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Review Article

Cuproptosis: A Review on Mechanisms, Role in Solid and Hematological Tumors, and Association with Viral Infections

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Abstract. Cuproptosis is a distinct modality of regulated cell death precipitated by an overload of intracellular copper, critically dependent on mitochondrial respiration. The underlying mechanism involves the direct interaction of copper ions with lipoylated components integral to the mitochondrial tricarboxylic acid (TCA) cycle. This binding event triggers the aggregation of these proteins, induces significant proteotoxic stress, and leads to the depletion of essential iron-sulfur cluster proteins, culminating in cell demise. Given that copper homeostasis is frequently dysregulated within cancer cells, rendering them potentially more susceptible to copper-induced toxicity, cuproptosis has rapidly become a focal point of oncological research. This systematic review meticulously analyzes and synthesizes findings from a curated collection of 45 research articles. It aims to provide a comprehensive description of the molecular intricacies of cuproptosis, explore its documented associations with a spectrum of solid tumors (including gastric, lung, liver, neuroblastoma, and ovarian cancers) and lymphoma, and examine its emerging connections with viral infections like COVID-19 and pseudorabies virus. The review elaborates on the reported prognostic significance of cuproptosis-related genes and associated pathways across various malignancies. Furthermore, it details the burgeoning therapeutic strategies designed to harness cuproptosis, encompassing the application of copper ionophores, the development of sophisticated nanomedicine platforms, and synergistic approaches that combine cuproptosis induction with immunotherapy, chemotherapy, or sonodynamic therapy. The potential clinical utility of cuproptosis-associated biomarkers for predicting patient prognosis and therapeutic response is discussed based on the evidence presented in the reviewed literature.

Keywords: Cuproptosis; Solid tumors; Lymphoma.

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Introduction. Regulated cell death (RCD) represents a collection of genetically encoded, tightly controlled cellular suicide programs essential for multicellular life. These processes are fundamental for embryonic development, tissue homeostasis, and the elimination of damaged, infected, or superfluous cells. Consequently, dysregulation of RCD pathways is intrinsically linked to the pathogenesis of numerous human diseases, with cancer being a prominent example where evasion of cell death is a recognized hallmark.[1] Historically, apoptosis was the most extensively characterized form of RCD. However, research over the past two decades has unveiled a richer tapestry of cell death modalities, including necroptosis, pyroptosis, and ferroptosis, each distinguished by unique molecular triggers, executioner mechanisms, and physiological outcomes.[2]

Copper (Cu) is an essential trace element necessary for the proper functioning of various metabolic enzymes involved in numerous critical physiological processes. These include mitochondrial energy production, neurotransmitter and tyrosine metabolism, maintenance of redox balance, and extracellular matrix remodeling. Maintaining systemic copper levels within a narrow optimal range is crucial to prevent either copper deficiency or toxicity.[3-4]

The absorption of dietary copper primarily takes place in the duodenum and small intestine through the copper transport protein 1 (CTR1). The absorption process involves metalloreductases such as STEAP (six-transmembrane epithelial antigen of the prostate) and DCYTB (duodenal cytochrome b), which convert divalent copper (Cu2+) into monovalent copper (Cu+), the ionic form transported by CTR1. After absorption, copper enters the bloodstream, bound to proteins like albumin, transcuprein, histidines, and macroglobulins, and is transported to the liver. Hepatocytes in the liver also utilize CTR1 to facilitate copper uptake. Inside the hepatocytes, copper is either distributed to specific enzymes through specialized chaperone proteins such as ATOX1, CCS, and COX17 or stored by binding to metallothionein (MT).[5-8]

The liver plays a critical role in regulating systemic copper balance by secreting excess copper into bile for elimination through fecal excretion, the primary pathway for removing copper from the body. Other elimination pathways, such as urine, sweat, and menstruation, contribute minimally to copper loss. Copper homeostasis is dynamically maintained through adjustments in intestinal copper absorption and biliary excretion in response to fluctuations in dietary copper intake.

At the cellular level, copper homeostasis involves a complex and precise regulation network consisting of copper transporters, chaperones, and enzymes. The primary cellular copper transporter, CTR1, adjusts its expression according to cellular copper levels—upregulated during copper deficiency and downregulated during copper overload—to regulate copper uptake effectively.

Within cells, copper trafficking and distribution involve specific copper chaperones:

- ATOX1 delivers copper to copper-transporting ATPases (ATP7A and ATP7B), enabling copper incorporation into critical enzymes like ceruloplasmin, tyrosinase, and lysyl oxidase.
- CCS (copper chaperone for superoxide dismutase) transfers copper to superoxide dismutase 1 (SOD1), which is essential for neutralizing reactive oxygen species and maintaining oxidative balance in the cytoplasm and mitochondria.
- COX17 transports copper into the mitochondria, delivering it to mitochondrial chaperones SCO1 and COX11 for assembly into cytochrome c oxidase, a crucial enzyme for mitochondrial oxidative phosphorylation and energy production.

