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Understanding Programmed Cell Death

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Abstract

Recent studies emphasize the critical role of various types of programmed cell death (PCD), such as apoptosis, autophagy, pyroptosis, and necroptosis, as well as their respective signaling pathways. These processes are essential for regulating cellular balance, responding to stress, and triggering immune defenses. Apoptosis, commonly known as "cellular suicide," is a tightly controlled mechanism that allows cells to die without inducing inflammation. This process is key for tissue development, immune regulation, and cancer prevention. Alterations in apoptotic pathways may result in uncontrolled cell proliferation or excessive cell death, potentially leading to conditions such as cancer, neurodegenerative diseases, and autoimmune disorders. Autophagy, another PCD mechanism, involves the degradation and recycling of cellular components. This self-preservation process is vital for cell maintenance, especially during nutrient shortages or stress. Although autophagy typically supports survival, excessive activation can result in cell death, making it an important focus in cancer research due to its dual roles in tumor suppression and promotion, depending on the context. Inflammatory cell death is a type of pyroptosis that often triggered by infections. Unlike apoptosis, pyroptosis leads to the release of pro-inflammatory cytokines, which help alert the immune system. While this process is crucial for eliminating pathogens, its dysregulation can drive inflammatory diseases. Necroptosis is a regulated form of necrosis that triggers inflammatory cell death through a caspase-independent mechanism. It shares similarities with both apoptosis and necrosis and has been implicated in inflammatory responses, immune defense, and diseases such as ischemia-reperfusion injury and neurodegenerative conditions. A deeper understanding of these PCD mechanisms could pave the way for new therapeutic interventions that target specific targets in the treatment of various diseases. Disease related. As research continues, understanding the nuances of this process will lead to the development of new targets.

Keywords: Programmed cell death (PCD), apoptosis, autophagy, pyroptosis necroptosis

INTRODUCTION

Cell theory, first proposed in the 19th century, establishes that all living organisms are composed of cells, with each cell arising from a pre-existing one. Both healthy and cancerous cells experience damage or death, often influenced by their interaction with neighboring cells. Programmed cell death, particularly apoptosis, is a crucial biological mechanism that has evolved to remove damaged or unnecessary cells. While cell death has long been observed in cancer, it was initially associated with necrosis in hypoxic regions of tumors. However, cells can also undergo apoptosis in response to various stimuli, including therapies.

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Apoptosis is a critical biological and physiological mechanism across the animal kingdom, from worms to mammals. It serves as a type of cellular "suicide" that ensures the removal of damaged or potentially harmful cells. For example, cells with irreparable DNA damage can initiate apoptosis through the activation of tumor suppressor proteins like p53. This protein, in turn,

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triggers the production of pro-apoptotic factors such as Puma and Noxa, leading to the controlled demolition of the damaged cell. Mutations that prevent cells from undergoing apoptosis can lead to the unchecked growth of abnormal cells, contributing to the development of cancer.

Cell suicide: process of cell suicide thoroughly understood, basically known as the "intrinsic," "mitochondria," where BCL-2 regulated or BCL-2 X protein (BAX) Bcl2 homologous antagonist killer (BAK)-dependent mechanism of apoptosis. We focused on activation of BAK, and BAK allows effectors of apoptosis to permeabilize the outer mitochondrial membrane.

Here is the release of cytochrome c in the cytoplasm, where it binds to the APAF1 and regulates the formation of apoptosis, first activating caspase-9.

Pathways of cell death:

1. Apoptosis.
2. Autophagy.
3. Pyroptosis.
4. Necroptosis.

APOPTOSIS

Apoptosis is the most studied so-called programmed cell death. Kerr, Wyllie, and Currie were the first to introduce the concept of apoptosis and outline its morphological characteristics, which include cell shrinkage, membrane bleeding, nuclear fragmentation, and chromatin condensation [1, 2]. The apoptotic pathway is divided into two primary mechanisms: the intrinsic and extrinsic pathways (Figure 1).

