagy and necrosis (Dixon et al., 2012). Ferroptosis is caused by excessive lipid peroxidation due to toxic levels of iron that are not inhibited by inhibitors of other regulated death mechanisms. Cells in which the ferroptosis death mechanism is observed do not have features of apoptosis such as chromosomal condensation and apoptotic bodies (Masaldan, Bush, Devos, Rolland, & Moreau, 2019). Metabolic pathways such as iron metabolism, lipid metabolism, and amino acid metabolism affect the occurrence and development of ferroptosis. Ferroptotic death, loss of lipid peroxide repair ability by glutathione peroxidase-4 (GPX4), lipid reactive oxygen species (L-ROS) formed by oxidation of polyunsaturated fatty acid (PUFA) in the cell membrane, and the presence of redox active iron (Fe2+) are the characteristic features of ferroptosis (Dixon et al., 2012).

The increase in redox iron within the cell is the main cause of ferroptotic death. Cells that die from ferroptosis often show morphological changes similar to necrosis, such as burst damage to the plasma membrane, swollen cytoplasm, swollen cytoplasmic organelles, and moderate chromatin condensation. Ferroptosis propagates among cancer cells in a wave-like manner, leading to cell death through osmotic mechanisms. Biochemically, ferroptosis is always accompanied by the accumulation of iron and lipid peroxides. The most important feature and marker of ferroptosis is the increase in ROS and lipid peroxidation levels after iron accumulation [87]. Transferrin receptor (TFRC) is important for taking iron from outside the cell into the cell, making TFRC a biomarker of ferroptosis.

The mechanism of ferroptosis begins with inhibition of the system with Xc-erastin or direct inhibition of GPX4 activity with RSL3 and ends with cell death. Lipid ROS are responsible for the ferroptotic death process. Peroxidation of the polyunsaturated fatty acid PUFA found in the cell membrane plays an important role in the ferroptosis pathway. On the other hand, excessive iron accumulation within the cell also plays a fundamental role in lipid ROS accumulation and, consequently, in the ferroptosis mechanism (Lu et al., 2018).

Although ferroptosis shows a normal morphology with an intact and non-ballooning cell membrane, a normal-sized nucleus with no chromatin condensation, it is mainly defined by shrunken mitochondria with reduced cristae and collapsed membranes (Latunde-Dada, 2017). Ferroptosis induction can be detected by administering ferroptosis inhibitors to the medium and measuring the amount of lipid peroxide.

9.5 Pyroptosis

Pyroptosis is an inflammatory state of programmed cell death in immune cells that fight against intracellular pathogens, discovered after apoptosis and necrosis. As in apoptosis, pyroptotic cells undergo nuclear condensation and DNA fragmentation (Albert et al., 2004). Inflammasome receptors of infected macrophages recognize flagellin components of pathogens. The protein complex that will then activate caspase 1 forms inflammasomes (Bergsbaken, Fink, & Cookson, 2009). Activated caspase-1 mediates membrane pore formation by cleavage of gasdermin D, a protein encoded by the GSDMD gene located on chromosome 8 in humans, allowing the cell to rupture. During this time, DNA condenses and separates into fragments (Liu et al., 2016). Pyroptosis plays an important role in the pathogenesis of some diseases, especially malignant tumors.

Multiple signaling pathways and inflammatory mediators released during pyroptosis are closely related to tumor formation (Nagarajan et al., 2019). Additionally, contrary to this situation, pyroptosis may prevent the formation and development of tumors. It has been observed that pyroptosis plays a stimulatory/inhibitory role in some tumor types (Xia et al., 2019). Pyroptosis, a form of proinflammatory cell death, is mostly stimulated by intracellular pathogen infection and serves as a part of the host defense system. It is stimulated in two ways: classical and non-classical inflammatory pathways. Classical pyroptosis is mediated by caspase-1 triggered by damage-associated molecular patterns (ATP, IL-1α) and pathogen-associated molecular patterns. Non-classical

pyroptosis is dependent on human caspase 4/5 and mouse caspase 11 and is stimulated by intracellular lipopolysaccharides. (Lamkanfi & Dixit, 2014). The morphological features of the cell are similar in caspase-1-dependent and caspase-1-independent pyroptosis. Both are characterized by disruption of cell membrane integrity, chromatin condensation and DNA fragmentation. After the cell membrane swells and ruptures, balloon-shaped vesicles form around the nucleus (Fink & Cookson, 2005).

