Demiroglu Science University Florence Nightingale Journal of Transplantation 2022;7(1-2):22-31
doi: 10.5606/dsufnjt.2022.7

Ferroptosis, apoptosis, necroptosis

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ABSTRACT

Cell death processes developed to preserve tissue homeostasis and remove potentially hazardous or expired cells inside an organism, such as cells with damaged deoxyribonucleic acid that might cause illness. Cells have evolved various programmed cell death (PCD) pathways. Depending on the type of death signal in the cell, cell death occurs by activating the relevant death pathway and downstream components. Ferroptosis, apoptosis, and necroptosis, which are types of PCD, play an active role in many pathological and physiological processes, especially cancer, inflammation, neurodegenerative disorders, and immune system diseases. Although each pathway has its own set of stimuli and modulators, they do interact with one another. The downstream components of the relevant molecule involved in PCD and the molecules it interacts with enable the cell to choose the most ideal death pathway for the benefit of the cell. In this regard, identifying PCD pathways and their downstream components is critical for the creation of more effective disease treatments and medications, as well as for overcoming treatment resistance. This review article discussed the mechanisms of ferroptosis, apoptosis, and necroptosis as well as associated diseases.

Keywords: Apoptosis, ferroptosis, necroptosis, programmed cell death.

Cells use various death pathways to preserve homeostasis after the conclusion of several pathological and physiological processes, such as the end of a cell's viability, aging, deoxyribonucleic acid (DNA) damage, and inflammation. Programmed cell death (PCD) pathways, which are naturally present in cells and regulate the cellular death process, play a role in this process.[1] Programmed cell death is of great importance in maintaining the balance between cell death and proliferation. Some cells are unable to receive and respond to death signals, and the homeostasis of the cell is disrupted and the cell progresses toward cancer, neurodegenerative disorders, etc.[2,3] Therefore, understanding PCD pathways and mechanisms is important for cellular survival and therapeutic efficacy. Programmed cell death may prefer many different death pathways depending on the type of death signal (DNA damage, biochemical, immunological, etc.) coming to the cell. In this article, as the PCDs species ferroptosis, apoptosis, and necroptosis are emphasized.

FERROPTOSIS

Ferroptosis was identified in 2012 as a compound consisting of growth-inhibiting small molecules "erastin" and "RAS-selective lethal 3 (RSL3)" in cancer cells with RAS mutation. Therefore, it is closely related to the death process of cancer cells.[4,5] Unlike apoptosis and autophagy, ferroptosis is an iron-dependent PCD that is controlled by extremely high levels of lipid peroxidation. In addition to lipid metabolism; iron metabolism, cyst(e)/glutathione (GSH)/glutathione peroxidase 4 (GPX4) pathway, GTP cyclohydrolase 1 (GCH1)/tetrahydrobiopterin (BH4)/dihydrofolate reductase (DHFR) pathway, ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10) biosynthesis and oxidative stress have also been described for ferroptosis.[5,6] However, basically, three features of ferroptosis are characterized by reduction of lipid peroxide repair mediated by phospholipid hydroperoxide GPX4, iron accumulation, and oxidation of phospholipids, different from other death pathways.[7]

Received: October 21, 2022
Accepted: November 05, 2022
Published online: December 05, 2022

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Cite this article as:
Açıkgöz S, Odabaşı M, Erbaş O. Ferroptosis, apoptosis, necroptosis. D J Tx Sci 2022;7(1-2):22-31.