The intrinsic, or mitochondrial, pathway is triggered by imbalances within the cell, such as oxidative stress, DNA damage, or stress in the endoplasmic reticulum. This pathway is also called cell suicide through the mitochondrial outer membrane permeability (MOMP). MOMP releases the pro-apoptotic factor, including cytochrome c and the second activator of caspases (SMAC), which are derived from mitochondria. From mitochondrial space into the cytoplasm, where cytochrome c binds to the apoptotic protease activating factor-1 (APAF-1) pro-caspase 9 in the form of apoptosomes. In the apoptosomes, caspase-9 activates itself and dissects pro-caspase-3, even pro-caspase-7. Once activated, cleaved caspase-3 and caspase-7 serve as key "executioners" in the apoptosis process, leading to cell death. SMAC encourages apoptosis by suppressing the activity of inhibitors of apoptosis proteins (IAPs) [3, 4].

Extrinsic apoptosis is usually controlled by several proteins, particularly those from the B-cell lymphoma 2 (BCL-2) family. These proteins are classified into three groups:

1. Pro-apoptotic proteins, such as Bcl-2-associated X protein (BAX) and Bcl-2 antagonist/killer 1 (BAK). Upon receiving an apoptosis signal, pro-apoptotic proteins are activated and oligomerize on the mitochondrial outer membrane, leading to increased membrane permeability, a critical step in the apoptosis process [5].
2. Anti-apoptotic proteins, such as Bcl-2, Bcl-xl, Bcl-w, and Mcl-1, help maintain mitochondrial membrane stability.
3. BH3-only proteins, including BAD, BID, BIM, and BIK, trigger apoptosis by activating pro-apoptotic proteins and neutralizing anti-apoptotic proteins [4, 6].

The extrinsic pathway is also called the death receptor pathway. This is because there is a protein in this pathway that basically receives a signal when any foreign ligand tries to enter the cell; that protein is death, including the signaling complex (DISC). There are some transmembrane proteins that usually bind to the extracellular specific ligands and then transduce an apoptotic signal into cells.

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Death receptors come from the receptor gene superfamily, and this contains cysteine-rich extracellular domains as well as intracellular domains that keep homologous amino acid residues. Intracellular domain has death domain (DD), it also called FAS ligand and play the key role in apoptosis.

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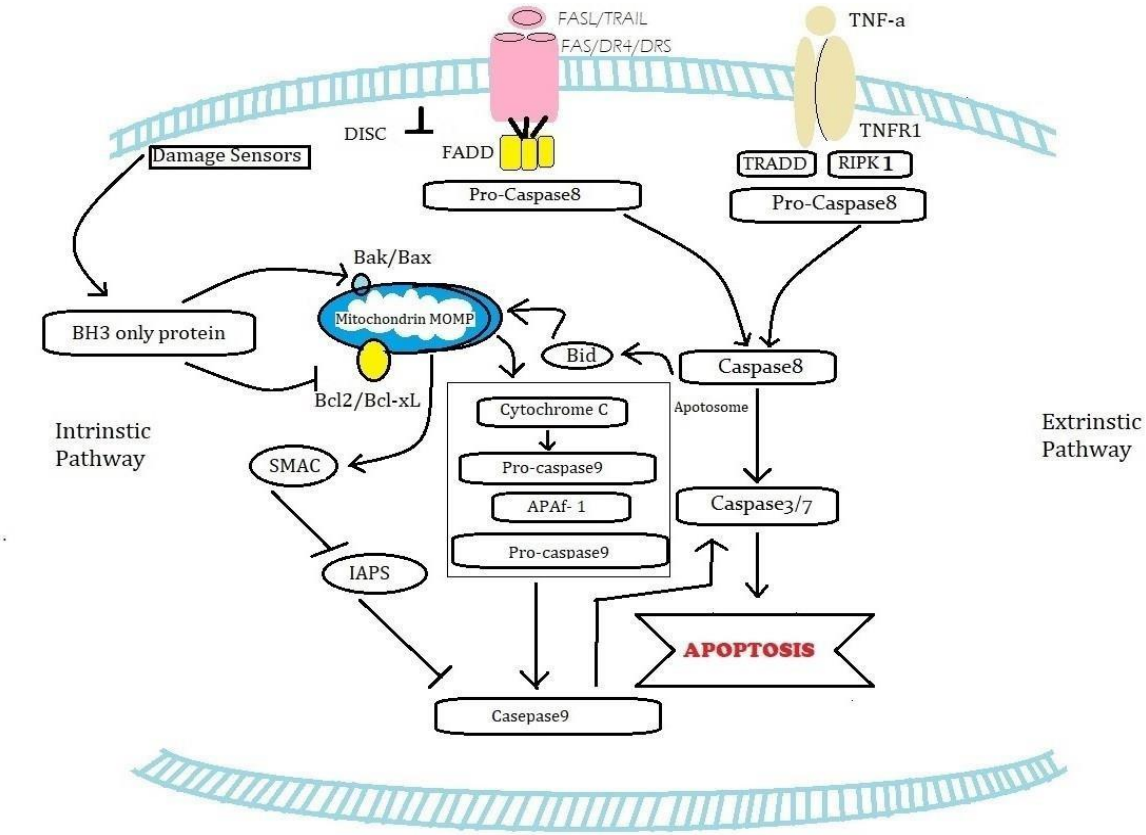