9.6 Necroptosis

Necroptosis, defined as programmed necrosis, is a programmed cell death that occurs when an abnormal situation inside or outside the cell is detected by specific death receptors (Vanlangenakker, Vanden Berghe, & Vandenabeele, 2012). Necroptosis begins with tumor necrosis factor receptor (TNFR) and Fas ligand activation in a Caspase-independent manner. It is characterized by receptor-interacting protein kinase activation through multiple signaling pathways. Although it is a programmed death mechanism, it is morphologically similar to necrosis with membrane rupture and organelle loss. Necroptosis is a caspase-independent process and RIPK1 and RIPK3 play key roles. Receptor-interacting protein kinases are activated from various cell surface receptors to macromolecules, forming the key components of the necrosome, RIPK1 (Receptor-interacting protein kinase 1) and RIPK3 (He et al., 2009). It has been observed that in leukemia and colorectal cancer, when the apoptosis of tumor cells is impaired, it works as a defense mechanism that acts as a tumor suppressor (Feng et al., 2015; Höckendorf et al., 2016). It has been characterized as a component of some inflammatory diseases such as Crohn's disease, pancreatitis, and myocardial (Günther et al., 2011; Linkermann & Yesil, 2014).

9.7 Cuproptosis

Cuproptosis, briefly defined as the copper-related cellular death pathway, is a controlled cell death that is different from other cell death pathways that occur by increasing the Cu concentration within the cell through copper ionophores. It is a new death pathway triggered by copper ions (Cu+2) that targets lipoylated proteins in the tricarboxylic acid (TCA) cycle of Cu2, causing mitochondrial protein aggregation and degradation of iron-sulfur (Fe-S) clusters, thus triggering cell death (Sherr, 2000). It triggers cell death by degradation of Fe-S clusters in the mitochondria by causing lipoylated DLAT proteins to come together in the TCA cycle (Tsvetkov et al., 2022). Mitochondrial respiration, which can be inhibited in different conditions such as cuproptosis and oxygen deficiency, is highly related to mitochondrial antioxidants, mitochondrial function inhibitors and the lipoic acid (LA) pathway.

By increasing the intracellular Cu+2 concentration using the elesclomol (ES) ionophore, Cu+2 ions bind to the lipoylated proteins of the TCA cycle in the mitochondria, causing their aggregation and degradation of mitochondrial Fe-S protein clusters, triggering cell death. It has been reported that cellular death induced using ES-Cu could not be rescued by other known cell death inhibitors, including necroptosis, apoptosis, and ferroptosis, but only Cu+2 chelator treatment had a strong rescue effect on cuproptosis. It has been observed that Cu levels are high in cancer cells, which require higher levels of Cu+2 than normal cells (Shanbhag et al., 2021). Cu+2-binding proteins and different signaling pathways activated by Cu+2 are involved in tumor formation, proliferation and angiogenesis (Itoh et al., 2008; He et al., 2019; Qiu, Ding, Zhang, & Kang, 2012). Cu+2 is of critical importance on tumor development, proliferation and angiogenesis by directly or indirectly affecting different signaling pathways in cancer cells (Baldari et al., 2019; Turski et al., 2012; McAuslan & Reilly, 1980).