Glutathione peroxidase 4 selenoprotein, a peroxidation inhibitor, is the sole glutathione peroxidase member implicated in ferroptosis control. It becomes a substrate for oxidants such as GSH, hydrogen peroxide (H_2O_2), lipid hydroperoxide, and phospholipid hydroperoxide. The RSL3 can also directly bind GPX4 and inactivate it, preventing additional reactive oxygen species (ROS) production and triggering ferroptosis. Furthermore, RSL3 activates transferrin (TF) and promotes ROS formation by increasing iron buildup, which promotes peroxidation via the "Fenton reaction", so driving ferroptosis.[5]

It is critical to understand the ferroptosis pathways and reasons and prevent ferroptosis in terms of illness detection and therapy. With the discovery of various ferroptosis pathways and inhibitors since 2012, studies are still ongoing. Currently, studies have shown that four classes of small molecule drugs, namely Class 1 ferroptosis inducers (FINs), Class 2 FINs, Class 3 FINs, and Class 4 FINs, induce ferroptosis.[4,8] Class 1 FINs target GSH consumption and superoxide elimination in the cell. Glutathione concentrations are four times greater in cancer cells than in normal cells. It is also recognized to have a key function in cell death resistance.[5,9] Erastin, a Class 1 FIN, is a model ferroptosis inducer that directly inhibits system Xc- and lowers GSH levels. They prevent the proliferation of ovarian and cervical cancer cells.[10] It targets the mitochondrial voltage-dependent anion channel (VDAC) and RAS genes in addition to system Xc-. Any mutation in the cell's VDAC or RAS genes might cause resistance to erastin therapy.[11] Erastin can trigger ferroptosis in cancer cells while also increasing the effectiveness of anti-cancer medications such as doxorubicin, temozolomide, and cisplatin.[12-14] Sorafenib, currently in clinical use, is also a Class 1 FIN ferroptosis inducer.[4] Induction of ferroptosis via Class 1 FINs is not always successful. Some cells may resist ferroptosis due to increased expression of proteins such as heat shock protein HSPB1. Cells in which GSH is not consumed cannot go to ferroptosis. In such cancer cells, GPX4 targeting and ferroptosis induction are tried to be achieved through Class 2 FINs. The RSL3 is a Class 2 FIN that inactivates GPX4 directly via the selenocysteine alkylation route and targets enzymes with a nucleophilic domain. Altretamine, which is authorized by the Food and Drug Administration (FDA), is also used to promote ferroptosis in the treatment of ovarian cancer. Class 3 FINs aim to consume the CoQ10 (endogenous antioxidant pathway) pathway along with the SQS-mevalonate pathway as well as GXP4 consumption. FIN56, a ferroptosis inhibitor, is utilized for this purpose. By elevating labile iron pool (LIP2), Class 4 FINs cause intracellular iron oxidation and lipid peroxidation. In this way, it can open up new perspectives for illness prevention and therapy. Withaferin A induces ferroptosis in neuroblastoma via increasing LIP. It also inhibits HMOX1-mediated heme degradation, and GXP4 consumption happens at the same time.[4,8]

LIPID METABOLISM

Iron-dependent lipid peroxidation is an important mechanism seen in all pathways of ferroptosis. Membrane phospholipids must be oxidized for the progression of ferroptosis signaling, and free-form polyunsaturated fatty acids (PUFAs) are used as substrates for lipid signal transduction.[4]

Arachidonic acid (AA) or phosphatidylethanolamine (PE), which includes its derivative adrenaline, is the main phospholipid molecule in ferroptosis signaling. Lysophosphatidylcholine acyltransferase 3 (LPCAT3), arachidonate 15-lipoxygenase (ALOX15), and acyl-CoA synthetase long-chain family member 4 (ACSL4) contribute to the biosynthesis and remodeling of PE so that PUFAs become activated and lose their transmembrane properties. In this way, ferroptosis is regulated. ACSL4, ALOX15, and LPCAT3 are important enzymes in the regulation of ferroptosis. Under normal conditions, LPCAT3 stimulates phosphatidylcholine in the liver by mediating the reactions of unsaturated fatty acyl-CoAs and saturated lysophosphatidylcholines. However, in the case of LPCAT3 deficiency, the amount of AA on the membrane is significantly reduced and induces lipid peroxidation and membrane degradation by the accumulation of triacylglycerol in the plasma. The ACSL4 interacts with arachidonic acid, increasing the peroxidation of arachidonic acid-CoA (AA-CoA), adrenic acid-CoA (AdA-CoA), and PUFA-CoA, as well as the production of six fatty acids, which causes

membrane breakdown. The loss of ACSL4 reduces AA-CoA and AdA-CoA levels in the membrane, which helps to reduce ferroptosis resistance by reducing membrane breakdown. ALOX15 is an iron-containing dioxygenase enzyme like AA and AdA. It is a member of the LOX family in humans. It increases the quantity of oxidized PUFA and causes erastin and RSL3-mediated ferroptosis when overexpressed.[5,15]