Disruptions or mutations in these copper transporters or chaperone proteins can severely impact copper metabolism, leading to developmental disorders, mitochondrial dysfunction, oxidative stress, and various copper-related diseases.[9-12]

In 2022, a novel form of copper-induced RCD, termed "cuproptosis," was described. This pathway was shown to be mechanistically distinct from previously known forms of cell death, crucially dependent on mitochondrial respiration, and initiated by the direct binding of copper to lipoylated mitochondrial proteins.[3] This discovery opened a new avenue of investigation, particularly relevant to cancer biology, as many cancer cells exhibit altered copper metabolism, often characterized by increased copper uptake and accumulation, potentially creating a specific vulnerability.[3,5] This differential copper handling between normal and malignant cells suggests a potential therapeutic window for selectively targeting cancer cells through the induction of cuproptosis.

This review aims to consolidate and analyze the current understanding of cuproptosis, drawing exclusively from the available scientific publications up to April 2025. The specific objectives are to: (1) describe the reported molecular mechanisms governing cuproptosis; (2) investigate the documented associations between cuproptosis and various solid tumors, focusing on its relevance for prognosis and therapy; (3) examine the reported relationship between cuproptosis and lymphoma; (4) review the described connections

between cuproptosis and viral infections; and (5) summarize the therapeutic strategies reported in the literature that aim to modulate cuproptosis for cancer treatment. By synthesizing these findings, this review seeks to provide an organized and comprehensive overview of the state of cuproptosis research as represented in the selected articles, highlighting potential clinical implications and areas warranting further investigation.

Mechanism of Cuproptosis. The reviewed literature characterizes cuproptosis as a unique cell death pathway initiated by an excess of intracellular copper, with a defining dependence on mitochondrial respiration and a direct molecular interaction with specific mitochondrial proteins.[3] The process hinges on protein lipoylation, a relatively rare post-translational modification where lipoic acid is covalently attached to specific lysine residues of mitochondrial enzymes involved primarily in oxidative metabolism. The central initiating event reported is the binding of excess intracellular copper, potentially facilitated by reduction from Cu2+ to the more reactive Cu+ state, to the lipoyl moieties of key TCA cycle enzymes.[3] Among these, dihydrolipoamide S-acetyltransferase (DLAT), a component of the pyruvate dehydrogenase (PDH) complex, and other lipoylated proteins involved in α-ketoglutarate metabolism are highlighted as primary targets.[3]

This copper-protein interaction is reported to cause the abnormal oligomerization and aggregation of these lipoylated proteins within the mitochondrial matrix. This aggregation event is not merely structural; it precipitates a cascade of detrimental downstream consequences. A key reported outcome is the destabilization and subsequent loss of iron-sulfur (Fe-S) cluster-containing proteins, which are vital for numerous mitochondrial functions, including electron transport and metabolic catalysis.[2] The combined effect of lipoylated protein aggregation and Fe-S cluster protein loss results in profound proteotoxic stress and metabolic catastrophe within the mitochondria, ultimately leading to cell death (**Figure 1**).[2,13]

Several key molecular players regulating sensitivity to cuproptosis have been identified in the reviewed articles. Ferredoxin 1 (FDX1), a mitochondrial reductase, acts upstream and is essential for cuproptosis induction, possibly by reducing copper to its more toxic Cu+ form, thereby facilitating its interaction with lipoylated targets.[13] Consequently, cells lacking FDX1 exhibit resistance to this form of cell death. Similarly, enzymes involved in the biosynthesis of lipoic acid, such as lipoic acid synthetase (LIAS), are critical, and their absence also confers resistance.[13,16] Conversely, proteins involved in copper transport and buffering significantly influence cuproptosis sensitivity. The copper chaperone ATOX1, for instance, was reported to modulate intracellular copper transport and influence cuproptosis sensitivity in the context of lymphoma cell proliferation.[17,18] Metallothioneins, cysteine-rich proteins known for their ability to bind and sequester heavy metals, including copper, act as protective factors. One study demonstrated that metallothionein could mitigate doxorubicin-induced cardiomyopathy, a condition associated with mitochondrial dysfunction, specifically by reducing cuproptosis (**Figure 1**).[14]

The cellular environment also plays a regulatory role. Hypoxia-inducible factor-1α (HIF-1α), a master regulator of cellular responses to low oxygen, was identified as a driver of cancer cell resistance to cuproptosis.[19] This finding suggests that the tumor microenvironment, particularly oxygen availability, can significantly impact a cell's susceptibility to this death pathway. Furthermore, mitochondrial integrity and function are central, as evidenced by studies analyzing mitochondrial alterations and depolarization signatures in cancers like hepatocellular carcinoma[20] and non-small cell lung cancer,[21] linking these features to cuproptosis-related genes and prognosis.

