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REVIEW

Research Progress on Cuproptosis in Cisplatin-Resistant Ovarian Cancer

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ABSTRACT: Ovarian cancer (OC) is the most lethal gynecologic malignancy. The current first-line treatment still relies primarily on cisplatin-based chemotherapy, yet cisplatin resistance strongly predicts poor patient prognosis. Cuproptosis is a newly identified cell death modality driven by copper overload and impaired mitochondrial respiration. This review outlines the core molecular mechanisms of cuproptosis and examines its complex association with cisplatin resistance in ovarian cancer. Their interplay involves shared transport systems. In cisplatin-resistant ovarian cancer cells, copper influx transporter Copper Transporter 1 (CTR1) downregulation and efflux transporter ATPase copper transporting alpha/beta polypeptide (ATP7A/B) upregulation reduce the intracellular cisplatin concentration and concurrently disrupts copper homeostasis. Furthermore, metabolic reprogramming in cisplatin-resistant cells—including elevated tricarboxylic acid (TCA) cycle activity as a survival adaptation—provides the metabolic basis for cuproptosis. Targeted induction of cuproptosis in ovarian cancer cells thus represents a promising strategy to reverse cisplatin resistance. Currently, copper ionophores that induce cuproptosis have emerged as a research hotspot for overcoming cisplatin resistance, though this strategy faces substantial challenges. Further insights into cuproptosis mechanisms and advances in nanomaterials will ultimately enable targeted cuproptosis induction in tumor cells. It potentially offers new and effective treatment options for patients who experience chemotherapy failure due to cisplatin resistance.

KEYWORDS: Cuproptosis; ovarian cancer; cisplatin resistance; copper transporter 1 (CTR1); ATPase copper transporting alpha/beta polypeptide (ATP7A/B)

1 Introduction

Ovarian cancer (OC) is the most lethal malignancy of the female reproductive system. More than 70% of patients are diagnosed at an advanced stage due to its insidious early symptoms and a lack of effective screening modalities. Globally, OC accounts for approximately 300,000 new cases annually, and it has the highest mortality rate among gynecological malignancies [1]. A large-scale study of 1049 advanced OC patients indicated that the 5-year survival rate remains below 50% [2]. Currently, the primary OC therapeutic regimen is platinum-based chemotherapy (e.g., cisplatin), yet greater than 70% of patients will eventually experience recurrence [3]. Most patients with recurrent disease eventually develop cisplatin resistance due to progressively shortened chemotherapy intervals. Moreover, a considerable proportion of patients initially sensitive to cisplatin also acquire resistance during subsequent treatment, resulting in disease progression [4].

Cisplatin resistance in OC is a multifactorial phenomenon driven by the aberrant activation of diverse molecular signaling pathways, cancer stem cell enrichments, and increased drug efflux, among other

factors [5,6]. Recurrence within 6 months of cisplatin treatment completion is clinically defined as platinum-resistant recurrence, and it is associated with an extremely poor prognosis [4]. Novel strategies for platinum-resistant OC have been continuously explored. These have included the implementation of antibody-drug conjugates and poly ADP ribose polymerase (PARP) inhibitors. However, the overall survival benefits remain marginal. Therefore, a deeper elucidation of the molecular mechanisms that underlie cisplatin resistance and the identification of effective strategies to circumvent it are paramount to improve the prognoses of OC patients.

Cuproptosis has been recently discovered, and it offers a completely new avenue to address cisplatin resistance in OC. It is a distinct form of regulated cell death (RCD), similar to apoptosis and ferroptosis. Cuproptosis is a novel RCD form that is mechanistically dependent on mitochondrial respiration and copper overload [7]. A recent study has suggested that the targeted induction of cuproptosis could enhance tumor cell sensitivity to cisplatin, providing a promising direction to overcome the challenge of platinum resistance in OC [8].

2 Cuproptosis

Copper (Cu) is an essential trace element that is indispensable for numerous physiological processes within the human body [9]. However, when intracellular copper homeostasis is disrupted, the excessive accumulation of copper ions (Cu^{+}, Cu^{2+}) triggers a recently discovered form of programmed cell death (PCD) termed cuproptosis [10].

2.1 Copper Homeostasis

The maintenance of intracellular copper homeostasis relies on a finely regulated network. Copper is absorbed in the intestine and then taken up into cells as cuprous ions (Cu^{+}) on the cell membrane via the CTR1 copper transporter (also known as solute carrier family 31 member 1(SLC31A1)) [11]. This copper is then utilized to synthesize various cuproenzymes, such as cytochrome c oxidase (CcO), which is essential for ATP production. Thus, the proper synthesis of cuproenzymes is a cornerstone of mitochondrial function maintenance [12]. Copper immediately binds upon cell entry to a series of copper chaperone proteins. This prevents excessive free radical generation and oxidative damage during intracellular trafficking. Copper is transported in the Cu^{+} form within the cytoplasm. Specifically, antioxidant 1 copper chaperone(ATOX1) delivers Cu^{+} to the Golgi apparatus, copper chaperone for superoxide dismutase (CCS) transports Cu^{+} to the cytoplasm and mitochondria to activate superoxide dismutase 1 (SOD1), and proteins, such as cytochrome c oxidase copper chaperone 17(COX17), deliver it into the mitochondria for cytochrome c oxidase assembly [13–15]. When the intracellular copper level becomes elevated, efflux mechanisms are activated. ATP7A translocates to the plasma membrane and facilitates copper excretion via exocytosis [16], where ATP7B, primarily expressed in the liver, mediates excess copper excretion into the bile. This ultimately leads to its elimination through the feces [17].