Products such as malondialdehyde and 4-hydroxynonenal (4-HNE) derived reactive aldehydes or elevated amounts of lipid hydroperoxides are generated as a result of lipid peroxidation. The resulting hydroperoxides promote the progression of ferroptosis. Moreover, various electron transfer proteins such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) in the cell membrane also contribute to the production of ROS for lipid peroxidation. Biological activities such as lipid production, the tricarboxylic acid cycle, and glutamine breakdown may potentially contribute to ferroptosis induction.[4]

IRON METABOLISM

The iron content in cells that undergo ferroptosis is dramatically raised. And cells are continuously in need of iron. Reactive oxygen species can be produced through mitochondria-mediated or direct Fenton reaction as a result of excessive accumulation of free-form Fe^{2+} in the cell and the formation of a LIP. Under normal conditions, Fe^{3+}, which is mediated by lactotransferrin or serotransferrin as an important component of the circulatory system, associates with cell membrane transferrin receptor 1 (TFR1) via endocytosis to form endosomes. The STEAP3 metalloreductase reduces Fe^{3+} to Fe^{2+}'in endosomes and releases it into the cytoplasm. Excess Fe^{2+} is stored in ferritin. Increased TFR1 expression or RAS gene mutation increases the amount of Fe^{2+} in LIP in the cell by decreasing ferritin production and iron transporters. In this way, ferroptosis is induced cellularly. Furthermore, excessive activation of heme oxygenase 1 (HMOX1), which has antioxidant capabilities, may cause the heme group to be converted to carbon monoxide, biliverdin, and loaded iron, resulting in increased Fe^{2+} ferroptosis in the cell.[4] In addition to these factors, increasing expression of the divalent metal transporter 1 (DMT1) in conjunction with increased inflammation may change intracellular iron levels and result in ferroptosis. Nuclear receptor coactivator 4 (NCOA4) is a selective cargo receptor for a ferritin autophagic turnover (ferritinophagy). While the degradation of NCOA4 inhibits ferroptosis with low iron levels; a high amount induces ferroptosis.[5]

Increasing evidence shows that ferroptosis has important roles in many diseases, as in other death pathways such as apoptosis and autophagy. Cancer, neurological disorders, blood diseases, and immune system diseases are examples of diseases where ferroptosis is defective. It can be a driving force in the emergence of diseases as well as a significant target in disease therapy.[3]

Given the relationship between ferroptosis and cancer, the quantity of lipid peroxidation in the cell may vary depending on the cell type from which cancer originates. For example, it has been discovered that smoking induces ferroptosis in pulmonary epithelial cells, which leads to carcinogenesis in lung cancer. Unlike cigarettes, high levels of zinc also induce ferroptosis in non-small cell lung cells, which has been considered as an anti-cancer therapeutic strategy. Therefore, targeting ferroptosis in the treatment of cancer cells is an important approach both for anti-cancer therapy and for overcoming drug resistance. Ferroptosis is essential in terms of brain and neurodegenerative disorders since many brain diseases are characterized by iron accumulation. For example, plaque formation is increased as a result of ferroptosis in ischemic stroke disease. As a result, neuronal damage is increased in animal models with ischemic stroke.[5] Blood cells pass the blood-brain barrier after traumatic brain injury (TBI), disturbing brain homeostasis. Traumatic brain injury causes an increase in iron buildup, and the inactivation of GPX genes causes an increase in ferroptosis genes.[16,17]