While cuproptosis possesses a distinct mechanism, evidence from the reviewed literature suggests potential interplay with other cell death pathways. The redox-active protein High-Mobility Group Box 1 (HMGB1), known for its role in inflammation and various forms of cell death, is discussed within the broader context of redox signaling and cell death, potentially intersecting with the oxidative and proteotoxic stress characteristic of cuproptosis.[2] Moreover, certain therapeutic interventions appear capable of activating multiple death programs simultaneously. For example, the drug disulfiram was reported to induce cell death in endometrioid epithelial ovarian cancer cells through mechanisms involving both apoptosis and cuproptosis.[22] This observation is mirrored in the design of novel nanotherapeutic strategies explicitly aimed at co-inducing cuproptosis alongside ferroptosis[23] or apoptosis,[24,25] suggesting that leveraging multiple pathways might offer synergistic advantages in cancer therapy.

Cuproptosis in Solid Tumors. The relationship between cuproptosis and the biology of solid tumors has been a major focus of investigation within the reviewed articles, driven by the frequent observation of altered copper metabolism in cancer cells and the potential for therapeutic exploitation of this phenomenon. Research has spanned various aspects, from identifying prognostic markers to developing novel therapeutic strategies across a diverse range of solid malignancies.

Prognostic Significance and Biomarker Development. A recurrent theme across numerous studies is the exploration of cuproptosis-related genes and associated non-coding RNAs, particularly long non-coding RNAs

