Targeting cell death pathways in acute myeloid leukemia: Molecular mechanisms and clinical implications (Review)

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Abstract. Acute myeloid leukemia (AML) is a highly heterogeneous hematologic malignancy, characterized by complex molecular features and mechanisms of treatment resistance, which lead to a poor prognosis and high relapse rates. The complexity of multi-pathway interactions and the dysregulated dynamics of tumor cell death pathways may contribute to the wide range of clinical outcomes observed despite advancements in current therapies. Most current research focuses on a single form of cell death, neglecting the mechanisms of other death pathways and their synergistic interactions, which hinders the development of novel therapeutic approaches. The present review systematically integrates and compares the molecular features of key cell death modalities in AML, including autophagy, apoptosis, pyroptosis, necroptosis, ferroptosis and cuproptosis. The present review analyzes their specific triggers, signaling hubs and regulatory networks within the metabolic microenvironment, and discusses the dynamic crosstalk among these pathways. A key focus is the therapeutic potential of exploiting this crosstalk to design synergistic combination therapies. To overcome the limitations of conventional treatments and improve patient outcomes, it is essential to further investigate the transition mechanisms of various cell death modes in AML progression, drug resistance and relapse. Additionally, establishing a theoretical foundation for the development of innovative therapies that synergistically regulate multiple death pathways is crucial.

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1. Introduction

Acute myeloid leukemia (AML) is a highly aggressive hematologic malignancy in adults, characterized by a high relapse rate and persistent treatment resistance, which translates to a 5-year overall survival of <10% (1,2). Although advances in molecular typing and targeted therapies have improved the prognosis of patients with specific subtypes, the heterogeneity of AML, its driving mechanisms, and complex interactions between leukemia stem cells (LSCs) and the bone marrow microenvironment remain unclear (3). High-intensity chemotherapy and allogeneic hematopoietic stem cell transplantation are the current standard of care; however, due to their severe toxic side effects, harm to normal hematopoiesis, and limitations in eliminating LSCs and overcoming drug resistance, novel therapeutic approaches that are more effective and selective are urgently required (4,5).

Targeting of regulated cell death (RCD) has attracted increasing attention from researchers in recent years (6-9). The primary benefit of this method is its ability to specifically target LSCs while reshaping the immunosuppressive bone marrow microenvironment to enhance anti-leukemic efficacy and minimize damage to normal tissues (10). Studies have shown that selective modulation of RCD pathways, such as autophagy, apoptosis, pyroptosis, necroptosis, ferroptosis and cuproptosis, can effectively target and eliminate leukemic clones resistant to traditional therapies (11-16). Furthermore, these RCD pathways form a highly interconnected regulatory network that operates through dynamic interactions

rather than functioning in isolation (17). This complexity suggests that combinatorial interventions targeting multiple death pathway nodes synergistically may more effectively disrupt the death-resistant barriers of leukemia cells, thereby opening multidimensional attack pathways to overcome therapeutic bottlenecks caused by AML clonal evolution and microenvironmental sheltering (18).

The present review aims to achieve three objectives: i) To assess the latest developments and challenges in targeting RCD in AML treatment by systematically integrating the understanding of six major RCD pathways; ii) to explore the crosstalk and synergistic potential between these pathways, a critical yet underexplored area; and iii) to apply these insights in developing a framework for future combinatorial therapies. To provide novel concepts and strategies for overcoming AML treatment resistance and improving patient outcomes, the present review examines the RCD modes of action, their key functions, and potential synergistic effects in maintaining LSCs, chemoresistance and bone marrow microenvironment remodeling. The present review also explores the potential for developing a customized therapeutic system through precise targeting of the death pathway network. The profiles of each type of cell death are illustrated in Fig. 1 (8,19).

2. Autophagy

Overview of autophagy. Autophagy is a highly conserved cellular process that involves the formation of autophagosomal vesicles. These vesicles encapsulate damaged organelles, misfolded proteins and other cytoplasmic components within double-membrane structures. Cellular component recycling occurs when autophagosomes fuse with lysosomes, where the enclosed contents are enzymatically degraded into smaller molecules (20).

Autophagy can be classified into three types based on its mechanism: Microautophagy, chaperone-mediated autophagy and macroautophagy. Macroautophagy is the most widely studied type of autophagy and involves the encapsulation of damaged organelles or denatured proteins by double-membrane autophagic vesicles. These vesicles then transport the contents to fuse with lysosomes, where enzymatic degradation occurs (21). Lysosomal-associated membrane protein 2 mediates the highly specific pathway of chaperone-mediated autophagy, in which heat shock protein 70 recognizes KFERQ motifs in target proteins and unidirectionally translocates them into the lysosomal lumen for selective degradation (21). Unlike the first two autophagic pathways, microautophagy does not involve the formation of distinct autophagosomal structures. Instead, it involves creation of phagocytic vesicles through lysosomal membrane invagination, directly engulfing cytoplasmic components or organelles and delivering them to the lysosomal lumen for enzymatic degradation via membrane fusion (22).

Autophagy is a five-stage molecular process involving initiation, nucleation, membrane extension, fusion and degradation (23). When cells experience nutrient deprivation, the activity of mTOR, a key energy-sensing kinase, is suppressed, triggering the autophagy signaling cascade (24). The UNC-51 like kinase 1 (ULK1) complex, which consists of essential components including ULK1, ATG13 and FIP200, is phosphorylated by AMP-activated protein kinase. This phosphorylation reverses the inhibitory effect of mTOR on the complex (25). Upon activation, the complex migrates towards the autophagy initiation site, where ULK1 catalyzes the phosphorylation of FIP200 and ATG13 (25). This phosphorylation event recruits downstream ATG proteins to initiate the formation of the pre-autophagosome complex (26). The nucleation phase of autophagy begins with the activation of the phosphatidylinositol-3-kinase class III complex, which catalyzes the formation of a lipid-signaling platform at the membrane surface through phosphatidylinositol 3-phosphate (27). This platform recruits effector proteins containing the FYVE/PX domain, which promote the assembly of pre-autophagosomal structures (28). Membrane expansion during autophagy is driven by two ubiquitin-like modification processes: Atg7 functions as an E1-like enzyme in the Atg5-Atg12 coupling system, facilitating the covalent binding of Atg12 to Atg5 (29). This complex then associates with autophagy related 16-like 1 to regulate membrane curvature and promote the growth of autophagic vesicles (29). In the LC3 lipidation pathway, Atg4 cleaves the LC3 precursor to generate LC3-I, which is then covalently linked by Atg7 to Atg3, forming membrane-anchored LC3-II that integrates into the autophagosome membrane, promoting membrane extension and serving as a marker for substrate recognition, thereby facilitating targeted transport (30). The two pathways collaborate to complete autophagosome maturation (31). Ultimately, the autophagic vesicle membrane closes, enabling fusion with the lysosome to form an autophagic lysosome. During this process, the autophagosomes are degraded, and the resulting molecules are recycled for use by the cell (32,33). Fig. 2 illustrates the three types of autophagy and their respective processes (24).

Autophagy in AML. AML development is marked by the dynamic bidirectional regulation of autophagy (34). By eliminating oxidatively damaged DNA, autophagy maintains the metabolic balance and protects the genomic integrity of hematopoietic stem cells, preventing their malignant transformation under normal conditions (35,36). Autophagy undergoes a dynamic shift during leukemia progression: In the early stages, it promotes oncogenesis by limiting genomic instability, while in the later stages, it becomes an adaptive mechanism that supports tumor cell survival and helps leukemia cells endure stressful environments through metabolic remodeling (37,38). This dichotomy suggests that autophagy dysfunction may contribute to leukemia development, with an imbalance in its regulatory network accelerating the emergence of malignant phenotypes (39).

Research has elucidated the mechanisms by which autophagy contributes to AML development. Targeting the ATF4-dependent autophagy pathway could offer a therapeutic approach for patients with Fms-like tyrosine kinase 3 (FLT3) mutations, as Fms-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) expression increases basal autophagy, which is essential for AML cell survival (40). KIT mutations increase the likelihood of AML relapse, which is directly linked to STAT3-mediated autophagy (41,42). Nucleophosmin 1 (NPM1) mutations are common in AML, where NPM1 induces autophagy through the oncogene PML, thereby promoting AML cell proliferation (43). By inhibiting autophagy, the TP53