APOPTOSIS

Aside from its involvement in embryonic development, homeostasis maintenance, and aging, apoptosis is a defensive process that eliminates diseases and wounded or altered cells as a result of radiation or chemotherapeutic treatments. This type of cell death involves activation of the evolutionarily conserved and tightly regulated

intracellular caspase cascade, which requires energy expenditure. The elimination of the cell without eliciting an immune response is a crucial property of apoptosis, sparing tissue harm. The explanation for this is that phagocytosis degrades cell contents without releasing them into the extracellular environment.[18]

Apoptosis is one of the best-characterized modes of cell death that is highly conserved throughout evolution and is involved in the regulation of various physiological conditions. Two major signal transduction pathways have been identified that lead to the induction of apoptosis, the receptor-mediated (external) pathway, and the mitochondrial (internal) pathway. Induction of the apoptotic mechanism through either of these two pathways ultimately proceeds through the activation of caspases, a family of cysteine proteases that function as death effector molecules in various forms of apoptosis by proteolytic cleavage of multiple cytoplasmic or nuclear substrates. Performing apoptosis, proteolytic degradation of intracellular material, including cytoskeletal proteins and nuclear DNA, produces marked changes in cell morphology, such as membrane swelling, nuclear fragmentation, cell shrinkage, and intracellular content is packaged into apoptotic bodies without being released outside and is rapidly cleared by phagocytes.[19,20]

EXTRINSIC PATHWAY

When the external route stimulates apoptosis, ligands, which are death receptors on the cell membrane's outer surface, become activated by binding to their related death ligands on the cell surface. Death receptors are members of the tumor necrosis factor (TNF) receptors (TNFR) superfamily, a broad family of transmembrane receptors that govern a variety of biological processes, including PCD and immunological functions. A "death domain" exists in the cytoplasmic domain of the death receptor family. This domain mediates protein-protein interactions and is crucial for the transfer of deadly signals from the outside to the interior of the cell. When it comes to the induction of cell death, two death receptor systems have been best characterized, namely the CD95 (APO-1/Fas) system and the TNF-related apoptosis-inducing ligand (TRAIL) receptor system. Both receptor systems contain transmembrane cell surface receptors harboring the intracellular death domain and a cysteine-rich extracellular domain that serves to bind cognate ligands. The CD95 receptor/CD95 ligand system plays an important role in regulating immune function. The CD95 system, for example, contributes to the adaptive immune response by regulating T cell activation-induced cell death. The trimerization of this protein complex activates caspase-8, one of the apoptotic effector caspases (transfers from the pro-caspase-8 form to the active caspase-8 form). Activated caspase-8 cleaves and activates pro-caspase-3, resulting in proteolytic processing of substrates that mediates cell lysis and nuclear fragmentation. Active caspase-8 activates the mitochondrial pathway by converting Bid protein, a member of the proapoptotic protein family, to the truncated-Bid (tBid) form. It supports mitochondrial membrane permeability as a result of its interaction with Bcl-2 proteins in mitochondria. This allows the release of Smac and cytochrome-c into the cytoplasm through the holes in the mitochondrial membrane. Then, in the cytosol, an apoptosome complex is generated, comprised of cytochrome c, apoptotic protease activating factor (Apaf)-1, adenosine triphosphate (ATP), and caspase-9 components, and promoting caspase-3 activation. Smac promotes apoptosis by attaching to and neutralizing the inhibitors of the apoptosis protein (IAP) family, which adversely regulates apoptosis. The development of the apoptosome complex causes apoptosis.[19,21]