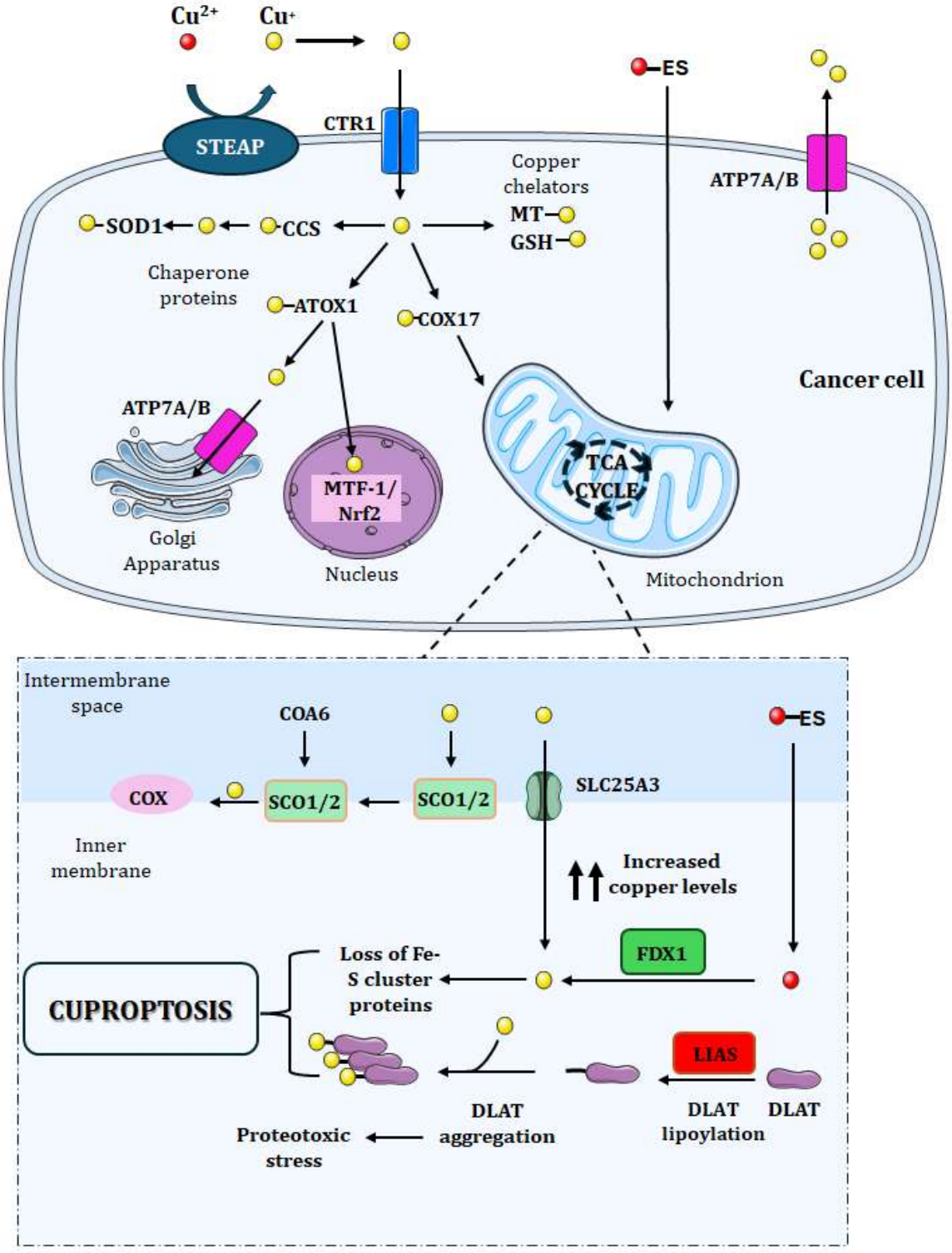

Figure 1. The figure illustrates the cellular mechanism of cuproptosis, a copper-induced cell death pathway. Copper enters cells via CTR1, is reduced by STEAP, and is trafficked by chaperones like ATOX1, CCS, and COX17 to destinations including the mitochondria. Excess Cu^{+} binds to lipoylated DLAT in the mitochondria, causing protein aggregation, Fe-S cluster loss, and proteotoxic stress. Elesclomol enhances this process, while MT, GSH, and transcription factors like Nrf2 help regulate copper levels. Cuproptosis is especially relevant in cancer cell metabolism. **ES** Elesclomol; **STEAP** Six-transmembrane epithelial antigen of the prostate; **CTR1** Copper transporter 1; **CCS** Copper chaperone for superoxide dismutase; **ATOX1** Antioxidant 1 copper chaperone; **COX17** Cytochrome c oxidase copper chaperone; **SOD1** Superoxide dismutase 1; **MT** Metallothioneins; **GSH** Glutathione; **COA6** Cytochrome c oxidase assembly factor 6; **SCO1/2** Synthesis of cytochrome c oxidase; **COX** Cytochrome c oxidase; **MTF-1** Metal Regulatory Transcription Factor 1; **Nrf2** Nuclear factor erythroid 2-related factor 2; **SLC25A3** Solute carrier family 25 member 3; **ATP7A/B** ATPase copper transporting alpha/beta.

(lncRNAs), as potential biomarkers for predicting patient outcomes in solid tumors. Pan-cancer analyses have systematically profiled the expression of cuproptosis gene sets, revealing widespread dysregulation across different cancer types and suggesting a fundamental role for this pathway in general cancer biology.[26] Building on

this, researchers have developed and validated prognostic signatures based on the expression levels of specific cuproptosis-associated genes or lncRNAs in various individual cancer types.

For instance, in gastric cancer, studies have assessed the prognostic value of genes associated with disulfidptosis (a related form of cell death involving disulfide stress, potentially overlapping with copper-induced redox stress)[27] and directly investigated the clinical significance and potential application of cuproptosis-related genes.[28] Furthermore, the prognostic marker Nucleophosmin 1 (NPM1) in gastrointestinal cancers has been linked mechanistically to both m6A RNA modification and cuproptosis pathways, suggesting complex regulatory interactions.[29]

Lung cancer, particularly non-small cell lung cancer (NSCLC) and lung adenocarcinoma (LUAD), has been a frequent subject of such investigations. Several independent research groups have reported the development of prognostic models based on cuproptosis-related lncRNA signatures[22,30,31] or gene expression patterns.[32] These signatures were often found to correlate not only with patient survival but also with characteristics of the tumor microenvironment, such as the infiltration levels of different immune cell types,[32] and potentially with sensitivity to treatments like radiotherapy.[21] An integrative analysis further strengthened this link by associating cuproptosis-related mitochondrial depolarization genes with prognosis in NSCLC.[21] Zhang and colleagues also specifically highlighted the prognostic value and immunological function relevance of cuproptosis-related genes in LUAD.[22]

Similar prognostic investigations have been conducted in other solid tumors. In neuroblastoma, distinct cuproptosis-related molecular subtypes and gene signatures have been identified and associated with the tumor's immunophenotype and patient prognosis.[33] Multi-omics approaches in neuroblastoma have explored how cell death pathways, potentially including cuproptosis, are regulated by other cellular processes like fatty acid metabolism,[23] while single-cell RNA sequencing has provided insights into the tumor microenvironment and cell death-related therapeutic targets within this malignancy.[34] For pancreatic adenocarcinoma, a prognostic model based on cuproptosis-related lncRNAs was proposed, which also aimed to predict the effectiveness of immunotherapy.[35] In colon adenocarcinoma, a novel prognostic signature derived from cuproptosis-related lncRNAs was developed, with reported predictive value for patient response to both immunotherapy and chemotherapy.[36] The broader relevance of regulated cell death pathways, implicitly including cuproptosis, has also been reviewed in the context of head and neck squamous cell carcinoma (HNSCC) development.[1] Even in hematological malignancies like acute myeloid leukemia (AML), comprehensive analyses have explored the predictive value of cuproptosis-associated lncRNAs and their related competing endogenous RNA (ceRNA) networks.[37]

The consistent finding across these diverse solid tumor types that the expression patterns of cuproptosis pathway components correlate with clinical outcomes strongly suggests that this cell death mechanism is fundamentally intertwined with tumor progression and patient survival. This body of work provides a solid foundation for the further development and validation of cuproptosis-related biomarkers for clinical applications in risk stratification and treatment guidance.

Therapeutic Strategies Targeting Cuproptosis in Solid tumors. The potential to selectively eliminate cancer cells by inducing cuproptosis, leveraging their often-altered copper metabolism, has spurred considerable effort in developing therapeutic strategies, as reflected in the reviewed literature. These strategies range from utilizing existing compounds to designing highly sophisticated nanomedicine approaches and combination therapies.