Figure 1. Signaling pathway of apoptosis, mitochondrial membrane permeabilization release the cytochrome c, then activate the pro-caspase9, which attached with APAF-1 after this casepase9 is activated. Mitochondria MOMP is directly activating the SMAC in the cytoplasm, and this activates the IAPs where it is binding with casepase9. Damage sensor signal release through the BH3 proteins; there is DISC-death including signaling complex that receives the FAS ligands signal to cell death. In the extrinsic pathway, TRADD and RIPK1 both release the signal from TNF-a. After the signal, it activates pro-casepase8 further, casepase8 activates and casepase8 activates BID. This BID blocks the BAX because this BAX creates the pore in the mitochondria. Casepase8 lets activate casepase3/7 to induce apoptosis.

This FAS receptor is always activated by the FAS-ligand protein with death domain (FADD) through the (DD). This FAS-ligand death domain recruits the pro-caspase8 by its death effector DISC-death including signaling complex. There are known death receptors in addition to TNFR1, FAS, DR3, DR4, and DR5, renowned for FAS [7].

DISC protein can directly activate casepase8 and casepase3 even, casepase7 to induce the apoptosis, and cut the BID into t BID and trigger MOMP to regulate apoptosis [8, 9].

AUTOPHAGY

"Autophagy" comes from the Greek word its meaning is that eating oneself, (destroying oneself); this was first carried out by the Christian de Duve over 40 years ago. Mitochondria and intracellular

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structure with the lysosome of rat liver perfused with pancreatic hormone, glucagon [1]. Such as damaged organelles as well as misfolded proteins to induce cellular homeostasis [10]. Autophagy is associated with various forms of caspase-independent cell death, often referred to as "autophagic" cell death [11]. It can be classified into three types:

1. Macro-autophagy,
2. Micro-autophagy, and
3. Chaperone-mediated autophagy, with macro-autophagy commonly simply called autophagy [12].

This process is tightly regulated by autophagy-related genes (ATG), with over 40 genes encoding ATG proteins identified in yeast. This system is evolutionarily conserved across species, including mammals (Figure 2) [13].

The autophagy process involves several interconnected steps: induction, assembly, and formation of the autophagosome, followed by its fusion with lysosomes for degradation and recycling of contents [14]. Autophagy can be triggered by nutrient deprivation; when the mTORC1 complex is inhibited or AMPK is activated, the ULK1 complex is stimulated and localized to the endoplasmic reticulum [15]. The ULK1 complex then phosphorylates and activates the Beclin-1-PI3KC3 complex, triggering the initiation of autophagy. This complex supports both autophagosome membrane formation and the increased activity of phosphatidylinositol 3-phosphate (PI3P). Moreover, the interaction of ATG5, ATG12, and ATG16L facilitates the expansion of the autophagosome membrane, with the assistance of ATG3, ATG7, and microtubule-associated protein 1 light chain 3 (LC3).