INTRINSIC PATHWAY

When apoptosis is induced via internal routes, such as the mitochondrial pathway, in response to signals such as growth factor deprivation and DNA damage from within the cell, anti-apoptotic Bcl-2 proteins are inactivated and pro-apoptotic proteins with the BH-3 domain are transformed into free form. Bad protein is activated by dephosphorylating and binds Bcl-Xl protein. As a result, two Bax proteins become liberated. As a result of the union of two Bax proteins, the pores to release cytochrome-c from the mitochondria are opened. With the formation of pores, pro-apoptotic proteins such as Smac, cytochrome-c, Apaf-1, and Omi are released into the cytoplasm from the mitochondria. The apoptosome complex is formed with the cytochrome-c, Apaf-1, which passes into the cytosol. With the formation of the

apoptosome complex, pro-caspase-9 becomes active caspase-9. In this way, the activation of effector caspases is stimulated, resulting in apoptosis. In most human malignancies, the equilibrium between pro- and antiapoptotic Bcl-2 family proteins is disturbed. Bcl-2 proteins have both proapoptotic and antiapoptotic members. Antiapoptotic Bcl-2 proteins such as Bcl-2, Bcl-XL, and Mcl-1 are typically overexpressed in human cancers, whereas proapoptotic family members are downregulated or inactivated. For example, somatic mutations of the Bax gene have been reported in colon carcinoma or hematological malignancies.[20,21]

NECROPTOSIS

Necroptosis, as Degterev et al.[22] explained in 2005, is a programmed, necrosis-like death process caused by death-associated receptors and sensors in the presence of receptor-interacting protein kinase 1/3 (RIPK1/3) and mixed lineage kinase-like (MLKL).[22-25] Organelles inflate, cellular volume rises, and morphological changes such as membrane rupture and cell content loss are observed during necroptosis. In necroptosis, which is involved in various pathological and physiological processes such as cellular response to stress, regulation of the immune system, and carcinogenesis; downstream signaling begins with the involvement of RIP1 and RIP3 kinases and formation of the necrosome complex, and they can also be selectively suppressed by necrostatins. Also, the necroptosis starter necrosome complex is produced by the interaction of kinases.[24]

NECROSOME COMPLEX

In the necrosome complex, the RIPK1, and RIPK3 kinases come together by heterodimerization and form a complex by incorporation into complex IIb. RIPK3 promotes the recruitment of RIPK1 into the necrosome complex. Complex II, composed of Fas-associated death domain (FADD), TNFR-associated death domain (TRADD), RIP1, and caspase-8, is the complex via which RIPK1 is released from post-deubiquitinaitone complex I into the cytoplasm. TRADD is also released from complex I as a result of the complex's inclusion of TNFR1. This step is critical for complex II formation.[24] RIPK1, best identified in the nuclear factor kappa B (NF-κB) pathway, is critical for both apoptosis and necroptosis due to its death domains. RIPK1 activity depends on the function of the small molecule inhibitor necrostatin-1 (Nec-1). Necrostatin-1 suppresses complex IIb formation. In order for the kinase activity of pronecrotic complex II to start, it is important to recruit RIPK1 to complex II. In contrast, RIPK1 activity is not required for the formation of complex I. RIP3 kinase, another necroptosis-associated RIP1 kinase family member, interacts with RIPK1 through the RIP homotypic interaction motif (RHIM) region. It is not affected by the RIPK1 inhibitor Nec-1. It is triggered by phosphorylation at the Ser199 site, which results in necroptosis induction. Necroptosis progression requires interactions between RIPK1 and RIPK3 via the RHIM domain. Since this interaction happens in response to necroptotic stimuli, it is regarded as a distinct signaling route for necroptosis. Since RIPK1, which is normally inhibited by Nec-1, is reactivated when it interacts with RIPK3.[25] The creation of this complex activates the RIPK1 and RIPK3 kinases via autophosphorylation. As a result, necroptosis is induced. If caspase-8 activity is inhibited at this stage, RIPK1 and RIPK3 heterodimers may form an amyloid necrosome. RIPK3 attracts and collects free-form RIPK3s in the cytosol and forms a homodimer. This homodimer structure causes RIPK3 autophosphorylation, which is required for MLKL assembly and phosphorylation. Phosphorylation of RIPK3 is required for necroptosis to start.[22] Necroptosis begins with the development of the necrosome complex and at this point is similar to apoptosis. When the death signal is received, the death ligand targets bind to TNFR1, so that necroptosis proteins in the cytoplasm are activated by binding.[26,27] On the one hand, caspase-8-FLIP(L) is involved in regulating complex IIb's activity state and determines whether necroptosis starts or not. Caspase-8 activity enzymatically cleaves RIPK1 and RIPK3 in complex IIb and prevents the formation of the necrosome complex. On the other hand, the caspase-8-FLIP(L) heterodimer structure has no enzymatic function and cannot be enzymatically cleaved RIPK1/3. Thus, it induces necroptosis. Most investigations employ the pancaspase inhibitor zVAD-fmk in conjunction with TNF-α and Smac mimics to reduce caspase-8 activity