One direct approach involves the use of copper ionophores, molecules that facilitate the transport of copper ions across cellular membranes, thereby increasing intracellular copper concentrations to potentially toxic levels. Elesclomol is a prominent example of such an agent, known to transport copper into mitochondria and effectively trigger cuproptosis.[3,38] A review by Tarin et al. details the discovery, mechanism of action targeting mitochondria, and potential applications of Elesclomol.[39] Drug repositioning offers another avenue; for instance, Disulfiram, an established drug used for treating alcoholism, has been investigated for anti-cancer activity and was reported to induce cell death in endometrioid epithelial ovarian cancer cells through both apoptosis and cuproptosis pathways.[22]

Nanotechnology has emerged as a powerful tool for developing targeted cuproptosis-inducing therapies. Numerous studies report the design and preclinical evaluation of various nanoplatforms engineered to deliver copper or cuproptosis-inducing agents specifically to tumor sites, often incorporating features for controlled release or activation. Examples from the reviewed articles include: Elesclomol encapsulated within copper oxide nanoplatforms;[40] near-infrared light-activatable copper nanoplatforms designed to synergize with chemotherapy prodrugs like 5-azacytidine;[40] metal-phenolic networks tailored to eliminate hypoxic tumor cells by inducing oxidative and proteotoxic stress;[41] cystine-modified lignin-copper coordination nanocarriers intended to enhance tyrosine kinase inhibition via cuproptosis;[42] p-n heterojunction sonosensitizers;[16] dual-responsive biomimetic "cyto-

nanos" for precision mitochondrial intervention;[43] bioactive layered double hydroxides;[41] bimetallic iron-copper metal-organic frameworks (MOFs) designed as "cellular Trojan horses";[23] tumor microenvironment-activated immunomodulatory nanosheets loaded with copper(II) and the chemotherapeutic 5-FU;[25] copper-coordinated covalent organic frameworks generating Fenton-like effects;[44] and intelligent cell-derived nanorobots.[45] These diverse nanostrategies often aim to overcome limitations of systemic copper administration by enhancing tumor accumulation and minimizing off-target toxicity, sometimes employing triggers like tumor acidity, hypoxia, or external stimuli (light, ultrasound) for activation.

A significant trend in developing cuproptosis-based therapies is the combination with other treatment modalities to achieve synergistic effects and overcome potential resistance. Synergies have been actively explored with immunotherapy, based on the premise that inducing cuproptosis, particularly if it leads to immunogenic cell death (ICD), can stimulate anti-tumor immune responses. Several nanoplatforms are explicitly designed not only to induce cuproptosis but also to modulate the tumor immune microenvironment or elicit ICD.[16,24,38,41,44] Combination with conventional chemotherapy is another approach, exemplified by nanocarriers co-delivering copper and agents like 5-azacytidine prodrug[40] or 5-FU.[25] Sonodynamic therapy (SDT), which uses ultrasound to activate sonosensitizers and generate cytotoxic reactive oxygen species, has also been combined with cuproptosis induction. Several nanoplatforms described function as sonosensitizers that, upon ultrasound irradiation, trigger both SDT effects and cuproptosis, leading to enhanced tumor killing and potentially improved immune responses.[16,41,43] Furthermore, recognizing the complexity of cell death regulation, strategies are being developed to simultaneously trigger multiple RCD pathways, such as combining cuproptosis with ferroptosis[23] or apoptosis,[22,25] aiming to maximize cancer cell killing and circumvent resistance mechanisms specific to a single pathway.

Understanding and overcoming resistance to cuproptosis induction is critical for successful therapeutic translation. Factors conferring resistance have been identified, including the protective role of metal-binding proteins like metallothioneins[14] and the influence of the tumor microenvironment, particularly hypoxia, which can activate HIF-1α and subsequently drive resistance to cuproptosis.[19] Developing strategies to counteract these resistance mechanisms will be essential for the clinical success of cuproptosis-targeting therapies.

Cuproptosis, Lymphoma and Therapeutic Strategies. The role of cuproptosis has also been specifically investigated in the context of hematological malignancies, particularly lymphomas like Diffuse Large B-Cell Lymphoma (DLBCL) and related conditions such as Multiple Myeloma (MM),[44-50] acute lymphoblastic leukemia,[51] and myeloid neoplasms,[52-66] as documented in the reviewed articles. These studies explore the pathway's relevance for prognosis, its mechanistic involvement in lymphomagenesis, and its potential as a therapeutic target.

Similar to the findings in solid tumors, several studies focused on the prognostic significance of cuproptosis-related molecular signatures in DLBCL. Researchers have developed and validated prognostic models based on the expression levels of specific cuproptosis-associated genes[67-68] or cuproptosis-related lncRNAs. These models aim to improve risk stratification for DLBCL patients beyond traditional clinical parameters. Further refining this approach, one study developed a combined prognostic model incorporating markers of both cuproptosis and immunogenic cell death, suggesting potential interplay between these processes in determining DLBCL outcomes.[69] The consistent ability of these signatures to predict prognosis underscores the intrinsic involvement of the cuproptosis pathway in the pathobiology of DLBCL.