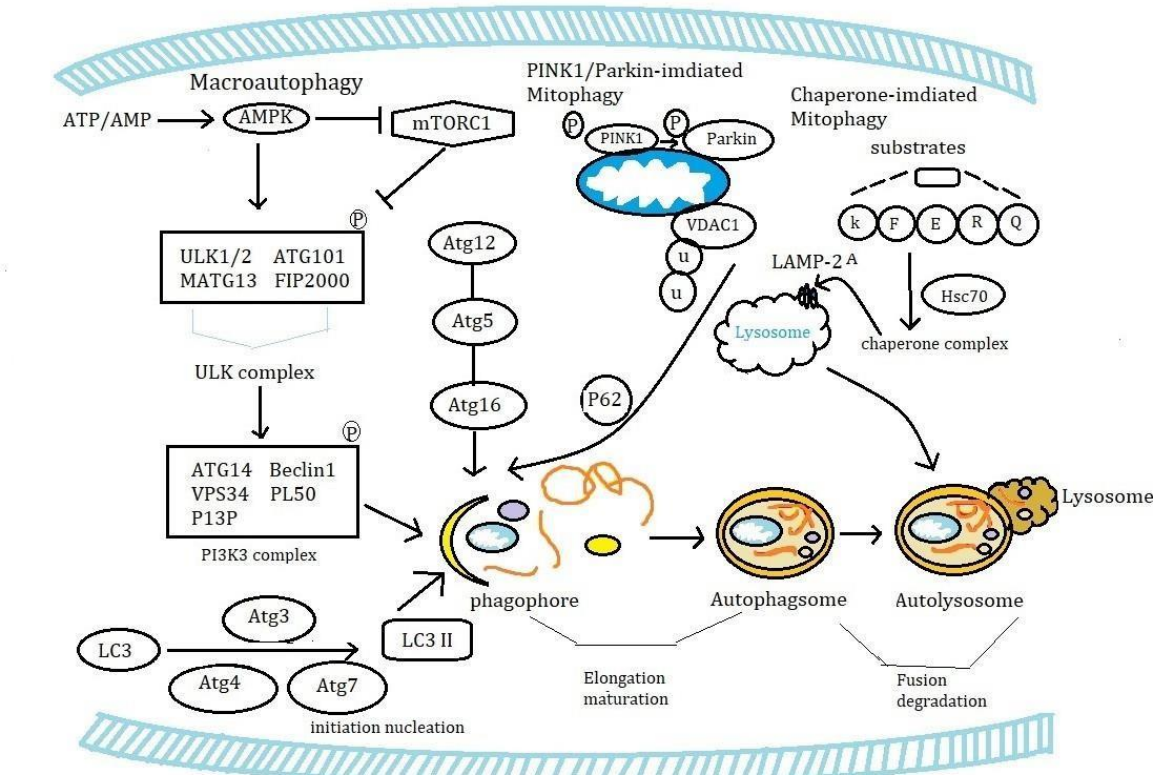

Figure 2. It is a signaling pathway of autophagy.

- *Macroautophagy:* ATP/AMP activating the (AMPK) where the mTORC1 is blocked (Unc -51). The ULK complex is phosphorylated, triggering the nucleation phase of autophagosome formation. This process involves ATG4, ATG7, and ATG3. Additionally, the microtubule-associated protein LC3 is converted into its mature form, LC3-II. Chaperone-imdiated mitophagy and its substrates K, F, E, R, and Q, which are chaperone complexes, this activating the LAMP-

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2A further and activating the fusion degradation through the autophagsome and autolysosome.

- *PINK1/Parkin-imdiated mitophagy:* PINK1 phosphorylating the parkin, then this complex induces the process of phagophore called elongation maturation.

It is modified by the cellular lipid phosphatidylethanolamine (PE) and converted into LC3-II. LC3-II assists in sequestering ubiquitinated materials into the developing autophagosome, which is then broken down by lysosomal enzymes [16, 17]. Mitochondria, known as the powerhouse of the cell, generates energy in the form of ATP through the electron transport chain (ETC). This energy powers all cellular activities. When mitochondria are broken down through autophagy, the process is referred to as mitophagy [18]. Mitochondrial autophagy can be categorized into ubiquitin-mediated and receptor-mediated processes. The PINK1/parkin pathway is central to ubiquitin-mediated mitochondrial autophagy. Under normal conditions, PINK1 (PTEN-induced putative kinase 1) is cleaved by presenilin-associated rhomboid-like protease (PARL). However, when mitochondria are damaged, the depolarization of the inner mitochondrial membrane prevents PINK1 from entering the inner mitochondrial space. After being recognized by ubiquitin-binding proteins like p62, the damaged mitochondria are engulfed by autophagosomes for degradation [19, 20].