9.8 Anoikis

Anoikis, which means 'homeless' in Greek, is called apoptosis caused by inadequate or inappropriate integrin-mediated cell-matrix interactions (Frisch & Francis, 1994; Meredith, Fazeli, & Schwartz, 1993). It is programmed cell death that is specifically initiated when cells lose adequate attachment to the surrounding extracellular matrix required for survival. Anoikis maintains the cell number required for high turnover epithelial tissues. The clearest evidence for this is that the breakdown of anoikis contributes to neoplasia. This is very important for maintaining cellular number and order in multicellular organisms, and prevents the migration of cells into inadequate histological environments where they can contribute to pathological diseases such as cancer. In addition to preventing uncontrolled cell migration and tumor formation, it is critical in

embryogenesis processes that depend on correct cell adhesion and migration for the healthy growth of the organism. When cells cannot adequately bind to the extracellular matrix, a signal is sent to them to die by the anoikis death mechanism, preventing irregular growth and deformations.

Misunderstanding of the anoikis mechanism can lead to problems in various diseases such as cancer. For example, when tumor cells acquire the ability to frequently avoid anoikis, this may cause them to form metastases (Streuli & Gilmore, 1999). It is involved in a wide variety of tissue homeostatic, developmental and oncogenic processes. The main challenge in the anoikis mechanism is to understand how integrin-mediated cell adhesion signals control the apoptotic mechanism. In particular, it is essential to elucidate the initiation of the caspase cascade (Shanmugathasan & Jothy, 2000).

9.9 Parthenatosis

Parthenatosis is the product of a complex process that occurs at the cellular level and develops in response to DNA damage. It is a form of regulated cell death that occurs when Poly (ADP- ribose) polymerase I (PARP1), a component of the response mechanism against DNA damage, is more active than normal. Poly (ADP-ribose) polymerase I (PARP1) enzyme plays a key role in repairing damaged DNA. Under normal conditions, the activity of PARP1 helps the cell repair DNA damage and maintains cellular integrity. However, excessively increased PARP1 activity can rapidly deplete cellular energy resources, causing regulated cell death called parthenatosis. Studies on parthenatosis have shown that PARP1 inhibitors can slow or stop the process of the disease by preventing cell death by preventing excessive PARP1 activity. Elucidating and controlling the parthenatosis mechanism is very important for treatment approaches of diseases. The main factors that activate the parthenatosis pathway are nitrosative stress (NO), hypoxia and hyperglycemia. Accumulation of reactive nitrogen species causes excessive activation of PARP1 in neurons. This situation causes death in neurons (Zhang et al., 1994). One of the other factors that activate parthenatosis is the combination of mitochondria-associated apoptosis activating factor 1 (AIF) with poly (ADP-ribose) polymer.

As a result of this association, AIF is released in the cytosol and moves into the nucleus, causing DNA fragmentation and chromosome clustering (Mulay et al., 2019).

Parthenatotic DNA fragmentation is an important mechanism in cell death, often associated with apoptosis. However, parthenatotic DNA fragmentation occurs independently of known RCD (regulated cell death) accelerators such as apoptotic caspases and endonuclease G (ENDOG) (Xu et al., 2010). Apoptotic caspases are proteases that are very important in cell death. They ensure the breakdown of important molecules in the programmed death process of the cell and the controlled death of the cell. Endonuclease G, a mitochondria-derived nuclease, plays a critical role in the fragmentation of DNA. Parthenatotic DNA fragmentation can occur independently of these two factors. PARP enzymes are activated in single and double DNA strand breaks and take part in DNA repair. The fact that the PARP enzyme takes part in DNA repair indicates that PAR chains must be added to itself or to other proteins involved in the repair process (Hassa & Hottiger, 2008). Abnormal activation of the PARP-1 enzyme plays a role in pathological conditions such as Parkinson's disease, stroke, diabetes, and trauma (Hassa & Hottiger, 2008; Martire, Mosca, & d'Erme, 2015; Berger et al., 2018). Such excessive PAR accumulation causes different types of cell death called Parthanatos (Lee et al., 2013; Weaver & Yang, 2013). Addition of excessive PAR chains to other proteins (PARylation) causes the transport of apoptosis-inducing factor (AIF) from the mitochondria to the nucleus, which causes faster DNA recombination and cell death (Cipriani et al., 2005; Hong, Dawson, & Dawson, 2004; Yu et al., 2002; Plesnila et al., 2004). Studies have shown that excessive activation of PARP plays an important role in the degeneration process, and that it protects photoreceptors in hereditary retinal degeneration by both pharmacological inhibition and inactivation of PARP1(Sahaboglu et al., 2010; Sahaboglu et al., 2016; Sahaboglu et al., 2017).