Mechanistic investigations have begun to shed light on how cuproptosis pathways might directly influence lymphoma cell behavior. A key finding reported by Xie et al. implicates the cuproptosis-related gene ATOX1, which encodes a copper chaperone protein, in promoting DLBCL proliferation.[17] This study suggested that ATOX1 achieves this by modulating intracellular copper transport and potentially influencing downstream signaling pathways like MAPK signaling.[17] This provides a direct link between the cellular machinery regulating copper homeostasis, which is central to cuproptosis, and the control of lymphoma cell growth. The specific mechanisms and therapeutic potential of cuproptosis in lymphoma have also been the subject of focused reviews,[13] and broader narrative reviews on novel therapeutic approaches in DLBCL acknowledge the potential relevance of targeting tumor metabolism, including copper pathways.[24]

Building on these prognostic and mechanistic insights, therapeutic strategies targeting cuproptosis are being explored for lymphomas and related B-cell malignancies. For instance, Wang et al. described the development of UiO-66 metal-organic framework (MOF)-based nano-sonosensitizers designed for ultrasound-activated immunotherapy against B-cell lymphoma.[70] While the precise contribution of cuproptosis needs further clarification, such approaches targeting cellular stress pathways, potentially including copper-induced stress, represent innovative therapeutic directions. In the context of Multiple Myeloma (MM), another B-cell malignancy, Wang and colleagues reported an intriguing

finding related to drug resistance.[16] They found that the protein MUC20, whose expression was regulated by extrachromosomal circular DNA, could modulate cuproptosis sensitivity and thereby attenuate resistance to proteasome inhibitors, a standard class of drugs used in MM treatment.[16] This suggests that manipulating cuproptosis sensitivity could represent a novel strategy to overcome or circumvent acquired drug resistance in MM and potentially other lymphomas. All the abovementioned studies regarding the interplay between cuproptosis and lymphoproliferative disorders are summarized in **Table 1**.

Collectively, the reviewed literature indicates that cuproptosis is a relevant biological process in lymphoma. Molecular signatures related to this pathway hold prognostic value in DLBCL, specific pathway components like ATOX1 are implicated in regulating lymphoma cell proliferation, and targeting copper metabolism or inducing cuproptosis is emerging as a potential therapeutic avenue, including strategies aimed at tackling drug resistance in related malignancies.

Cuproptosis and Viral Infections. The intersection between cuproptosis and viral infections represents a relatively nascent but potentially significant area of investigation, with a few studies in the reviewed set providing initial insights into these interactions.

Research related to the COVID-19 pandemic explored potential links between cuproptosis and the host response to SARS-CoV-2 infection. Luo et al. employed machine learning techniques to identify distinct molecular subtypes of COVID-19 based on the expression of cuproptosis-related genes and developed a novel predictive model for disease outcomes.[71] This suggests that alterations in cuproptosis pathways might correlate with disease severity or specific host response patterns during SARS-CoV-2 infection. Another study focused on patients with non-small cell lung cancer (NSCLC) who were co-infected with COVID-19.[49] Li and colleagues investigated the prognostic impact of cuproptosis-associated lncRNAs in this specific patient population, indicating a potential complex interplay between the underlying cancer, the viral infection, and the regulation of this particular cell death pathway.[37] These findings hint that cuproptosis might be involved in the systemic metabolic and inflammatory disturbances characteristic of severe COVID-19, or that the virus itself might modulate cellular copper handling or mitochondrial function.

Evidence for viral manipulation of host cell death pathways also comes from studies on other viruses. Cao et al. utilized transcriptomic analysis to investigate how Pseudorabies Virus (PRV) infection affects cell death regulation in neuroblastoma cells.[15] Their findings indicated that PRV infection leads to a suppression of host cell death pathways, likely as a viral strategy to promote its own replication and survival within the host cell.[15] While cuproptosis was not explicitly confirmed as one of the suppressed pathways in the provided summary, this study highlights the general principle that viruses can evolve mechanisms to counteract host cell death programs. Although direct studies linking cuproptosis and Epstein-Barr Virus (EBV) were not present in the reviewed literature, EBV is known to manipulate host cell metabolism, including mitochondrial functions, to support latent infection and B-cell transformation. Therefore, investigating potential intersections between EBV infection and cuproptosis pathways via shared mitochondrial metabolic pathways could be a relevant future direction.

In summary, the reviewed articles provide preliminary but intriguing evidence suggesting that cuproptosis may play a role in the context of viral infections, potentially influencing host responses (as suggested for COVID-19) or being targeted by viruses to evade host defenses (as suggested for PRV). Further research is clearly warranted to elucidate the specific mechanisms and functional significance of cuproptosis during various viral infections.