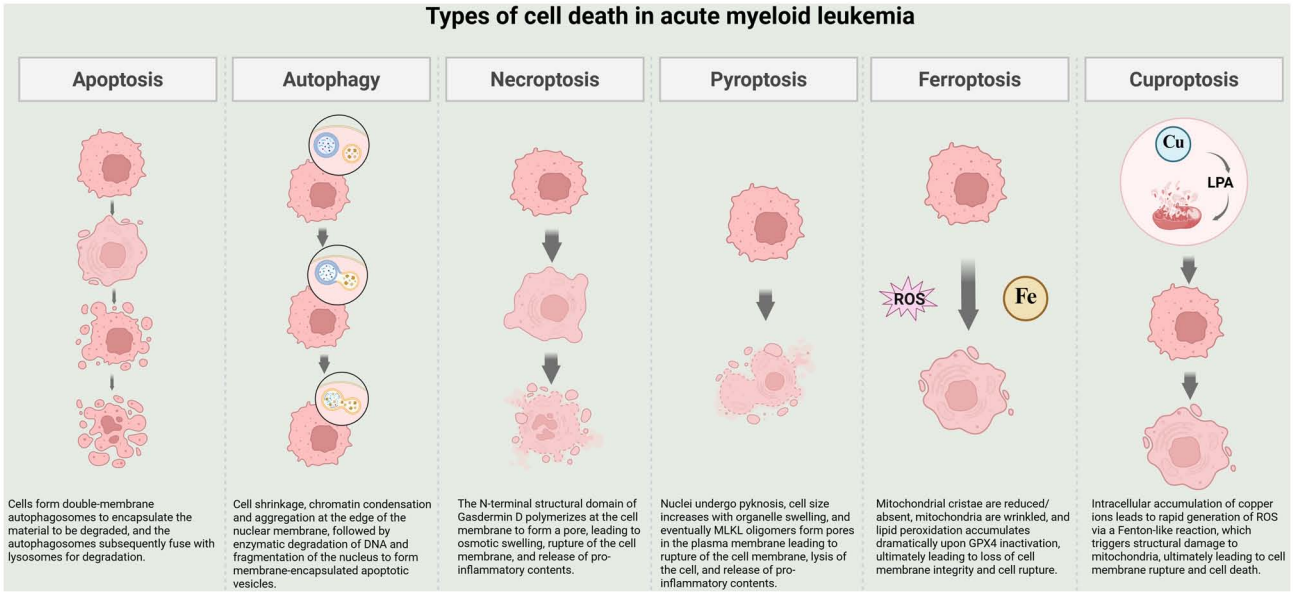

Figure 1. Summary of the profiles of six subtypes of cell death (autophagy, apoptosis, pyroptosis, necroptosis, ferroptosis and cuproptosis). Created with BioRender.com. GPX4, glutathione peroxidase 4; LPA, lysophosphatidic acid; MLKL, mixed lineage kinase domain like pseudokinase; ROS, reactive oxygen species.

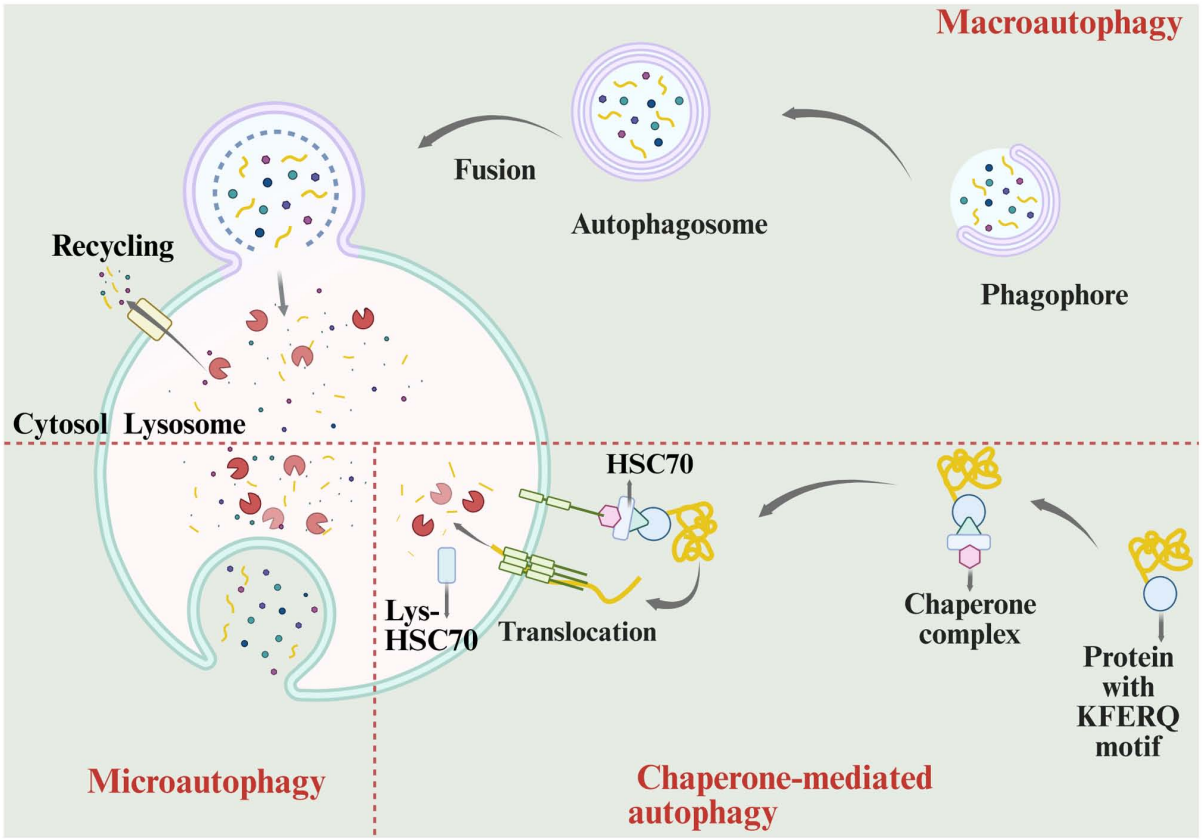

Figure 2. Three types of autophagy: Macroautophagy (the degradation of macromolecules or organelles via the autophagosome-lysosome pathway), micro-autophagy (the direct invagination of lysosomal membranes to phagocytose the substrate) and molecular chaperone-mediated autophagy (HSC70-dependent recognition of specific motifs for the targeted transport of soluble proteins to the lysosome for degradation), involved in non-selective scavenging, selective metabolic regulation and the maintenance of precise proteostasis, respectively. Created with BioRender.com. HSC70, heat shock protein 70.

mutation, which is less common in hematological cancers than in solid tumors, increases p53 expression and triggers apoptotic responses dependent on p53-upregulated modulator of apoptosis and BAX, leading to AML cell destruction (44). Glycolysis, a key metabolic pathway in AML, influences the disease process by promoting abnormal invasion, proliferation

and drug resistance (45). Research has demonstrated that combination of autophagy inducers with glycolysis inhibitors enhanced leukemia cell sensitivity to chemotherapy (46,47). In relapsed cases, LSCs promote mitochondrial oxidative phosphorylation by stimulating fatty acid β-oxidation, creating a distinct metabolism-dependent drug resistance mechanism (48). Fatty acid metabolism is also directly linked to AML progression (49-51). The interconnections among these metabolic pathways create a complex regulatory network that supports AML cell survival and treatment resistance. Some of the aforementioned research has translated into clinical practice, with studies showing that combination of autophagy inducers with chemotherapeutic drugs enhanced their effectiveness (52-54). For instance, the mTOR inhibitor rapamycin, when combined with chemotherapy drugs, can increase AML cell sensitivity to treatment and promote apoptosis, providing a novel approach to enhance chemotherapy efficacy (55). Combining autophagy inhibitors with targeted therapies has also improved efficacy. Inhibition of autophagy enhances the anti-leukemic effect of FLT3 inhibitors in FLT3-ITD-positive AML, offering a novel strategy to overcome resistance to targeted therapies (56). Furthermore, combination of multiple autophagy regulators can more effectively control the autophagy process in AML cells. For example, co-treatment with an mTOR inhibitor and a Beclin-1 activator increases autophagy levels, promoting cell differentiation and apoptosis, suggesting the potential therapeutic benefits of using multiple regulators simultaneously (57). Further research on the mechanisms of AML autophagy, as well as on the clinical efficacy and specific applicability of related therapies, is required.

3. Apoptosis

Overview of apoptosis. Apoptosis is a genetically regulated process of programmed cell death that requires ATP to execute a series of typical events (58). Endogenous and exogenous apoptosis are two distinct pathways, and both are regulated by caspases (59).

Proteins from the Bcl-2 and caspase-9 families are crucial to the endogenous, or mitochondrial, apoptotic pathway. The members are classified into pro-apoptotic proteins, which contain only the BH3 domain, and anti-apoptotic proteins, based on their function (60). Anti-apoptotic proteins form heterodimers with pro-apoptotic proteins through the BH1-3 domains, thereby inhibiting their pro-apoptotic activity (61). Bax, a pro-apoptotic protein, is upregulated and undergoes a conformational change upon DNA damage or oxidative stress, triggering apoptotic signaling (62). Bax then translocates from the cytoplasm to the outer mitochondrial membrane, where it oligomerizes to form channels (63). Meanwhile, BCL2 antagonist/killer, originally located in the outer mitochondrial membrane, is activated by BH3-only proteins, triggering a cascade that leads to oligomerization and the formation of a transmembrane pore (58,64). The two interact to increase mitochondrial outer membrane permeability, resulting in the release of cytochrome c (CytC) from the intermembrane space into the cytoplasm (65). Upon binding to apoptotic protease activating factor-1, free CytC oligomerizes into heptameric apoptotic vesicles, driven by deoxyadenosine triphosphate. The exposed caspase recruitment domain (CARD) then recruits and activates the initiator caspase-9, which subsequently cleaves the effector caspase-3, triggering apoptosis (66).

Exogenous apoptotic pathways are mediated by transmembrane death receptors (67). Upon binding of the death ligand, the death domain of the intracellular region of the receptor recruits Fas-associated death domain protein (FADD) via the adaptor protein TNFRSF1A-associated death domain, forming the death-inducing signaling complex (68). The death effector domain of FADD then recruits and activates initiator caspase-8/10, which undergoes autocleavage to form an active dimer (69). Activated caspase-8 subsequently triggers a cascade of effector protein cleavages, driving apoptosis. Caspase-3/6/7-mediated breakdown of nuclear fibrillar proteins leads to nuclear membrane disintegration and inactivation of DNA repair enzymes (70). Genome breaks are exacerbated by poly (ADP-ribose) polymerase, leading to classic apoptotic phenotypes, including cell membrane vesiculation and apoptotic vesicle formation (71,72). This method also activates the mitochondrial system, initiating an apoptosis signaling amplification loop through cleavage of the BH3-interacting-domain death agonist (BID) protein, producing the active truncated BID fragment and ensuring irreversible cell death (73). Fig. 3 illustrates the complete process of both endogenous and exogenous apoptosis mechanisms (74).