10. PROGRAM-FREE CELL DEATH MECHANISM

10.1 Necrosis

Unprogrammed cell death is an uncontrolled event that occurs suddenly, mostly due to environmental factors. Necrosis is the uncontrolled death of cells and tissues, usually due to various external factors such as trauma, injury, infection, toxins or lack of oxygen. This can cause damage, inflammation and disease in environmental tissues. For this reason, it is essential for the organism to respond quickly and

repair such sudden cellular damage. Toxic substances such as arsenic, cyanide, insecticides and heavy metals also cause necrosis. A controlled death process does not occur as in the apoptotic death mechanism. Since it is a pathological process that develops suddenly, when cells undergo necrosis, they cause inflammation and damage to surrounding tissues. The cell cannot maintain its biological functions, cell membrane integrity is disrupted, and cell contents leak out.

When necrosis occurs, cells become unable to produce energy, the cell membrane loses its integrity, and intracellular components leak into the surrounding tissues. Additionally, if necrotic tissue is perceived as a foreign body, it can activate the immune system. For the treatment of necrosis, it is important to know the cause. For example, treatments to improve blood flow in necrosis caused by obstruction of blood flow can be used, and if it occurs due to infection, antibiotics and other medications can be used. During the necrosis process, mitochondrial ROS production increases, non-apoptotic proteases become active, ATP production decreases and Ca++ channels open (Golstein & Kroemer, 2007; Nicotera, Bernassola, & Melino, 2004).

Since tissue loses its ability to regenerate and function when it dies, there are different types of necrosis depending on these characteristics: Coagulation necrosis, the most common type of necrosis, is seen in all types of ischemic events. In coagulation necrosis, cytoplasm proteins are coagulated and the nucleus disappears. It is the cause of hypoxic death in all tissues except the brain. Liquefaction necrosis, which occurs by enzymatic digestion of tissue, is characterized by liquefaction of the tissue and is most commonly seen in brain tissue and abscesses. In caseous necrosis, which occurs with tuberculosis and causes a cheese-like appearance, eosinophilic heterogeneous cell masses accumulate in the center of the granulomas. The necrosis that occurs when fatty acids formed by lipase enzymes combine with calcium in damaged pancreatic cells and macrophages is called Fat necrosis. Necrosis, which occurs in cases of large and deep injuries and is caused by bacteria settled in the tissue, is called Gangrenous necrosis. Necrosis, which is mostly seen in autoimmune diseases and occurs with the accumulation of fibrin-like protein material in the connective tissue and vascular walls, is called Fibrinoid necrosis.

Physical and chemical warnings from the environment, It causes disruption of the ion balance within the cell. PARP (Poly ADP-ribose polymerase), the nuclear enzyme responsible for DNA repair, splits NAD+ into two, causing NAD loss and ATP deficiency, leading to ion pump deficiency in the cell. This causes an increase in fluid in the cell, swelling of the organelles, disruption of the plasma membrane, and explosion of the cell due to osmotic pressure. Unlike apoptosis and autophagy, in this degradation the cellular content is not completely digested. It causes cellular debris to remain among other surrounding cells, causing inflammation (Leist & Jaattela, 2001; Wu et al., 2012; McCall, 2010). Inflammation occurs when cell contents flow into the intercellular space. The characteristic feature of this process is the migration of macrophages and neutrophils into the necrotic tissue and the phagocytosis of these cells into the necrotic tissue. For this reason, inflammation is an important sign of necrosis (Golstein & Kroemer, 2007; Nicotera, Bernassola, & Melino, 2004).