PYROPTOSIS

Pyroptosis is described by Cookson and Brenan in 2001 [21]. Pyroptosis is the process in which pores are created in the membrane, and cells keep doing the inflammation till they demolish and release the inflammatory factor into the extracellular space, even making a strong inflammatory response [22]. This pathway is classified into two pathways: classical and non-classical pathways (Figure 3). The classical pathway quite depends on the caspase1. There are three most comprised components:

1. Receptor proteins, like NLRP1, NLRP3, NLRC4, AIM2, and pyrin, of NLRP3, which is researched.
2. There is an adaptor protein, ASC, which contains the CARD. This CARD plays the vital role of recruitment of pro-caspase-1. Additionally, there are recognized receptors such as PRR that can directly recruit pro-caspase-1 [23].
3. This third one is effector protein pro-caspase-1 [24]. After the formation of an inflammasome, pro-caspase is hydrolyzed into proper cleaved caspase-1. This caspase-1 can rupture or cleave GSDMD to GSDMD-C and GSDMD-N. the GSDMD-N transfer to the membrane, and this also creates the non-selective pores with an inner diameter of 10-14 nm, then it begins to cell swelling and rupture. Caspase-1 also removes the pro-IL-IBETA and pro-IL-I8 into the mature IL-18, which is quite released to the extracellular space through the pores [4, 24–25]. Caspase4/5/11 and caspase4/5 can be directly controlled by the LPS in the cytoplasm. After activating caspase-4/5/11 can cleave the GSDMD, besides this pro-IL-Ibeta and pro-IL-I8.

Membrane pores work with GSDMD-Ns to the efflux of intracellular potassium ions. After this, it activates the NLRP3; these are both inflammasomes and classical pathways of pyroptosis. Results show the cleavage and release of pro-IL-Ibeta and pro-IL-I8 [24, 26].

Furthermore, whenever cells are infected through the viral infection, GSDME may also be cleaved to GSDME-N by the caspase-3/8. GSDME-Ns can form pores in the cytoplasmic membrane, which subsequently triggers pyroptosis [27, 28]. Recent studies have shown that granzyme A and granzyme B are also capable of cleaving GSDMB; process results in the formation of pores in the cytoplasmic membrane, indicating the involvement of a granzyme-driven pathway for pyroptosis [29, 30].

NECROPTOSIS

In 2005, Degterev and colleagues identified necroptosis as a form of programmed cell death (PCD) that occurs independently of caspases [31]. While it shares morphological similarities with necrosis, it is a regulated process of cell death.

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There is some comparable to those of apoptosis; during morphological changes such as cell swelling, plasma membrane break with chromosome condensation releases the damage-associated molecular pattern, which is DAMPs, inflammatory cytokines, and chemotaxis factor (Figure 4) [3, 32–33].