Apoptosis in AML. In AML, the anti-apoptotic protein BCL-2 is upregulated, enabling leukemia cells to evade apoptosis and continue their growth (75,76). Based on the understanding that BCL-2 interacts with pro-apoptotic proteins, scientists have developed several BCL-2 inhibitors, including oblimersen, obatoclax mesylate (GX15-070), ABT-737, ABT-263 (navitoclax), ABT-199 (venetoclax) and S6384559 (77). Venetoclax, one of the most extensively studied medications, has demonstrated strong clinical efficacy both as a monotherapy and in combination with other drugs, particularly low-dose cytarabine or demethylating agents, improving patient survival and remission rates (78-80). Venetoclax resistance has become increasingly evident as research progresses, primarily due to dysfunction in pro-apoptotic mechanisms and the upregulation of compensatory anti-apoptotic proteins, such as myeloid cell leukemia-1 (MCL-1). To overcome venetoclax resistance, appropriate inhibitors are being developed in parallel (10,81). Despite the use of venetoclax, additional apoptosis inducers are emerging. For instance, second mitochondrial-derived activator of caspases (SMAC) analogs targeting inhibitor of apoptosis protein (IAP) can antagonize IAPs and promote apoptosis by mimicking endogenous SMAC proteins (82). A pivotal clinical study has demonstrated that SMAC analogs, when combined with conventional chemotherapies or targeted therapies, can enhance the cytotoxic effects on AML cells (83).

P53, a key pro-apoptotic transcription factor, is closely associated with complex karyotypes, treatment resistance and poor survival outcomes in patients with AML. This unique clinical-molecular feature suggests that dysregulation of the TP53 signaling pathway is not only a key pathogenic mechanism of AML, but also a potential marker for molecular stratification and a target for targeted therapies, supporting the optimization of precision treatment strategies (12). Thus, drugs such as MDM2 inhibitors and P53 reactivators are being investigated for patients with TP53 mutations who have poor prognoses (84-86).

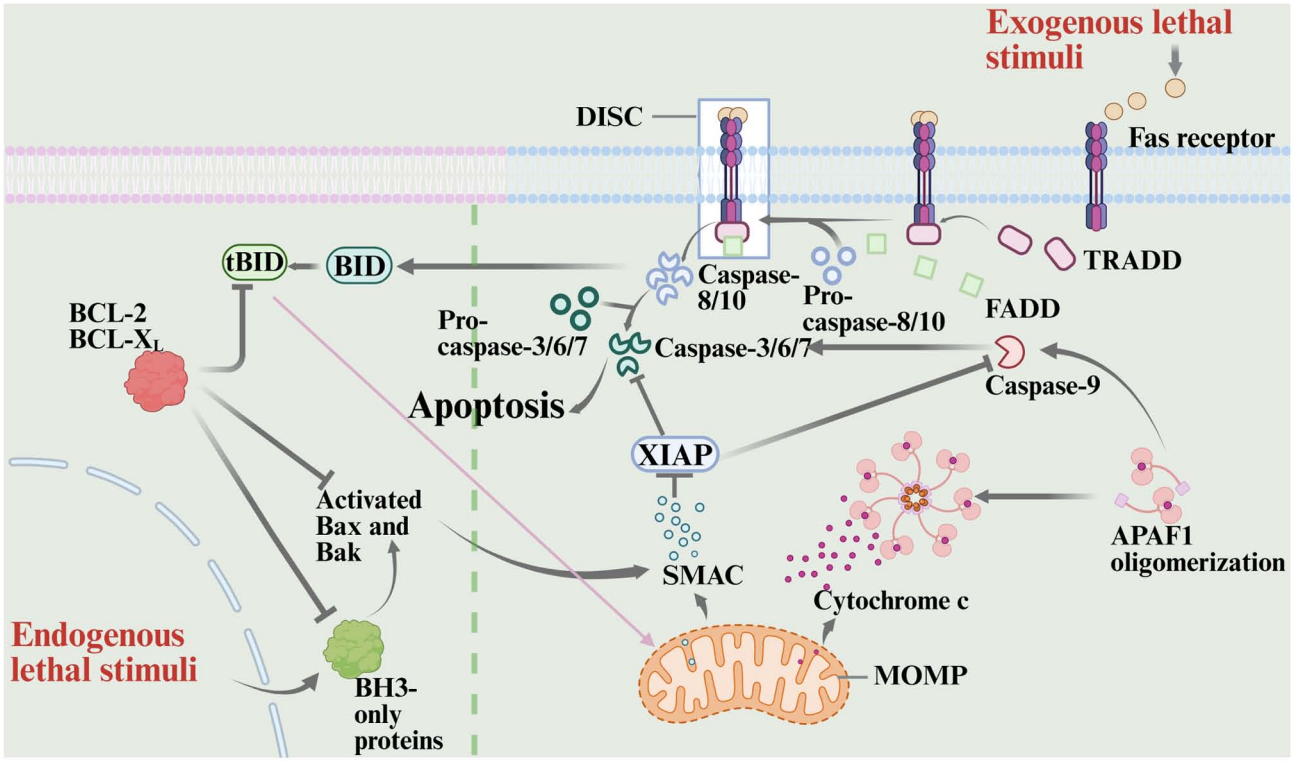

Figure 3. Apoptosis regulation mechanisms can be divided into two categories: Endogenous and exogenous processes. A key commitment step in endogenous apoptosis is MOMP, which is triggered by upstream signals including BH3-only proteins. MOMP leads to the release of cytochrome c, apoptosome formation with APAF1/caspase-9, and ultimately activation of the executioner caspase-3. By contrast, the exogenous pathway is activated through the aggregation of death receptors, such as Fas, leading to the formation of a DISC. The DISC activates the initiator caspase-8, which then cleaves and activates effector caspases, including caspase-3. This pathway serves a key role in immune homeostasis. The two mechanisms eventually converge on the activation of the executioner caspases. Furthermore, they are linked via signaling through BID protein-mediated mitochondrial crosstalk. Created with BioRender.com. APAF1, apoptotic protease activating factor-1; Bak, BCL2 antagonist/killer; BID, BH3-interacting-domain death agonist; DISC, death-inducing signaling complex; FADD, Fas-associated death domain protein; SMAC, second mitochondrial-derived activator of caspases; tBID, truncated BID; TRADD, TNFRSF1A-associated death domain; XIAP, X-linked inhibitor of apoptosis; MOMP, mitochondrial outer membrane permeabilization.

Numerous studies have demonstrated that leukemia cells can also undergo apoptosis via activation of the death receptor pathway, offering a potential basis for immunotherapy in AML (87,88). AML cell apoptosis is strongly influenced by the bone marrow microenvironment (89). Components of this microenvironment, such as the extracellular matrix, regulate the expression of apoptosis-related proteins in AML cells, affecting their sensitivity to chemotherapy (90).

Future studies on apoptosis and AML should focus on enhancing the efficacy and availability of current treatments while minimizing their side effects to provide more effective AML therapies.

4. Pyroptosis

Overview of pyroptosis. The gasdermin (GSDM) family includes six members (GSDMA, GSDMB, GSDMC, GSDMD, GSDME and pejvakin), which are primarily expressed in tissues such as the gastrointestinal tract and skin, and serve a key role in regulating pyroptosis (91-93). GSDMD-induced pyroptosis can be categorized into classical and non-classical pathways.

The classical pyroptosis pathway begins with pattern recognition triggered by pathogen infection and proceeds through the inflammatory vesicle-GSDMD axis. When intracellular NOD-like receptors detect pathogen-associated molecular patterns, the pyrin domain (PYD) recruits the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC). This forms a platform for multimerization and recruits pro-caspase-1, which assembles into a functional inflammatory vesicle complex (94,95). When the complex activates caspase-1, it cleaves GSDMD. This cleavage releases the C-terminal domain of GSDMD, thereby relieving its inhibition of the N-terminal pore-forming domain. The released GSDMD N-terminal oligomerizes and embeds in the cell membrane, forming a nanoscale pore that disrupts cellular osmolality, causes content leakage and triggers pyroptosis, characterized by cell swelling (96-98). The primary mechanism of the anti-infective immunity of the host involves processing the precursors of IL-1β and IL-18, which are released extracellularly through the GSDMD pore in their mature forms. This recruits neutrophils and other inflammatory cells, triggering a cascade amplification effect (94,99). This is achieved through membrane pore-mediated 'inflammatory death', which eliminates infected cells while tightly regulating the local inflammatory response (100).