The general mechanism of necrosis can be briefly expressed as follows; Damage to the cell, disruption of the cell membrane, collapse of energy metabolism, increase in intracellular calcium, release of lysosomal enzymes, disintegration of the cell nucleus, destruction of cell tissue and inflammation (Palmer, Greengrass, & Cavalla, 2000; Galluzzi et al., 2006; Baines, 2010; Zong & Thompson, 2006).

10.2 Basic Molecular Mechanism of Necrosis

After necrosis occurs, certain processes occur in the cell and surrounding tissues with the activation of various proteins. These mechanisms are very important for regulating the inflammatory response, clearing dead cells and cellular debris, correct guidance of immune cells and tissue repair. There are major proteins, molecules and cellular mechanisms that play a role in damage limitation and repair after necrosis.

Molecules and Proteins and Mechanisms Formed After Necrosis:

10.3 DAMPs (Damage-Associated Molecular Patterns)

These molecules, released in cases of cellular damage or stress, stimulate the immune system and take part in the formation of the immune response. It attracts immune cells to the area to eliminate tissue damage as the inflammatory

Table 2. The general mechanism of necrosis

Cell Damage				Deterioration of Cell Membrane	Collapse of Energy Metabolism	Increase in Intracellular Calcium	Release of Lysosomal Enzymes	Disintegration of Nucleus	Destruction of Cell Tissue and Inflammati on
Physically	Chemical Damage	Biological	Ischemia	-Structural deteriorations as a result of lipid peroxidation and protein denaturation in the cell membrane -Deterioration Of the cell's internal-external ion balance due to increased membrane Permeability.	Loss in ATP production. - Failure of Na+/K+ ATPase pump to work - intracellular calcium and sodium accumulation, extracellular potassium accumulation	As a result of calcium increase Damage to the cytoskeleton and membrane structure due to the activation of cell-destructive enzymes Such as proteases, phospholipases and endonucleases	disintegration of cellular structures by the release of hydrolytic enzymes	disintegration of DNA and other nuclear components Nucleus pyknosis, karyorrhexis and karyolysis formation.	Destruction of surrounding tissues by materials leaking from the dying cell.
Trauma, Temperature (Burning or Freezing), Radiation	Poisons, Toxins	Infections, Bacteria, Viruses	Decreased or complete cessation of blood flow Lack of oxygen and nutrients						

response occurs. DAMPs are very important molecules in responding to endogenous cell damage. Some examples of DAMPs are HMGB1 (High Mobility Group Box 1), ATP (Adenosine Triphosphate), Heat Shock Proteins (HSP), Uric Acid, S100 proteins.

HMGB1, released during cell necrosis, is a nuclear protein and triggers a strong inflammatory response. When ATP is released from necrotic cells, it attracts inflammatory cells. Heat shock proteins such as HSP70 and HSP90 are secreted from necrotic cells and are recognized by the immune system, triggering inflammation. Uric acid crystals released during cell necrosis stimulate the inflammatory response. S100 Proteins, calcium-binding proteins, are released during cell necrosis and promote inflammation.

Nrf2 (Nuclear Factor Erythroid 2-Related Factor 2): Reduces cellular damage by increasing the expression of antioxidant defense genes.

10.4 Anti-inflammatory Cytokines and Molecules

Cytokines are substances with a protein or glycoprotein structure that are secreted by immune cells (macrophages, T cells) and other cells, provide intercellular communication, and regulate the immune system and inflammatory responses. They play a critical role in processes such as defense against infections, wound healing and tissue repair. Major cytokines include interleukins (IL), interferons (IFN), tumor necrosis factors (TNF) and chemokines. Anti-inflammatory cytokines are secreted as a response to increased pro- inflammatory cytokines. They play an important role in controlling the inflammatory response and cause suppression of the immune system (Christelle et al.,2000).

Anti-inflammatory cytokines are very important molecules in limiting the damage caused by suppressing inflammation and regulating the immune response. Some important anti-inflammatory cytokines are:

IL-10 (Interleukin-10)

IL-10 is one of the most powerful anti-inflammatory cytokines and its main functions are to suppress the activity of macrophages and dendritic cells, reduce the release of inflammatory cytokines and regulate the responses of T cells.