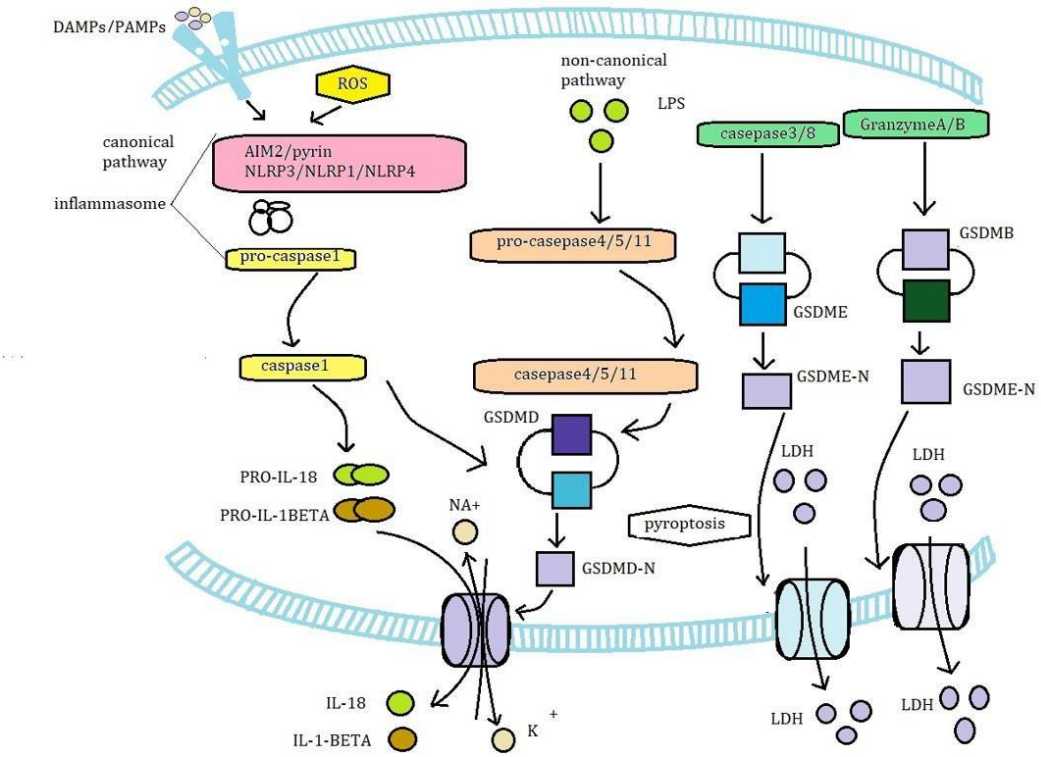

Figure 3. Signaling pathway of pyroptosis is initiated when pathogen- or damage-associated molecular patterns (PAMPs or DAMPs) activate receptors like NLRP3, NLRC, AIM2, or pyrin. These receptors then interact with ASC and pro-caspase-1, facilitating the assembly of inflammasomes. Caspase-1 is activated in this process and cleaves gasdermin D (GSDMD), producing the GSDMD-N fragment. This fragment assembles into non-selective pores on the cell membrane. Additionally, caspase-1 converts the inactive forms of IL-1β and IL-18 into their active states. These mature cytokines are then released into the extracellular space via membrane pores, triggering a robust inflammatory response. Non-canonical pathway of pryoptosis: this LPS directly binds to the caspase-4/5/11. Activated caspase-4/5/11 also cleave GSDMD, but it cannot activate the pro-IL- Ibeta and pro-IL-I8. GSDME-N can form pores in the plasma membrane. Both granzyme A and granzyme B can contribute to the formation of these membrane pores, triggering pyroptosis.

Iron-transferrin binds to the TfR1, which induces the endosome in the presence of DMT1, where the fenton reaction is happening from Fe^{2+} to Fe^{3+}, even though H_2O_2 is removing the OH and activating the ROS. This activates the PL-PUBA-OOH, later it induces lipid peroxidation to enhance ferroptosis. In addition to this, ferroptosis takes place through the many proteins that are crucial to starting ferroptosis such as PUBA, PUFA-coA, and PL-PUFA. These are proteins activated with each other by the (ACSL4) and (LPCAT3). Research shows that SLC7A11 plays a crucial role in glutamine metabolism and influences the dependency of cancer cells on both glucose and glutamine. GSH biosynthesis: It activates the conversion of GSH to GSSG through GPX4, which is linked to the regulation of ROS.

When TNFα binds to its receptor, the intracellular domain of TNFR1 recruits various proteins to form a signaling complex, known as complex I. In this complex, cellular inhibitor of apoptosis proteins

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(cIAPs) regulate the ubiquitination of receptor-interacting serine/threonine kinase 1 (RIPK1) [34]. During CYLD deubiquitinates RIPK1, and this converts the complex I into complex II. In complex II, FADD recruits procaspase-8, when RIPK1 newcomer RIPK3. When RIPK3 is absent even at a low level, caspase-8 activates and induces apoptosis. This caspase-8 inhibited the RIPK3-rich cells, and RIPK1 always recruits the RIPK3 condition for necroptosis; beside this, it can be directly activated by the TIR-domain-containing adapter-inducing interferon-beta (TRIF); in addition to this, there is an adaptor protein of toll-like receptors (TLRs). Once RIPK3 is activated, it phosphorylates MLKL, leading to the release of mitochondrial DNA, uric acid, histones, and ATP into the extracellular space through plasma membrane pores. This release triggers an inflammatory response [33, 35–36].