Discussion and Future Directions. This review underscores the rapid emergence of cuproptosis as a distinct and significant field within cell death research, possessing considerable relevance for oncology, hematology and potentially infectious diseases. Its unique mechanism, fundamentally linked to copper overload disrupting mitochondrial function through the aggregation of lipoylated proteins and subsequent proteotoxic stress,[13] sets it apart from apoptosis, necroptosis, and ferroptosis. This distinctiveness offers novel avenues for both understanding disease pathogenesis and developing targeted therapeutic interventions.

A major theme emerging from synthesized literature is the profound connection between cuproptosis pathways and cancer biology. The consistent identification of prognostic signatures based on cuproptosis-related genes and lncRNAs across a wide array of solid tumors-including breast,[35] gastrointestinal,[27,28,29,36] lung,[21,22,30-32] neuroblastoma,[23,33] and pancreatic[26]-as well as in lymphoma,[34,68,69] strongly supports the fundamental role of copper metabolism and this specific cell death modality in tumor progression and clinical outcome. These molecular signatures hold considerable promise as biomarkers for improved patient stratification, prediction of treatment response (to immunotherapy, chemotherapy, or radiotherapy),[31,36] and potentially guiding personalized medicine approaches, although rigorous prospective validation remains a critical next step.

The therapeutic potential of deliberately inducing cuproptosis in cancer cells is arguably the most dynamic

Table 1. This table lists key studies on cuproptosis in hematologic cancers, focusing on multiple myeloma (MM), AML, and DLBCL. Each entry includes a reference and a brief statement of the study's main findings.

Reference		Outcomes
Wang X et al., 2024 [16]	MM	Demonstrated that MUC20, via eccDNA regulation, sensitizes MM cells to proteasome inhibitors through cuproptosis modulation.
Xie J et al., 2024 [17]	MM	Found that ATOX1 boosts copper transport and MAPK signaling, promoting DLBCL proliferation and offering a therapeutic target.
Zhang B et al., 2023 [44]	MM	A prognostic gene signature linked to cuproptosis was identified, which stratifies multiple myeloma patient outcomes.
Wang H et al., 2023 [45]	MM	Developed a prognostic model for MM using cuproptosis-related genes, improving risk prediction and patient stratification.
Liu H et al., 2024 [46]	MM	Established a gene signature associated with immune suppression and prognosis in MM based on cuproptosis-related genes.
Chen Y et al., 2023 [47]	MM	Revealed that specific lncRNAs correlated with cuproptosis can predict MM patient prognosis.
Chen Y et al., 2025 [48]	MM	Showed that MAMDC2-AS1 activates cuproptosis mechanisms in resistant MM, suggesting a new therapeutic avenue.
Li T et al., 2023 [49]	MM	Correlated oxidative stress genes tied to cuproptosis with poor prognosis in MM, providing potential biomarkers.
Gao XH et al., 2025 [50]	MM	Identified prognostic markers among cuproptosis genes in MM, supporting personalized medicine approaches.
Zhang B et al., 2025 [51]	ALL	Developed a cuproptosis-based signature predicting immune heterogeneity and drug response in ALL.
Luo D et al., 2023 [52]	AML	Characterized AML immune microenvironment through cuproptosis gene analysis, aiding prognostic evaluation.
Li Y & Kan X, 2024 [53]	AML	Highlighted MTF1 and LIPT1 as novel prognostic indicators in AML, linked to cuproptosis activity.
Li P et al., 2022 [54]	AML	Built a lncRNA-based prognostic tool for AML, emphasizing the relevance of cuproptosis pathways.
Tao Y et al., 2023 [55]	AML	Identified AML subtypes through cuproptosis profiling and developed a corresponding prognostic model.
Wu M et al., 2024 [56]	AML	Created a prognosis model integrating ferroptosis and cuproptosis genes for enhanced AML outcome prediction.
Qin Y et al., 2024 [57]	AML	Applied machine learning to identify biomarkers for AML prognosis by integrating cell-death pathways.
Li H et al., 2024 [58]	MDS	Showed that xCT-GSH-GPX4 inhibition depletes GSH and enhances DSF/Cu-induced cuproptosis in MDS.
Chai Z et al., 2025 [59]	AML	Linked cuproptosis-associated lncRNAs with AML stemness and survival outcomes, indicating prognostic utility.
Song Y et al., 2024 [60]	AML	Found that MICAL1 contributes to AML progression and correlates with prognosis and immune infiltration.
Wang X et al., 2024 [61]	AML	Developed a stacked ML model predicting AML outcomes using cuproptosis-related genes.
Abulimiti M et al., 2024 [62]	AML	Validated the prognostic and therapeutic roles of copper-related gene dysregulation in AML patients.
Cao J et al., 2024 [63]	AML	Proposed a prognostic model for childhood AML incorporating cuproptosis genes and CNN3 expression.
Zhang T et al., 2023 [64]	AML	Demonstrated that cuproptosis-related lncRNAs can forecast prognosis in AML patients.
Zhu Y et al., 2023 [65]	AML	Developed a lncRNA signature predicting AML prognosis via cuproptosis-related gene expression.
Moison C et al., 2024 [66]	AML	SF3B1 mutations were identified as sensitizing factors to copper ionophores in AML, revealing a vulnerability.
Chen W et al., 2025 [67]	NHL	Showed FDX1 enhances PANoptosis in DLBCL via IRF3/IFN-β, especially under elesclomol treatment.
Bai X et al., 2024 [68]	NHL	Defined a lncRNA signature linked to cuproptosis that serves as a prognostic tool in DLBCL.
Zhang B et al., 2023 [69]	NHL	Built and validated a prognostic model for DLBCL based on cuproptosis-associated gene expression.
Wang Z et al., 2025 [70]	NHL	Presented a MOF-based nanomedicine for ultrasound-triggered immunotherapy in B-cell lymphoma targeting copper metabolism.