and trigger necroptosis.[22] Caspases are a family of cysteine proteases. The death pathway that starts with the signaling of death receptors such as FasL, TRAIL, and TNF-α, which is generally encountered in apoptosis, is also seen in necroptosis.[25] However, RIPK3 is required in TNF-mediated RIPK1 phosphorylation.[24] Furthermore, it has been demonstrated that necroptosis can be triggered not only by death domain receptors but also by the apoptosis-inducing factor (AIF)-mediated chromatinolysis or alkylation-induced DNA damage.[7,15,22,28]

Tumor necrosis factor/TNFR signaling not only activates NF-κB and apoptosis, but it also drives necroptosis. The Binding of TNF and TNFR enables RIP1 and related proteins to be recruited to the receptor for the rapid formation of complex I. Complex I activates the NF-κB pathway via the downstream signaling pathway. Up to this stage, the course for apoptosis and necroptosis is the same. RIPK1 activates RIPK3 to generate a necroptosis-directing protein complex in caspase-8-deficient cells at this stage. RIPK3 also phosphorylates the MLKL domain, promoting its translocation. In this way, membrane damage is induced and necroptosis occurs. Decreased expression of many necroptosis modulators such as MLKL, cylindromatosis (CYLD), and RIPK3 has been reported in cancer cells. This indicates one aspect of avoiding necroptosis in cancer cells. Necroptotic properties, such as cell membrane rupture and the spilling of cellular contents into the extracellular environment, cause a proinflammatory response in cancer cells, promoting angiogenesis, invasion, and metastasis. Necroptosis is a more inflammatory process than apoptosis in this regard.[25,29]

It is hypothesized that ROS are also involved in necroptosis. In reaction to the TNF signal, some cell lines, including mouse fibroblast (L929) and mouse embryonic fibroblast cells, produce ROS. Reactive oxygen species have been proposed to oxidize MAP kinase phosphatases (MKPs) for JNK pathway signaling in addition to the recognized antioxidant response.[30,31] It has also been reported in the literature that metabolic enzymes such as glutamate-ammonia ligase (GLUL), glycogen phosphorylase (PYGL), and glutamate dehydrogenase 1 (GLUD1) interact with RIPK3.[12] These enzymes increase the amount of substrates used in oxidative phosphorylation, which is a cellular ROS source. In RIPK3-deficient cells, ROS levels in TNF signaling were reduced. This result indirectly supports the idea that ROS is associated with necroptosis.[25]