The nonclassical pyroptosis pathway is triggered by the direct sensing of lipid components, with caspase-4/5/11 detecting intracellular lipopolysaccharide (LPS) (101-103). Unlike the traditional system, this mechanism does not involve ASC bridging proteins. Caspase-4/5/11 directly binds LPS through its CARD and undergoes oligomerization for

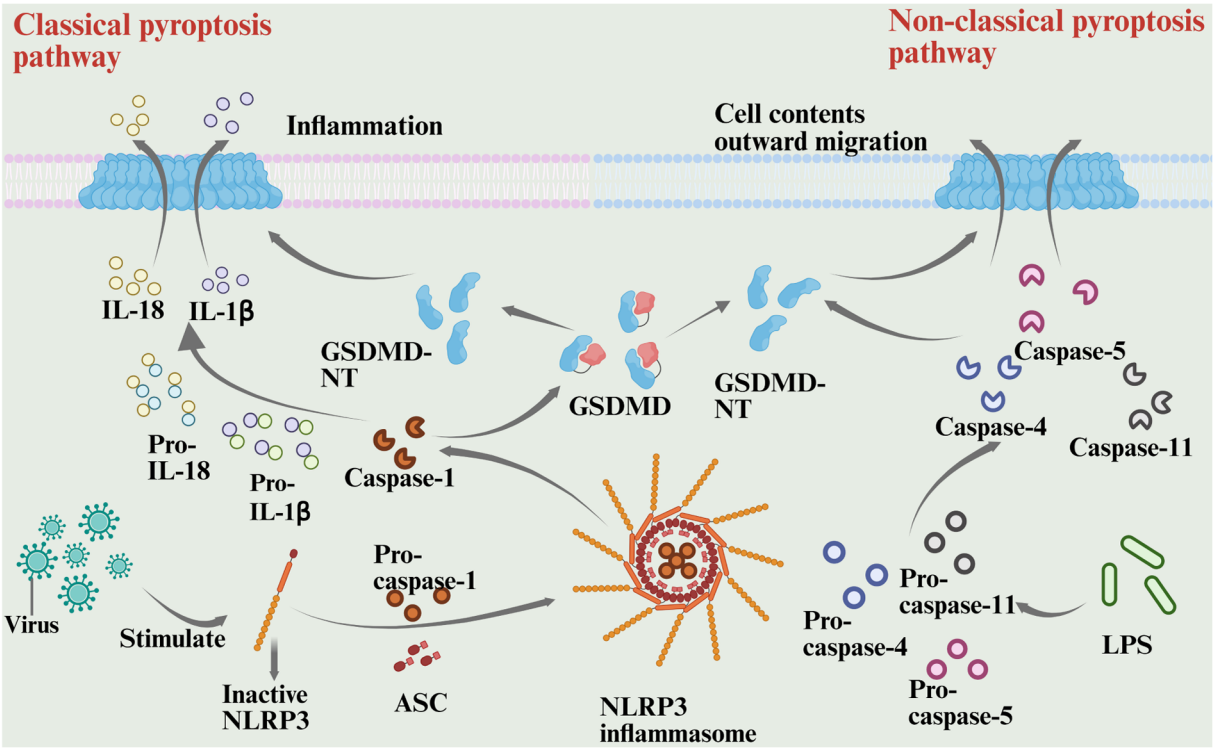

Figure 4. Pyroptosis pathway consisting of two main pathways: The classical and non-classical pathways. In the classical pathway, extracellular pathogen stimuli, such as viruses, bind to inactive NLRP3, activating the NLRP3 inflammasome, which contains ASC and pro-caspase-1. This activation triggers the self-cleavage of pro-caspase-1 into caspase-1, which then cleaves GSDMD to produce the GSDMD-NT fragment. GSDMD-NT forms pores in the cell membrane, causing the release of pro-inflammatory cytokines such as IL-1β and IL-18, leading to membrane rupture and an inflammatory response. The non-canonical pyroptosis pathway involves the activation of caspases-4, -5 and -11 in humans, which is directly triggered by intracellular pathogen-associated molecular patterns such as LPS. Activated caspases cleave GSDMD to generate GSDMD-NT, which forms pores in the membrane, releasing cellular contents and further promoting inflammation. Both pathways lead to programmed cell death and the release of inflammatory mediators, serving a crucial role in host defense against pathogens. Created with BioRender.com. ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, gasdermin D; GSDMD-NT, N-terminal pore-forming domain of gasdermin D; LPS, lipopolysaccharide; NLRP3, NACHT, LRR and PYD domains-containing protein 3.

self-activation (102-104). Activated caspase-4/5/11 specifically cleaves GSDMD to release the N-terminal pore domain (NT), leading to cell membrane perforation and pyroptosis (105). However, since NT does not directly process IL-1β/IL-18 precursors, the inflammatory response is only mildly activated (102,106). In non-immune cells, caspase-4 indirectly cleaves pro-IL-18 through conformational changes, amplifying local inflammatory signals (107) Similarly, by promoting the activation of inflammatory vesicles containing NACHT, LRR and PYD domains-containing protein 3 (NLRP3), caspase-11 enhances caspase-1-mediated IL-1β maturation and secretion, forming a synergistic network of classical and non-classical regulatory mechanisms (104).

The pathophysiological relevance of pyroptosis in infections, tumors and inflammatory diseases is underscored by the ability of certain GSDM family members (specifically GSDMD, GSDMB and GSDMC) to induce focal cell death via specific protease cleavage and link programmed death with the immune response through a multidimensional regulatory network (108-110). Both the classical and non-classical pathways of pyroptosis are illustrated in Fig. 4 (100).

Pyroptosis in AML. Research has shown that inflammasomes, key molecular complexes involved in pyroptosis, serve a dual role in the occurrence, progression and treatment of leukemia, with potential clinical applications (111). Evidence suggests that pyroptosis serves a critical, bidirectional role in both the progression of AML and its treatment response (111). Mechanistic research has demonstrated that chemotherapy or targeted therapies enhance anti-AML efficacy by activating the focal cell death pathway (18). A study by Ren *et al* (12) showed that estrogen receptor activation enhanced the anti-AML effect of the BCL-2 inhibitor vincristine, via the pyroptosis pathway. Demethylating agents can promote venetoclax-induced AML pyroptosis by restoring GSDME expression, offering a potential strategy to overcome resistance to BCL-2 inhibitors (14). In addition to enhancing existing targeted therapies and chemotherapy, pyroptosis could provide a novel target for AML treatment. Small molecule inhibitors targeting serine dipeptidyl peptidase (DPP)8/DPP9 have been shown to induce cellular pyroptosis in a majority of a panel of human AML cell lines and primary samples, suggesting that this target may offer a novel approach for AML treatment (112). Suppression of reticulocalbin 1 gene expression reduces bone marrow mononuclear cell activity in patients with AML, further confirming the crucial role of cellular pyroptosis in AML pathogenesis (113).

The 'immunogenic death' feature of pyroptosis, which releases cytokines that reshape the tumor immune environment and reduce immunosuppressive cells, underlies its significance in AML therapy by helping overcome immune escape (12). For example, receptor-interacting serine/threonine-protein kinase

3 effectively inhibits aberrant bone marrow proliferation in the FLT3-ITD mutant AML model by regulating IL-1β production via inflammatory vesicles. However, it can also modify the bone marrow microenvironment, impairing normal hematopoietic stem progenitor cell function while promoting LSC development (114-116). Cytarabine promotes IL-1β secretion through NLRP3 inflammasomes, offering a novel approach to improve treatment strategies (117). Ren *et al* (12) also demonstrated that targeted activation of G protein-coupled estrogen receptor improved vincristine efficacy by enhancing leukemic cell pyroptosis and $CD8^+$ T-cell immunity in patients with AML, a process mediated by IL-1β/18.

The challenge lies in the bidirectional regulation of pyroptosis, where its intensity must be carefully controlled to prevent inflammatory storms. Despite clinical studies demonstrating the therapeutic benefit and safety of pyroptosis-inducing therapies in AML, further research is needed to optimize these treatments and understand their long-term effects on patients (12,117).

5. Necroptosis

Overview of necroptosis. Necroptosis is a programmed cell death mechanism independent of cysteine proteases, typically induced when the apoptotic pathway is blocked by viruses or medications (118). Its molecular core involves the receptor interacting serine/threonine kinase 1 (RIPK1)-receptor interacting serine/threonine kinase 3 (RIPK3)-mixed lineage kinase domain like pseudokinase (MLKL) signaling axis (119). The activation pathway is complex and diverse. In the classical pathway, the TNF receptor superfamily recruits RIPK1 through its death domain when caspase-8, the main executor of apoptosis, is inhibited genetically or pharmacologically. This results in the formation of an amyloid-fibril-like signaling complex (necrosome) with RIPK3, triggering an autophosphorylation cascade of RIPK3 (118,120-122). By contrast, in pattern recognition receptor-mediated bypass, toll-like receptor 3 directly recruits RIPK3 via the TIR domain-containing adapter molecule 1 (TRIF), forming a nonclassical necrosome complex that bypasses RIPK1. This facilitates signal transduction upon recognition of viral double-stranded RNA or toll-like receptor 4 in response to endotoxin LPS (118,123). Additionally, Z-DNA binding protein 1 (ZBP1) acts as a nucleic acid sensor, detecting endogenous DNA/RNA released from viral replication intermediates or mitochondrial stress. ZBP1 specifically binds to RIPK3 through its receptor-interacting protein kinase homotypic interaction motif, initiating a necroptosis program independent of RIPK1 and TRIF (118,124). The multi-pathway signals converge, indicating that RIPK3 phosphorylates the MLKL pseudokinase domain, triggering a conformational change in MLKL and the formation of transmembrane pores. This leads to intracellular calcium overload, osmotic imbalance and loss of membrane integrity, resulting in the release of cellular contents and a potent pro-inflammatory response (118,125-129). Notably, the small molecule necrostatin-1 serves as a molecular tool for precisely modulating necrotic apoptosis subtypes by blocking RIPK1-dependent necroptosis through the ATP-binding pocket of the RIPK1 kinase domain. However, it is ineffective against ZBP1- or TRIF-mediated nonclassical pathways (130). The flexibility of this signaling pathway and multiple regulatory mechanisms make necroptosis potentially bidirectional in tumor microenvironment remodeling, chemotherapeutic resistance and immune escape, namely, it can exert both anti-tumor and pro-tumor effects depending on the context (131). The process of necroptosis is shown in Fig. 5 (132).