area highlighted in the reviewed literature. The strategies being explored are diverse, ranging from repurposing existing drugs like Disulfiram[22] and utilizing copper ionophores such as Elesclomol[38,39] to the rational design of sophisticated nanomedicine platforms.[16,23,25,38,40-43,68-70] These nanocarriers represent a significant advancement, offering potential solutions to challenges of systemic toxicity and enabling targeted delivery of copper or cuproptosis inducers to the tumor site, often incorporating stimuli-responsive release mechanisms. Furthermore, the emphasis on synergistic combinations-pairing cuproptosis induction with

immunotherapy,[16,24,38,41] chemotherapy,[25,40] sonodynamic therapy,[16,41,43] or even co-triggering other RCD pathways like ferroptosis[23]-reflects a sophisticated approach aimed at maximizing anti-cancer efficacy and overcoming the inherent heterogeneity and adaptability of tumors. However, translating these promising preclinical findings into effective clinical therapies will require overcoming significant hurdles, including optimizing delivery efficiency, ensuring acceptable safety profiles, and developing strategies to counteract intrinsic or acquired resistance mechanisms, such as those mediated by HIF-1α under hypoxia[19] or protective proteins like metallothioneins.[14] Buccarelli et al.[71] explore the combination of elesclomol with temozolomide, which enhances cytotoxicity in vitro and reduces tumor growth in vivo, suggesting a promising therapeutic strategy for glioblastoma.

The nascent exploration of links between cuproptosis and viral infections[15,30,72] opens another intriguing research frontier. Understanding the bidirectional interactions-how viral infections might perturb cellular copper homeostasis and mitochondrial function to modulate cuproptosis sensitivity, and conversely, how cuproptosis might contribute to antiviral host defense or viral pathogenesis and associated inflammation-could yield novel insights into infectious disease mechanisms and potentially new therapeutic targets. The hypothesis regarding a potential link with EBV, based on its known manipulation of mitochondrial metabolism, warrants investigation.

Despite the remarkable progress documented in these articles, several key areas necessitate further investigation. Firstly, a deeper mechanistic understanding is required, particularly regarding the precise downstream execution events following mitochondrial proteotoxic stress and Fe-S cluster loss, as well as the full spectrum of upstream regulatory inputs and crosstalk with other cellular pathways like autophagy. Secondly, the prognostic and predictive biomarkers identified primarily through bioinformatic analyses require stringent validation in large, independent, and prospectively collected patient cohorts, coupled with functional studies to confirm their mechanistic roles. Thirdly, the path to clinical translation for cuproptosis-inducing therapies requires careful navigation of challenges related to pharmacokinetics, biodistribution, long-term toxicity, and the development of robust strategies to monitor treatment response and manage resistance. Fourthly, recognizing the importance of context, future studies should delve deeper into how the role and regulation of cuproptosis vary depending on the specific cancer type, its genetic background, and the complexities of the tumor microenvironment. Finally, the potential involvement of cuproptosis in diseases beyond cancer and viral infections, such as neurodegenerative disorders, cardiovascular conditions (as hinted by the doxorubicin cardiomyopathy study),[14] or metabolic diseases where copper dyshomeostasis is implicated, remains largely uncharted territory ripe for exploration.

Conclusions. In conclusion, this review, based on the analysis of the available research articles, portrays cuproptosis as a distinct, copper-dependent mode of regulated cell death centered on mitochondrial dysfunction and proteotoxicity. The synthesized evidence strongly highlights its relevance as a prognostic factor in diverse malignancies, including numerous solid tumors and lymphomas, and underscores its potential as a novel therapeutic target in oncology. The development of innovative therapeutic strategies, particularly those employing nanomedicine for targeted delivery and synergistic combinations with other modalities like immunotherapy, reflects significant translational interest. Furthermore, emerging findings connecting cuproptosis to viral infections suggest broader physiological and pathological roles that warrant further investigation. Continued research dedicated to unraveling the intricate molecular mechanisms, validating clinical biomarkers, refining therapeutic approaches, and exploring the broader biological significance of cuproptosis holds substantial promise for advancing our fundamental understanding of cell death and potentially yielding new therapeutic paradigms for cancer and other human diseases.

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