2.2 Core Targets and Signaling in Cuproptosis

Mitochondria are the cellular powerhouses, and they utilize copper as an indispensable cofactor in the function of various mitochondrial enzymes [18]. Copper enters the mitochondrial matrix for storage via the SLC25A3 carrier located on the inner mitochondrial membrane [19]. Copper homeostasis disruption within the mitochondria results in high Cu concentrations and compromises the mitochondrial membrane integrity by increasing the membrane permeability and impairing the membrane potential. This process

triggers mitochondrial dysfunction and subsequent cell death [9]. Ferredoxin 1 (FDX1) plays a pivotal role in this intricate process [7].

FDX1 functions as a copper reductase. It converts the less toxic divalent copper ion (Cu^{2+}) into the highly cytotoxic monovalent form of Cu^{+}. This is a critical step that initiates a downstream cascade of toxicity [20]. Furthermore, FDX1 has been established as an upstream regulatory gene for protein lipoylation. FDX1 acts as an electron donor that directly or indirectly participates in the biosynthesis of lipoic acid and the subsequent lipoylation of target proteins [21]. Crucially, protein lipoylation is a prerequisite for the binding of Cu^{+} to tricarboxylic acid (TCA) cycle proteins. Conversely, FDX1 deficiency eliminates protein lipoylation, and the TCA cycle proteins become ineffective at binding Cu^{+} [7]. This finding underscores that the lipoyl moiety is an essential structural foundation of Cu^{+} binding. This conclusion confirms the necessity of FDX1 for the execution of cuproptosis, and it acts as an upstream lipoylation regulator. Thus, FDX1 is both the "molecular switch" that initiates cuproptosis and the "core hub" that links copper to downstream death signaling.

Lipoic acid synthase (LIAS) is the key rate-limiting enzyme that catalyzes the *de novo* synthesis of lipoic acid. It is responsible for covalently attaching the lipoic acid molecule to specific enzymes within the mitochondrial respiratory chain complexes and the TCA cycle. Under copper overload conditions, excessive Cu^{+} directly binds to these critical lipoylated proteins during the TCA cycle (e.g., dihydrolipoamide S-Acetyltransferase (DLAT)). This leads to their abnormal oligomerization and functional loss. This cascade triggers severe mitochondrial proteotoxic stress that includes the destruction of iron-sulfur cluster proteins, ultimately inducing irreversible cell death [7]. Additionally, the metal regulatory transcription factor 1(MTF1)metal-regulatory transcription factor can induce the expression of other genes involved in metal homeostasis. Recent studies have shown that MTF1 expression modulates copper homeostasis, thereby indirectly affecting sensitivity to cuproptosis [22,23]. This evidence highlights the close involvement of the cuproptosis pathway with the cellular metal homeostasis signaling network.

2.3 Formation of the Copper-Lipoylated Protein Complex

The four key rate-limiting enzymes that are essential for maintaining the normal operation of the TCA cycle are dihydrolipoamide branched-chain transacylase E2 (DBT), glycine cleavage system protein H (GCSH), dihydrolipoamide S-succinyltransferase (DLST), and dihydrolipoamide S-acetyltransferase (DLAT). These all undergo lipoylation modification [24]. Lipoylation is critical for the proper function of these enzymes, as it enables them to efficiently transfer acyl groups during metabolism. These lipoylated proteins also serve as direct molecular targets for copper ions. As illustrated in Fig. 1, Cu^{+} can bind directly to the lipoyl groups of these lipoylated proteins. This binding directly interferes with the normal conformation and catalytic activity of proteins such as DLAT, leading to TCA cycle inhibition and a consequent cellular energy metabolism collapse. Simultaneously, lipoylated proteins that bind to Cu^{+} undergo oligomerization and aggregation. This process results in insoluble toxic complex accumulations within the mitochondria. Subsequently, severe mitochondrial proteotoxic stress ensues, and this causes irreversible damage to the mitochondrial membrane and inhibits pyruvate dehydrogenase complex (PDHC) activity. Ultimately, the entire TCA cycle metabolism is disrupted, leading to a loss of the cellular respiratory function [7,25]. Furthermore, iron-sulfur (Fe-S) clusters are essential components of many mitochondrial respiratory chain proteins (such as complexes I and II) and other metabolic enzymes. Lipoylated protein aggregation and Cu^{+} indirectly induce the loss of iron-sulfur cluster proteins that not only exacerbate mitochondrial dysfunction but also trigger severe metabolic dysregulation, ultimately causing cell death [7].