Necroptosis in AML. The RIPK1/RIPK3/MLKL axis serves a crucial role in necroptosis, with its dysregulation in AML cells closely linked to disease progression (13). The role of RIPK3 in AML is complex and context-dependent. In early leukemogenesis, RIPK3 may act as a tumor suppressor by inducing necroptosis and promoting the differentiation of leukemia-initiating cells, thereby preventing myeloid leukemia progression (13,133). However, in established AML, the role of RIPK3 is often reversed. Clinical evidence shows that high RIPK3 expression is associated with poor prognosis in specific AML subtypes, such as NPM1-mutant AML (134). Wang *et al* (134) specifically reported that elevated RIPK3 expression was an independent predictor of poor overall survival in specific AML subtypes, such as FAB-M4/M5, normal karyotype and NPM1 mutation subtypes, a finding strongly supported by Kaplan-Meier survival analysis (log-rank P=0.021; hazard ratio, 1.8; 95% CI, 1.2-2.5). This paradox (tumor-suppressive role in initiation but oncogenic role in progression) highlights the dual role of RIPK3 and emphasizes the need for expression-based patient stratification in future therapeutic strategies (135). A study by Zhu *et al* (136) identified restoring RIPK3 expression to reverse R-2-hydroxyglutarate-induced necroptosis in isocitrate dehydrogenase-mutant AML cells as a potential therapeutic strategy for patients with AML. However, Hillert *et al* (137) suggested that targeting the RIPK1 pathway offered a more promising therapeutic approach for patients with FLT3-ITD-mutant AML. Targeting necroptosis pathways in combination with traditional chemotherapy or targeted therapies holds potential for effective treatment (138,139). Li *et al* (138) found that combination of the RIPK1 inhibitor 22b with cidabenamide enhanced its antileukemic effect in FLT3-ITD-positive AML cell lines and primary samples. Combining the RIPK1 inhibitor with the BCL-2 inhibitor venetoclax promotes apoptosis in AML cells and overcomes resistance to single-drug treatment (139). A study has shown that A20 deletion in AML restored sensitivity to anthracycline by inducing necroptosis (140). Although the aforementioned studies have demonstrated that targeting the necroptosis pathway is a viable strategy in AML, the clinical relevance of the RIPK1/RIPK3/MLKL axis remains unclear (135-137). Future research should focus on developing biomarkers to predict patient response to therapies targeting the necroptosis pathway, aiding in precision medicine.

6. Metal-RCD in the bone marrow microenvironment

Ferroptosis

Overview of ferroptosis. Ferroptosis is a form of programmed cell death driven by iron-dependent lipid peroxidation (141). Ferroptosis results from metabolic disruption caused by the imbalance of intracellular redox homeostasis (142). At physiological levels, iron serves as a key cofactor for redox

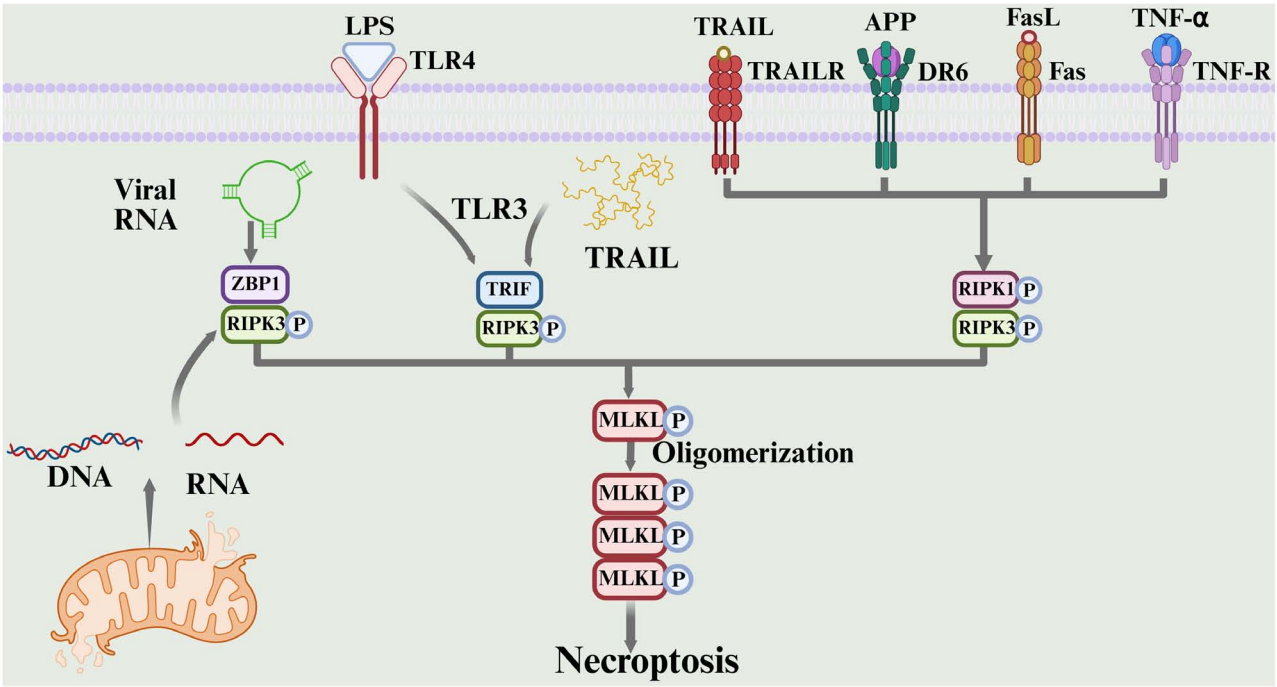

Figure 5. Core of necroptosis regulation depends on RIPK3 and MLKL, which are triggered by various pathways. The TNF receptor family (for example, TNF-R) activates RIPK3 through RIPK1, while activation of TLR3 or TLR4 recruits RIPK3 via the adapter protein TRIF; viral RNA or mitochondria-released nucleic acids, on the other hand, bind the ZBP1 receptor and directly recruit RIPK3 to trigger a pathway independent of RIPK1. Ultimately, RIPK3 phosphorylates MLKL, which leads to cell death. Created with BioRender.com. APP, amyloid precursor protein; DR6, death receptor 6; FasL, Fas ligand; LPS, lipopolysaccharide; MLKL, mixed lineage kinase domain like pseudokinase; P, phosphorylated; RIPK1, receptor interacting serine/threonine kinase 1; RIPK3, receptor interacting serine/threonine kinase 3; TLR3, toll-like receptor 3; TLR4, toll-like receptor 4; TNF-R, tumor necrosis factor receptor; TRIF, TIR domain-containing adapter molecule 1; ZBP1, Z-DNA binding protein 1; TRAIL, TNF-related apoptosis-inducing ligand; TRAILR, TRAIL receptor.

enzymes, contributing to electron transport and energy metabolism (143). Excess free iron (Fe^{2+}) generates reactive oxygen species (ROS) through the Fenton reaction, causing lipid peroxidation of the membrane (144). This disturbs cellular membrane integrity and organelle function (145).

The primary mechanism of ferroptosis is a dynamic imbalance of lipid peroxides, regulated by the glutathione (GSH) metabolic pathway and antioxidant defenses (146-149). Polyunsaturated fatty acid phospholipid hydroperoxide (PUFA-PL-OOH) is the key effector in this process, produced through the combined action of Fe^{2+}, lipoxygenases (arachidonate lipoxygenases), phosphatidylethanolamine-binding protein 1 complexes, cytochrome P450 reductase and ROS. These molecules collaborate to convert PUFA-PL into the harmful PUFA-PL-OOH (147). Ferroptosis suppressor protein 1 (FSP1) and GSH peroxidase 4 (GPX4) are the main mechanisms maintaining PUFA-PL-OOH at steady state. GPX4 reduces PUFA-PL-OOH via a GSH-dependent process, converting it to its non-toxic form (147). By contrast, FSP1 scavenges lipophilic free radicals and inhibits the lipid peroxidation chain reaction by producing the reduced form of coenzyme Q10 ($CoQH_2$) (148,149). In the absence of GPX4 inhibition or FSP1-$CoQH_2$ system dysfunction, lipid peroxides accumulate due to impaired scavenging. Furthermore, Fe^{2+} catalyzes the conversion of hydrogen peroxide into hydroxyl radicals via the Fenton reaction, intensifying lipid peroxidation and ROS bursts, and ultimately causing enzyme system collapse and cellular structural damage (146,147-152).