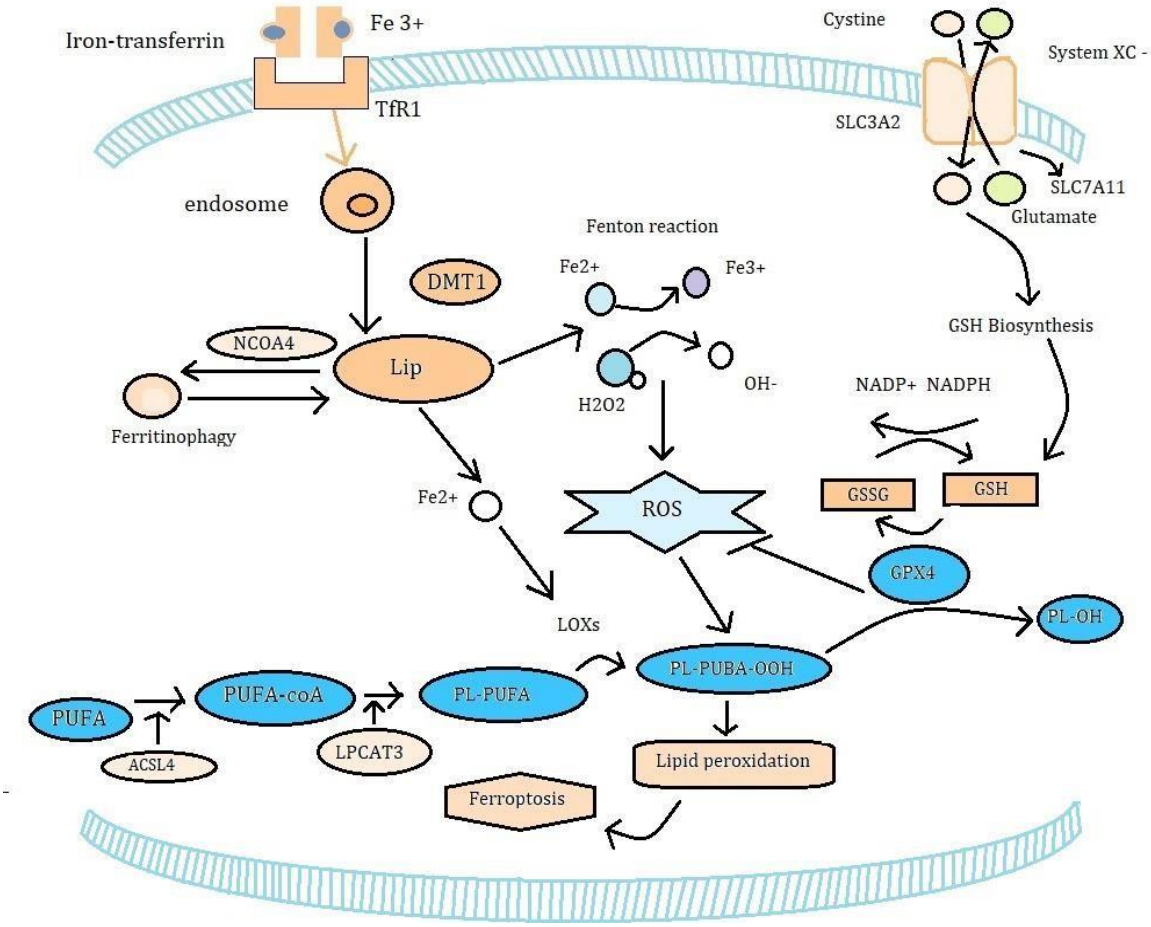

Figure 4. Signaling pathway of necroptosis.

CONCLUSION

PCD-related studies in cell death (1) Several types of PCD, including apoptosis, autophagy, pyroptosis, and necroptosis – these are all pathways demonstrating the cell death issue by which that cell is programmed to die. Each pathway is distinct from the others. Programmed cell death (PCD) is an essential biological process that plays a key role in regulating cellular homeostasis, development, and defense mechanisms. This research provides an overview of several distinct forms of PCD, each characterized by different mechanisms leading to cell death: apoptosis, autophagy, pyroptosis, and necroptosis.

Apoptosis is a well-defined process where cells undergo an orderly, energy- dependent death, often referred to as “cell suicide.” It is vital for removing damaged or unwanted cells without causing inflammation. Autophagy, on the other hand, involves the degradation and recycling of cellular components, allowing cells to survive under stress conditions. Excessive autophagy may result in cell

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death. Pyroptosis is a form of programmed cell death that is highly inflammatory, often initiated by specific infections, and is marked by cell swelling, rupture, and the release of pro-inflammatory molecules. Necroptosis shares features of both apoptosis and necrosis, leading to cell death through a regulated, but often inflammatory, pathway, acting as a backup when apoptosis fails.

Each of these PCD pathways contributes to the elimination of damaged or dangerous cells, but the mechanisms and outcomes differ. While apoptosis and autophagy generally aim to maintain cellular homeostasis with minimal impact on the surrounding environment, pyroptosis and necroptosis can provoke strong immune responses. Understanding these different PCD pathways is essential for developing therapeutic strategies for diseases where cell death is dysregulated, such as cancer, neurodegenerative disorders, and immune-related conditions. By elucidating the distinct features and roles of these pathways, researchers can better target specific forms of PCD for clinical interventions.

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