IL-4 (Interleukin-4)

Interleukin-4, produced by Th2 cells, enables macrophages to transform into the M2 phenotype and reduces the inflammatory response by suppressing Th1 cell responses.

IL-13 (Interleukin-13)

IL-13 secreted from Th2 cells plays a role in the response to allergic reactions by suppressing the inflammatory response.

TGF-β (Transforming Growth Factor-beta)

They are involved in regulating cell growth, cell differentiation, apoptosis and immune response. It promotes tissue regeneration by suppressing the activity of inflammatory cells.

IL-1β (Interleukin-1 beta)

It is a pro-inflammatory cytokine released by necrotic cells.

TNF-α (Tumor Necrosis Factor-alpha)

It is an important pro-inflammatory cytokine released after necrosis and initiates the inflammatory response (Arda et al., 1994; Stein & D'Agnolo, 1994).

10.5 Reactive Oxygen Species (ROS) and Antioxidant Defense Systems

Since ROS released from cells during necrosis can damage the surrounding tissues by increasing inflammation, it is very important to control oxidative stress to limit the damage.

SOD (Superoxide Dismutase)

It is responsible for reducing oxidative stress by detoxifying reactive oxygen species. Catalase and Glutathione Peroxidase.
It limits cellular damage by detoxifying hydrogen peroxide and other peroxides.

10.6 Phagocytosis and Clearance

Necrotic cell debris and extracellular matrix fragments are phagocytosed by macrophages. With the activation of macrophages, inflammatory cytokines are released, perpetuating inflammation. Macrophages activated by DAMPs accelerate the clearance process by secreting inflammatory cytokines and chemokines.

Neutrophils take part in breaking down cell debris into smaller pieces by secreting free radicals and proteases. They undergo apoptosis in a short time and are phagocytosed by macrophages.

Complement proteins activated by DAMPs take part in opsonization and cell lysis, enabling necrotic cells and microbes to be recognized and destroyed by phagocytes.

MMPs (matrix metalloproteinases) produced by fibroblasts break down excess or damaged collagen and other matrix proteins. While cell debris resulting from necrosis is cleared, neighboring cells may undergo apoptosis (Majno & Joris, 1995; Vanden Berghe et al., 2007).

10.7 Healing and Tissue Repair

Anti-inflammatory cytokines take part in tissue repair by ending the inflammatory response. Stem cells and progenitor cells contribute to the regeneration of damaged tissue. With fibroblast activation, tissue repair and wound healing are achieved by secreting extracellular matrix components such as collagen. Growth factors such as Vascular Endothelial Growth Factor (VEGF) promote Angiogenesis, creating new blood vessels and healing damaged tissue. Growth factors such as Hepatocyte Growth Factor (HGF) and Epidermal Growth Factor (EGF) are involved in cell proliferation and tissue regeneration. MMPs, together with Matrix metalloproteinase inhibitors (TIMPs), take part in the formation of a new and organized tissue structure (Vanden Berghe et al., 2014; Conrad et al., 2016).

In summary; After necrosis, many proteins and mechanisms come into play in the necrotic cell and surrounding cells. While DAMPs and inflammatory cytokines trigger the immune response, phagocytic cells are responsible for clearing dead cells. While the complement system provides opsonization and response to inflammation, extracellular matrix proteins and growth factors contribute to tissue repair.

Tissue homeostasis is restored by eliminating inflammation through anti-inflammatory mechanisms. The correct functioning of all these processes and mechanisms is of critical importance for tissue regeneration and healing after necrosis.

11. CONCLUSION

Programmed and unprogrammed cell death mechanisms are very important for the proper functioning of biological systems and the continuation of life. While programmed cell death (apoptosis) plays very important roles in the regulation and development of tissues, homeostasis, immune response and prevention of diseases, unprogrammed cell death (necrosis) is important in the rapid repair of tissue by clearing damaged cells and the clearance of pathogens.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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