Understanding PCD is a fascinating aspect of the therapy of many diseases, including cancer and neurological disorders, and it forms the treatment's backbone. Today, clinically FDA-approved and small-molecule drugs are available.[32] These medications attempt to inhibit carcinogenesis by causing ferroptosis in cancer cells. Cytogenesis between normal and malignant cells, for example, can be targeted by establishing extracellular physiological circumstances such as high extracellular glutamate concentrations (xCT is inhibited). As a result of the inhibition of xCT and GPX4 phospholipid-hydroperoxide, the sensitivity of cancer cells to cisplatin and gemcitabine was significantly increased. Examples of medications that are currently utilized in the clinic and have active potential include sorafenib, artemisinin, statins, and cyst(e)inase. Sorafenib, a multiple kinase inhibitor, is approved for the treatment of advanced cancers. Ferroptosis is induced by the inhibition of kinases in the system Xc, using sorafenib in the treatments of renal cell carcinoma, hepatocellular carcinoma, and pancreatic or lung cancer. It causes ferroptosis by increasing the amount of free iron in the body. Another medicine, statin, affects the mevalonate pathway, reducing protein synthesis of GPX4 and CoQ10. Thus, ferroptosis is induced. Cyst(e)inase is an enzyme that participates in the enzymatic breakdown of cysteine in serum. Enzymatic degradation of extracellular cysteine in chronic lymphocytic leukemia cells and prostate cancer cells results in cell death in vitro and in vivo. This enzymatic degradation of cysteine induces non-toxic ferroptosis.[33-35]

Ferroptosis is characterized by lipid peroxidation and iron buildup, both of which are common in neurodegenerative disorders. Therefore, diseases such as Alzheimer's, Parkinson's, and Huntington's are associated with ferroptosis. Aggregates generated as a result of the aggregation of amyloid beta (Aβ) and Tau protein, for example, are considered the fundamental cause of Alzheimer's disease, which affects roughly 50 million people worldwide.

Interestingly, there is considerable iron accumulation in these aggregates of Aβ and Tau protein. The effects of high iron-loaded protein aggregates on neuronal functions cannot be underestimated. As a result of the toxicity produced by iron excess, ROS builds in neurons when GSH is depleted. As ROS levels rise, so does GSH consumption, and this cycle promotes ferroptosis in neurons.[2,36]

Looking at Parkinson's, another neurodegenerative disorder, Parkinson's is involved in neurotransmitters and the nervous system. Iron overload in persons with Parkinson's disease is exacerbated by age-related issues with iron regulation. Symptoms of ferroptosis-related neuron damage include excessive iron buildup, lipid peroxidation, GSH depletion, and elevated ROS levels in Parkinson's patients. In addition, the depletion of ceruloplasmin in astrocytes, which is associated with iron transport, also causes neuron damage associated with iron accumulation in Parkinson's patients.[37]

Avoidance of apoptotic cell death can both facilitate tumor initiation and maintenance and promote therapeutic resistance. Furthermore, Koren and Fuchs'[20] study published in 2021 indicated that the rise of malignant leukemic B cells, which have both high and low amounts of antiapoptotic and proapoptotic Bcl-2 family members, is driven by reduced apoptosis rather than enhanced proliferation. It is also known to show similar protection against apoptosis when antiapoptotic Bcl-2 proteins are upregulated in other cancer cell types, including colon adenocarcinoma, prostate cancer, neuroblastoma, breast cancer, and glioblastoma. Finding a new repair mechanism for DNA damage may lead to resistance to chemotherapy and radiation. Therefore, the identification of DNA damage repair components and pathways is important in synthetic lethality and in the destruction of specific cancer cells. [38] In addition to triggering cellular death in a widely accepted way, apoptosis draws high attention, especially in terms of supporting carcinogenesis. Wang et al.[39] revealed in 2013 that the more malignant the tumor, the more apoptosis it shows, increasing the incidence of apoptosis in cancer, and they offered a novel notion that apoptosis plays a significant role in cancer malignant growth and metastasis. According to this idea, tumor cells develop, proliferate, and metastasize as a result of increased and unavoidable mortality induced by hereditary or environmental conditions such as ischemia and inflammation. In short, increased cell death is the source of malignancy. Apoptosis has long been known as a protective factor against carcinogenesis. As a result, developing the ability to 'resist apoptosis' is critical for tumor formation. Ironically, tumors frequently have a greatly greater frequency of apoptosis, which means that tumor tissues have a far higher apoptotic index than normal tissues. The increase in apoptosis rate will also modulate cell proliferation. The higher the apoptotic index, the more malignant the tumor. Conditions such as an immune attack, increased gene replication errors and genomic instability trigger a high rate of cell death in cancer cells. As a result of higher cell death, a greater proportion of cells will enter the cell cycle and reproduce. The greater the number of cells that die, the lower the fraction of cells in G0 and the weaker it gets. Tissue differentiation and structure cause more cells to die. This is shown as increased apoptosis and sometimes apoptosis-mediated necrosis. Bcl-2, also known as the proto-oncogene, is expressed in normal breast glandular tissues and low-grade breast cancers but not in high-grade breast cancers. In parallel, high-grade breast cancers have a much higher apoptotic index and proliferation rate. And increased apoptosis or necrosis is associated with shortened patient survival.[40] This method may accelerate tumor development.