The ferroptosis regulatory network is multilayered. At the metabolic input level, the System Xc^- transporter, composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2, mediates cystine uptake, providing essential precursors for GSH synthesis (147,153-155). Inhibitors of this system reduce intracellular GSH levels by blocking cystine uptake, impairing GPX4 function and triggering ferroptosis (156). At the enzymatic regulatory level, GPX4 activity can be directly inhibited by small molecules such as RAS-selective lethal 3 and ML162, while GSH production is blocked by buthionine sulfoximine (157). Iron homeostasis is crucial, with divalent iron either removed by chelating agents such as desferrioxamine and bipyridine or expelled via the exosomal pathway after being stored as Fe^{3+} in ferritin (158,159). In addition, external ROS stimulation or disruption of lipid peroxidation detoxification can disrupt the redox balance, leading to the accumulation of toxic lipid products and triggering ferroptosis (160). These multidimensional regulatory mechanisms collectively shape the complex biological effects of iron death in cell fate decisions (145). The process of ferroptosis, with its inhibitory factors and promoting factors, is illustrated in Fig. 6 (145).

Ferroptosis in AML. Ferroptosis, an iron-dependent form of non-apoptotic cell death, offers unique potential for pathological modulation and therapeutic intervention in AML (15). AML cells are more susceptible to ferroptosis due to metabolic reprogramming and disrupted redox homeostasis (161). This susceptibility is further supported by significantly lower GPX4 expression in primary AML samples compared with normal

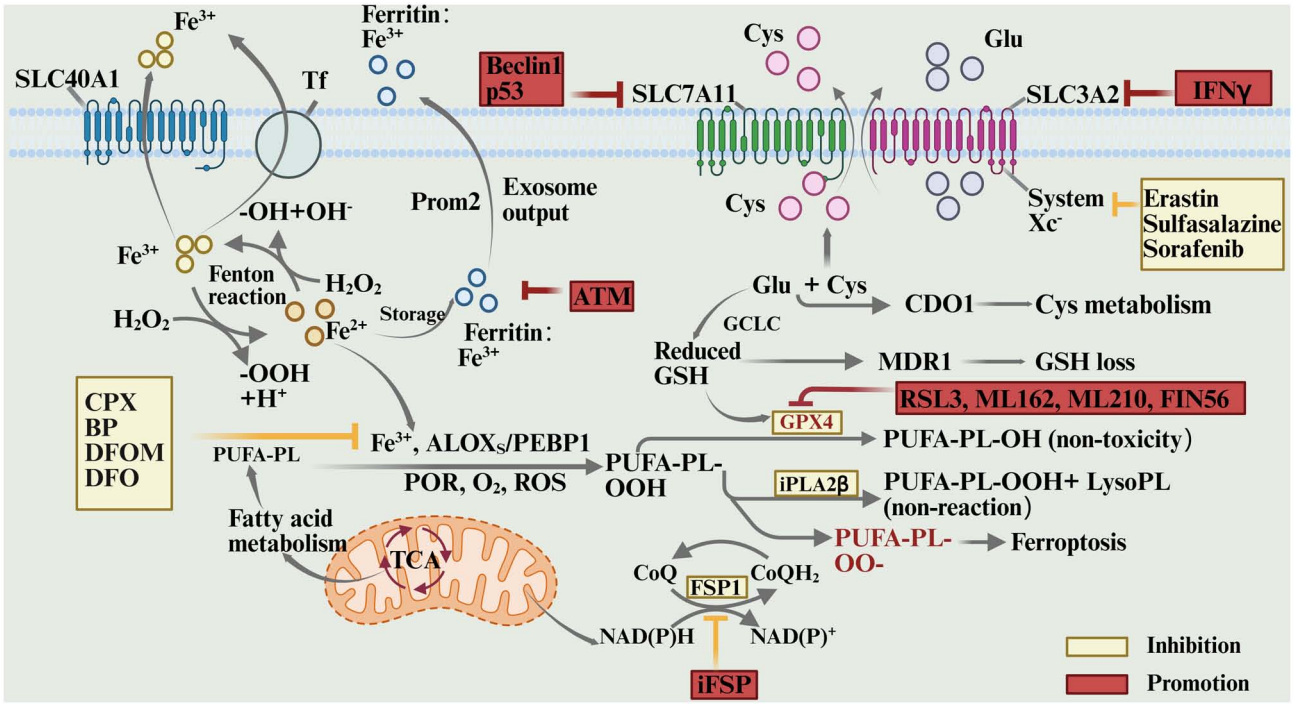

Figure 6. Central mechanism driving ferroptosis is a dynamic imbalance between lipid peroxidation and antioxidant defense systems. This process is highly dependent on the catalytic action of iron ions; free intracellular Fe^{2+} generates reactive oxygen radicals via the Fenton reaction, which triggers a peroxidative chain reaction of polyunsaturated fatty acids. A key regulatory step in lipid metabolism involves the conversion of free polyunsaturated fatty acids into membrane phospholipids and their subsequent oxidation to cytotoxic lipid peroxides. The main intracellular antioxidant barrier, the GPX4 enzyme system, is unable to reduce lipid peroxides to harmless substances due to blocked GSH synthesis or direct functional inactivation, ultimately leading to the irreversible accumulation of oxidative damage. Created with BioRender.com. $ALOX_S$, arachidonate 15-lipoxygenase; ATM, ataxia telangiectasia mutated; BP, 2,2'-bipyridine; CDO1, cysteine dioxygenase type 1; CoQ, coenzyme Q; $CoQH_2$, coenzyme Q2; CPX, ciclopirox; DFO, deferoxamine; DFOM, deferoxamine mesylate; FSP1, ferroptosis suppressor protein 1; GCLC, glutamate-cysteine ligase catalytic subunit; GPX4, glutathione peroxidase 4; GSH, glutathione; iFSP, inducible ferroptosis suppressor protein; iPLA2β, calcium-independent phospholipase A2β; LysoPL, lysophospholipid; MDR1, multidrug resistance protein 1; PEBP1, phosphatidylethanolamine-binding protein 1; POR, cytochrome P450 reductase; prom2, prominin2; PUFA-PL, polyunsaturated fatty acid phospholipid; PUFA-PL-OOH, polyunsaturated fatty acid-phospholipid-hydroperoxide; PUFA-PL-OO-, polyunsaturated fatty acid-phospholipid-alkoxy; ROS, reactive oxygen species; SLC3A2, solute carrier family 3 member 2; SLC40A1, solute carrier family 40 member 1; SLC7A11, solute carrier family 7 member 11; TCA, tricarboxylic acid cycle; Tf, transferrin; GCLC, glutamate-cysteine ligase catalytic subunit.

bone marrow ($P=1.3x10^{-6}$), along with reduced GSH levels and increased mitochondrial lipid peroxidation (162).

Ferroptosis holds significant potential in targeted therapy for AML. Research suggests that several natural products possess the potential to induce ferroptosis in cancer treatment (163). Crotonoside, a key constituent of *Crotonus sativus* listed in the Chinese Pharmacopoeia, induces ferroptosis in AML cells by stimulating lipid peroxidation and increasing autophagy, offering a novel approach for AML treatment (164). Birsen *et al* (165) demonstrated that APR-246-induced AML cell death was inhibited by iron chelators, lipophilic antioxidants and lipid peroxidation inhibitors, suggesting that APR-246 induced ferroptosis in AML cells. Lin *et al* (166) demonstrated that biomimetic high-density lipoprotein nanoparticles could disrupt intracellular cholesterol homeostasis by targeting the scavenger receptor class B type 1 receptor, which was upregulated in AML cells. This inhibited the GPX4-mediated antioxidant pathway and induced ferroptosis in AML cells at nanomolar concentrations, representing a major innovation in AML treatment.

Research indicates that M2 macrophage-derived growth differentiation factor 15 confers ferroptosis resistance in the tumor microenvironment, identifying a key drug resistance mechanism (167). AML cells are more resistant to mitoxantrone when co-cultured with M2 macrophages, providing a novel approach for overcoming AML microenvironment-mediated drug resistance (168). As a potent ferroptosis inducer and chemotherapeutic drug carrier for AML treatment, Yu *et al* (169) showed that the ferroptosis-inducing nanomedicine glutathione-capped ferrite nanoparticles successfully overcame AML resistance. Inhibition of nuclear factor erythroid 2-related factor 2 (NRF2) expression enhanced the anti-AML effect of vinpocetine by inducing AML cell death via the ferroptosis pathway (170). Pardieu *et al* (171) determined that SLC7A11 promoted AML cell survival by encoding the xCT cystine importer. The authors also demonstrated that combining daunorubicin with xCT inhibition achieved optimal anti-AML efficacy, suggesting that xCT inhibition combined with chemotherapy could be a promising strategy for AML treatment.

While ferroptosis has shown considerable promise in AML treatment, several challenges remain (172). These include the lack of techniques for monitoring ferroptosis dynamics, tumor heterogeneity-related differences in response and unclear mechanisms of microenvironment regulation. Addressing these issues is crucial for improving the long-term survival of patients with AML.

Cuproptosis

Overview of cuproptosis. Cuproptosis, a copper-dependent form of RCD, was first proposed by Tsvetkov *et al* (173) in 2022. The unique mechanism distinguishes cuproptosis from other death pathways, such as apoptosis, pyroptosis, necroptosis and ferroptosis. Cuproptosis is based on the direct binding of copper ions to lipoylase proteins in the tricarboxylic acid cycle, leading to abnormal aggregation (174). This copper-mediated interaction destabilizes iron-sulfur cluster proteins, disrupting key components of the mitochondrial respiratory chain and inducing protein homeostatic imbalance and oxidative stress, ultimately driving cell death via the proteotoxic stress pathway (175).

A key breakthrough in cuproptosis research was the 2019 discovery by Massachusetts Institute of Technology and Harvard teams of the copper ion carriers disulfiram and ilithromycin (ES), two small molecules that can specifically mediate copper ion transport across membranes, providing a central tool for studying copper-dependent cell death (176). As an anticancer treatment targeting mitochondrial metabolism, ES not only increases oxidative stress and ROS formation, but also triggers a novel cell death pathway through the accumulation of copper ions, according to recent findings (173). Tsvetkov *et al* (173) demonstrated that ES-induced cell death occurred without caspase-3 activation and was resistant to both classical apoptosis inhibitors and other death pathway blockers, confirming its independence from known death mechanisms. In-depth mechanistic studies revealed that ES penetrates the cell membrane by forming a complex with extracellular Cu^{2+}, reducing Cu^{2+} to Cu^{+}, and releasing highly reactive ROS in the mitochondria. Free ES then re-enters the circulatory system to transport Cu^{2+}, ultimately leading to copper overloading in mitochondria through the 'ion shuttle' mechanism (177-179). The lethal effects of ES were reduced by electron transport chain complexes and the mitochondrial pyruvate carrier, but not by mitochondrial uncouplers. Metabolomics analyses revealed a time-dependent increase in tricarboxylic acid cycle intermediates during ES treatment, suggesting that copper toxicity primarily disrupts the tricarboxylic acid cycle rather than oxidative phosphorylation (180,181).

Genetic evidence has indicated that ferredoxin 1 (FDX1)-knockout cells were resistant to cuproptosis, confirming that loss of FDX1, a key regulator of copper toxicity signaling, prevents the lipoylated protein aggregation cascade triggered by copper accumulation. This established that FDX1-mediated metabolic disruption is a core molecular pathway for cuproptosis execution (182). FDX1-mediated toxicity in cuproptosis occurs through the specific interaction of Cu^{+} with the mitochondrial lipoylase system, which triggers deleterious protein aggregation (173). Cu^{+} binds to the fatty acylated pyruvate dehydrogenase complex, inducing abnormal oligomerization and inactivation of the enzyme, which prevents pyruvate conversion to acetyl-CoA and disrupts metabolic flow via the tricarboxylic acid cycle (173,183). FDX1 serves multiple roles in this process: It catalyzes the lipid acylation of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, and enhances copper ion toxicity by converting Cu^{2+} to the more toxic Cu^{+} (184). Lipoic acid synthase, meanwhile, facilitates lipid acylation by synthesizing lipoic acid and aids the assembly of Fe-S cluster proteins in collaboration with FDX1, together forming the molecular network underlying copper ion toxicity (184). In this process, depletion of large Fe-S clusters disrupts the electron transport chain, while the blockage of the tricarboxylic acid cycle further impairs mitochondrial energy metabolism, ultimately leading to cell death through proteotoxic stress and metabolic disruption (173). This pathway aligns closely with the previously identified ES-induced cuproptosis pathway (173). Loss of FDX1 function inhibits both copper ion-mediated lipoylated protein aggregation and metabolic reprogramming, highlighting its critical role in cuproptosis signaling (185). The entire process of the cuproptosis pathway is illustrated in Fig. 7 (174).

Cuproptosis in AML. The copper-disulfide complex (Cu-DSF) binding system selectively targets cancer cells and cancer stem cells (186). The Cu-DSF exhibits dose-dependent cytotoxicity in LSCs, with minimal effects on normal hematopoietic progenitor cells. This selective toxicity is likely due to the enhanced copper ion enrichment in cancer cells (16). A study has demonstrated that patients with AML had reduced serum levels of zinc and selenium, accompanied by elevated copper levels, suggesting that disruptions in copper metabolism contribute to disease progression (187). Since LSCs contain higher copper levels than normal tissues, researchers have suggested using copper ion carriers to selectively transport copper ions into tumor cell mitochondria. This induces intracellular copper overload, triggering lethal effects such as oxidative stress, proteotoxicity and mitochondrial dysfunction, ultimately achieving the specific killing of tumor cells (188).

Current copper-targeted therapies for AML focus on the antitumor effects of copper chelators in hematologic malignancies (189-191). Disulfiram-copper complexes demonstrate anti-AML activity in both *in vitro* and *in vivo* assays, and partially overcome drug resistance in AML cells (192,193). Xu *et al* (16) demonstrated that disulfiram, either alone or in combination with copper, inhibited AML cell proliferation and induced apoptosis through mechanisms involving inactivation of the NRF2-NF-κB signaling pathway and activation of the ROS-JNK stress pathway due to copper accumulation. Furthermore, in the non-obese diabetic/severe combined immune deficiency mouse model, disulfiram also suppressed the growth of human $CD34^{+}/CD38^{+}$ AML cell xenograft tumors, further confirming its therapeutic potential *in vivo*. The clinical translation of copper-targeted therapies faces challenges, including off-target effects, systemic toxicity and drug resistance (194). For instance, copper chelators damage normal cells due to nonspecific binding, while long-term use of copper transporter inhibitors may lead to compensatory metabolic adaptation (195). A growing body of evidence underscores a strong association between cuproptosis and the pathogenesis of AML (196-198). This includes the dynamic expression of copper transporter proteins, the regulation of copper storage proteins, and the interplay between copper metabolism and the tumor microenvironment (188,194). Further research is needed to optimize copper carrier targeting with nanodelivery technologies and explore the synergistic effects of copper overload on cell death pathways, aiming to enhance therapeutic specificity and minimize the toxicity risk (194).

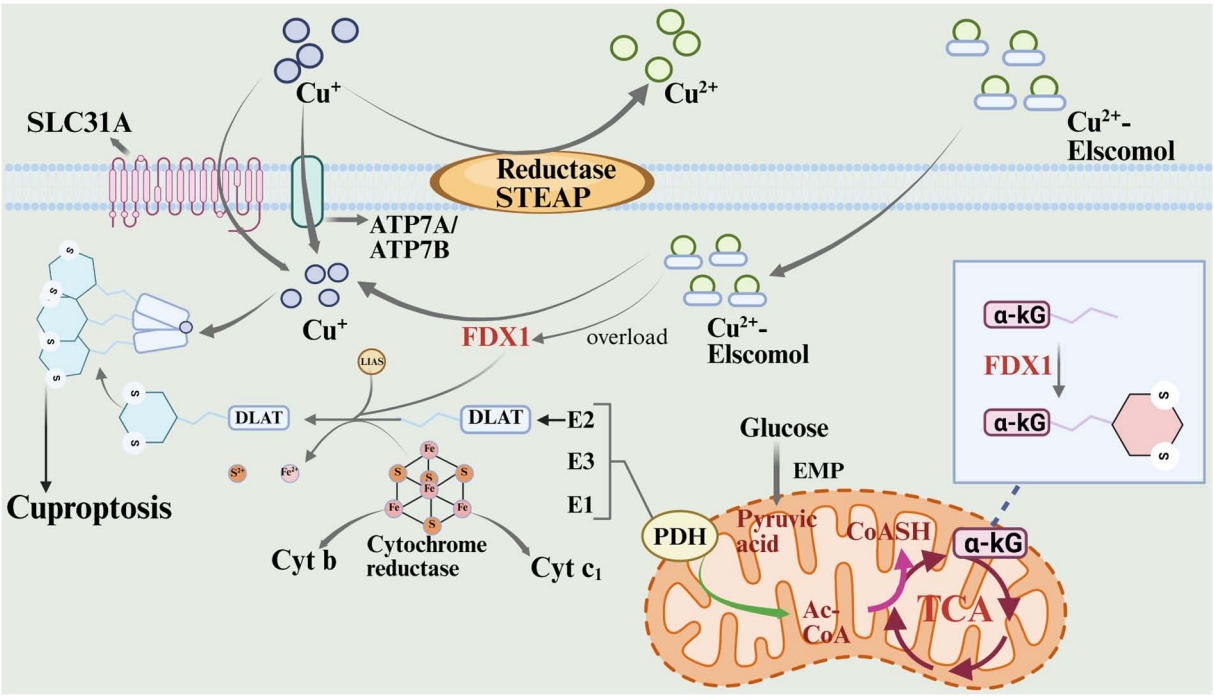

Figure 7. Cuproptosis is a mode of programmed cell death triggered by the aberrant accumulation of exogenous copper ions, and its core mechanism involves a dynamic imbalance of copper ions within the cell and their specific intervention in key metabolic pathways. Copper overload leads to the FDX1-mediated, copper-dependent aberrant oligomerization of the E2 subunit of the PDH complex. This process not only disrupts the normal functioning of the mitochondrial metabolic network but also leads to irreversible cell death by triggering a copper-dependent proteotoxic stress response. Created with BioRender.com. α-kG, α-ketoglutarate; Ac-CoA, acetyl-coenzyme A; ATP7, ATPase copper transporting 7; CoASH, coenzyme A in its reduced form; Cyt, cytochrome; DLAT, dihydrolipoamide S-acetyltransferase; E1, pyruvate dehydrogenase E1 component; E2, pyruvate dehydrogenase E2 component; EMP, Embden-Meyerhof-Parnas pathway; FDX1, ferredoxin; LIAS, lipoic acid synthase; PDH, pyruvate dehydrogenase; SLC31A, solute carrier family 31 member A; STEAP, six transmembrane epithelial antigen of the prostate; TCA, tricarboxylic acid cycle.