The complexes' effect on necroptosis differs depending on the cell type. For example, TNF-mediated modulation of FADD in MEF cells is required for necroptosis but not for leukemic Jurkat cells.[41] FADD, once again, acts as a negative regulator of necroptosis when T cells multiply. Understanding the downstream signaling components and alterations of RIP1/3 kinases, as well as the method of activating NF-κB, is critical for understanding how the cell chooses between apoptosis and necroptosis on the path to death. The cell makes its decision between apoptosis and necroptosis, depending on parameters such as cell type, death signal to the cell, and caspase activity. At this point, the most decisive factor is whether caspase-8 is

active or not. However, this situation is not always the same. Additionally, specific triggers can cause necroptosis and apoptosis. For example, Shikonin, a previously acknowledged apoptosis booster, has been demonstrated to promote necroptosis.[24,25]

According to numerous information, there is a link between necroptosis and autophagy. Nec-1, a RIPK1 inhibitor, reduced the expression of the autophagic marker LC3 in FADD-deficient cells; it has also been reported that necroptosis modulates autophagy by compensating for the turnover and proliferation of T cells in FADD-defective cells.[42] This finding supports the idea of the presence of a positive feedback loop between necroptosis and autophagy. However, there is evidence that autophagy can promote necroptosis. It can promote necroptosis by raising the quantity of ROS generated from mitochondria by autophagy and by boosting the expression of the DNA repair enzyme Poly [ADP-ribose] polymerase 1 (PARP1). In addition, suppression of autophagy is induced necroptosis by zVAD-fmk.[24,43] Necroptosis also serves as an immune system regulator. It is involved in the regulation of T-cell proliferation and macrophage survival. It has also been observed that the expression of genes linked with necroptosis is high in cells of the mouse immune system.[44] It has been shown that necroptosis in cancer can hasten cell death and improve tumor cell susceptibility to treatments. Necroptosis has been found to be significant in overcoming the resistance of children's acute lymphoblastic leukemia cells to glucocorticoid treatment. Studies have also revealed that necroptosis is a successful and powerful therapeutic target against chemotherapeutic resistance created by Bcl-xL and Bcl-2 and P-glycoprotein in cancer cells.[45-48]

Compared to apoptosis and some other death pathways, necroptosis, a new type of PCD, is a potential therapeutic target for many diseases. Necroptosis inhibition, particularly because of its proinflammatory properties, can protect cells against inflammation and trauma-induced damage. It is also a possible therapeutic agent candidate for disorders mediated by Nec-1, such as myocardial infarction and brain ischemic/reperfusion.[24] Various small molecules have been developed and used to target necroptosis in the clinic today. These compounds include emodin, ophiopogonin D, resibufogenin, bufalin, and shikonin. By means of these inhibitors, necroptosis was induced in various cancer cells such as glioma, prostate, colon, and pancreas and the proliferation of cells could be suppressed.[23,49,50]

In conclusion, considering all of these findings into account, it is necessary to elucidate the PCD pathways and components, the internal and external factors that direct the cell to these pathways, the relationships between the pathways, and the common points; treating diseases and providing homeostasis, therapeutic efficacy, and the discovery of new treatment methods will allow meaningful steps to be taken to overcome resistance to chemotherapeutic drugs. Furthermore, there is also a need for a genome-level study to better understand how therapy responses differ from person to person.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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