7. Crosstalk between targeted programmed cell death modalities

Cell death pathways are intricately interlinked, forming a complex signaling network that collectively governs cell fate (199). Autophagy also mitigates pyroptosis and its associated inflammation by removing inflammatory vesicle components, inflammatory factor precursors and damaged mitochondria (200). Autophagy serves a critical and bidirectional role in ferroptosis: Lipophagy scavenges lipid peroxides, while ferritin phagocytosis, a selective form of autophagy, releases ferric ions and drives ferroptosis (201). In the context of cuproptosis, autophagy may regulate the process by removing copper-induced aggregation of proteins or damaged mitochondria (173). Apoptosis, a conventional form of programmed cell death, is reciprocally suppressed by necroptosis: The apoptotic executor caspase-8 cleaves and inactivates RIPK1/RIPK3, key kinases involved in necroptosis (202). Necroptosis often serves as an alternative pathway when apoptosis is inhibited (203). By contrast, apoptosis and pyroptosis are linked by GSDM proteins; caspase-8 cleavage of GSDME converts apoptosis into an inflammatory form of cell death characterized by pyroptosis (203). Apoptosis and ferroptosis share common regulators, such as p53, which initiate both processes. Additionally, anti-apoptotic proteins can suppress ferroptosis, while mitochondrial damage induced by ferroptosis may also trigger apoptosis (204,205). Oxidative or endoplasmic reticulum stress caused by copper ion accumulation may indirectly activate apoptotic pathways (178). Necroptosis and pyroptosis are forms of inflammatory programmed necrosis that share the upstream signal RIPK1 (206). At the execution level, their terminal effectors, MLKL and GSDMD, can further interact through synergistic or competitive mechanisms during pore formation (207). Both necroptosis and pyroptosis share ROS triggers with ferroptosis. TNF produced by necroptosis or inflammatory factors released during pyroptosis can create a pro-oxidative environment that indirectly promotes ferroptosis (208). Additionally, damage-associated molecular patterns released by ferroptosis can activate inflammatory vesicles, triggering pyroptosis through a feedback mechanism (209). Although ferroptosis and cuproptosis have distinct core mechanisms, both involve metal ions and oxidative stress. Iron and copper metabolism are interconnected, with key regulatory nodes, such as mitochondrial function, ROS levels, inflammatory signaling and the balance of iron/copper/cystine, serving as pivotal points in the crosstalk between these death pathways (210). Understanding this complex network is crucial for explaining cell fate regulation during cancer pathogenesis and for developing precision treatments that target specific death pathways, as inhibition of one may trigger compensatory activation of another.

8. Clinical translation and therapy

Although preclinical evidence strongly supports targeting multiple RCD pathways in AML, clinical translation faces

Table I. Overview of therapeutic strategies targeting the RCD pathway in acute myeloid leukemia and their current clinical development status.

RCD type	Clinical development phase	Core strategy	Key points
Autophagy	Under investigation	Chloroquine/ hydroxychloroquine (inhibitors)	Complex effects (double-edged sword), requiring the development of more specific drugs.
Apoptosis	Approved	Venetoclax combination therapy	First-line treatment, with the current focus on overcoming drug resistance.
Pyroptosis	Preclinical/indirect induction	DPP8/9 inhibitor (in development)	Existing drugs can indirectly induce it, while specialized drugs have not yet entered clinical trials.
Necroptosis	Preclinical	RIPK1 activator (in development)	The investigational drug has not yet entered clinical trials; attention should be paid to its inflammatory toxicity.
Ferroptosis	Preclinical/indirect induction	GPX4 inhibitor (in development)	Targeting ferroptosis holds synergistic potential with multiple therapies and is a hot topic in research.
Cuproptosis	Early exploration	Disulfiram, electrochloral	Novel applications for existing drugs and novel ion carriers hold untapped potential.

DPP, dipeptidyl peptidase; GPX4, glutathione peroxidase 4; RCD, regulated cell death; RIPK1, receptor interacting serine/threonine kinase 1.

challenges due to variable patient responses (18). The most successful approach to date focuses on apoptosis, where the combination of the BCL-2 inhibitor venetoclax and hypomethylating agents has improved outcomes for elderly patients with AML or those ineligible for intensive chemotherapy. This strategy has been validated in phase III trials and has received regulatory approval, providing an effective means to overcome apoptosis escape (204). Current research is focused on overcoming venetoclax resistance, particularly by targeting complementary anti-apoptotic proteins such as MCL-1 or by combining it with other targeted therapies, such as FLT3 inhibitors. Several clinical trials are actively exploring these approaches (204,211,212).

By contrast, direct modulation of other RCD pathways, such as autophagy, necroptosis, pyroptosis and ferroptosis, is still in its early stages. Current clinical evidence primarily comes from observations where these death pathways are incidentally induced by conventional chemotherapies or targeted therapies. Targeting autophagy has been particularly challenging due to its context-dependent dual role, with non-specific inhibitors such as chloroquine showing limited efficacy, highlighting the need for more precise agents (213). For example, hypomethylating agents promote GSDME-mediated pyroptosis, while the p53 reactivator APR-246 induces ferroptosis, suggesting that the partial therapeutic efficacy of these agents may stem from non-apoptotic death mechanisms (14,158). However, first-in-class drugs designed to activate these pathways, such as DPP8/9 inhibitors for pyroptosis, RIPK1 activators for necroptosis and GPX4 inhibitors for ferroptosis, have yet to enter clinical trials for AML, highlighting a translational gap and the need for further research (13,103,159).

The copper ionophore disulfiram has been used for decades with sporadic anticancer activity, while its systematic evaluation in AML is still confined to an early-stage trial, highlighting a significant translational challenge for the cuproptosis pathway (214). The novel copper ionophore elesclomol is currently under early-stage investigation for solid tumors, and its potential to target mitochondria-rich LSCs in AML remains a hypothesis awaiting clinical validation (188).

Advancing this field requires overcoming several key challenges: The lack of reliable biomarkers for predicting treatment response and enabling precise patient stratification; managing the complex and often severe immune-related toxicities triggered by inflammatory cell death; the biological complexity and potential for overlapping toxicities when designing combination therapies to exploit synergistic effects across pathways; and the difficulty in creating targeted delivery systems that enhance efficacy while minimizing off-target effects. In summary, translation of mechanistic insights into clinical applications remains a dynamic frontier. The success of venetoclax demonstrates the potential of targeting cell death pathways. Future efforts should focus on translating insights from other RCD pathways into safe and effective clinical strategies, overcoming resistance and improving AML outcomes by expanding the therapeutic arsenal. The clinical development targeting the RCD pathway in AML is summarized in Table I (13,14,103,158,159,188,204,211-214).

9. Conclusion and prospects

AML is a highly aggressive hematologic malignancy in adults, characterized by a high recurrence rate and treatment resistance, both of which threaten patient survival (215). Despite advancements in molecular typing and targeted therapies that have improved the prognosis of some subtypes, the mechanisms driving AML heterogeneity and its microenvironmental interactions remain poorly understood (215). The limitations of chemotherapy and hematopoietic stem cell

transplantation have prompted researchers to explore novel strategies targeting programmed cell death. These approaches aim to enhance treatment efficacy while reducing damage to the normal hematopoietic system, either by selectively inducing LSC clearance or remodeling the bone marrow immune microenvironment. Studies have shown that regulation of cell death processes, including autophagy, apoptosis, necroptosis, pyroptosis, ferroptosis and cuproptosis, can successfully target drug-resistant clones (17,216,217). Notably, autophagy can exhibit a context-dependent dual role in this process. In LSCs, autophagy helps maintain chemoresistance through homeostatic functions; however, its overactivation may trigger type II programmed death, eliminating metabolically compromised cells (53). The BCL-2/MCL-1 balance in the apoptotic pathway is disrupted in drug-resistant clones, and BH3 mimics can alter mitochondrial apoptotic thresholds, thereby overcoming anti-apoptotic defenses. In the AML microenvironment, the RIPK1/RIPK3/MLKL necroptosis cascade is suppressed; however, its activation can bypass apoptosis resistance and induce inflammatory cell death. Pyroptosis-induced pore formation by GSDM family proteins and activation of inflammatory vesicles result in a dual mechanism that eliminates leukemia cells and reshapes the immunosuppressive microenvironment. Ferroptosis regulates lipid peroxidation via the GPX4/acyl-CoA synthetase long chain family member 4 axis, and targeting of GSH metabolism selectively eliminates resistant subpopulations that are dependent on antioxidant defenses. The emerging cuproptosis mechanism induces proteotoxic stress via FDX1-mediated copper ion overload, providing a novel strategy to target recalcitrant LSCs with abnormal mitochondrial metabolism. These RCD processes form a networked system of spatiotemporal regulation. A combinatorial intervention targeting multiple nodes can synergistically overcome the death-resistance barrier of leukemia cells, offering a multidimensional approach to address therapeutic challenges posed by AML clonal evolution and microenvironmental sheltering. Combination therapies targeting RCD are being clinically validated, but their long-term effects on clonal evolution, immune homeostasis and metabolic reprogramming remain to be fully explored. Future research should investigate the synergistic impact of different RCD modalities on AML stem cell maintenance, chemoresistance and microenvironmental remodeling in order to enable the development of personalized therapies that precisely target death pathways.

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Availability of data and materials

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Authors' contributions

RJ, HC and XY contributed to the conception of the review, conducted the literature search and screening, and wrote the original manuscript. LY, YG, CF, XH and GZ assisted with literature search, analysis of the published data and proofreading of the drafts. ZS, as the corresponding author, contributed to the design of the review framework, provided critical revisions for important intellectual content, and supervised the entire project. RJ and ZS confirm the accuracy and comprehensive nature of the literature review presented in this manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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