In summary, cuproptosis is a form of cell death that is directly induced by copper ion overload. It is uniquely characterized by its specific targeting of mitochondrial respiratory metabolism.

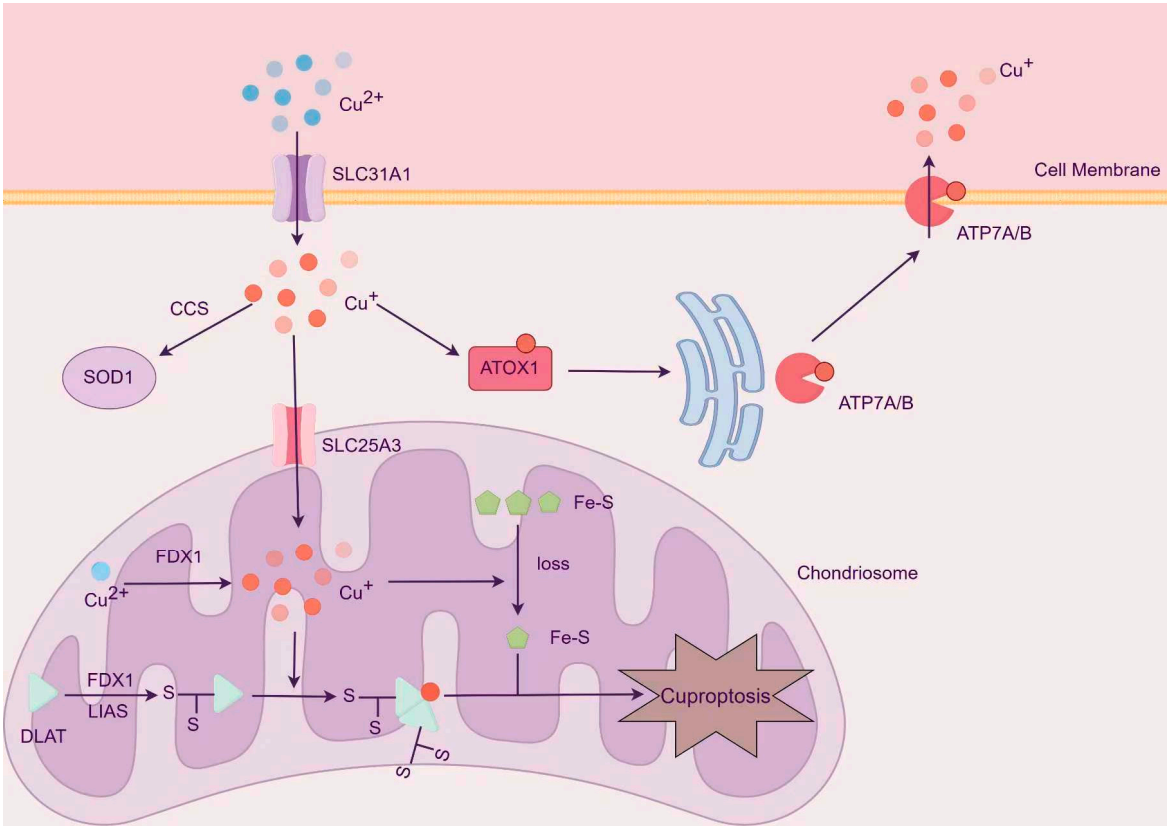

Figure 1: Under the mediation of SLC31A1, Cu^{2+} enters the cell in the form of Cu^{+}. CCS can bind to copper ions and activate SOD1. A portion of copper ions is transported by ATOX1 to the Golgi apparatus, where they bind to ATP7A/B and are subsequently exported out of the cell under their mediation. Within mitochondria, FDX1 acts as a copper reductase, reducing Cu^{2+} to Cu^{+}. Simultaneously, FDX1 and LIAS participate in the lipoylation of proteins such as DLAT. Cu^{+} can bind to the lipoyl groups of these lipoylated proteins, inducing their oligomerization and aggregation, thereby forming insoluble toxic aggregates that accumulate in mitochondria. Concurrently, the loss of iron-sulfur cluster proteins, together with this process, leads to mitochondrial dysfunction, triggering cuproptosis. CCS, Copper Chaperone for SOD1; SOD1, Superoxide Dismutase 1; ATOX1, Antioxidant 1 Copper Chaperone; FDX1, Ferredoxin 1; LIAS, Lipoic Acid Synthase; DLAT, Dihydrolipoamide S-Acetyltransferase.

3 Mechanisms of Platinum Resistance in Ovarian Cancer

The fundamental treatment strategy for ovarian cancer involves chemotherapy subsequent to the initial cytoreductive surgery, typically utilizing platinum-based and taxane-based drugs. Due to the limitations of treatment, even following an initial response, chemotherapy resistance, particularly to platinum agents, frequently emerges during the treatment process, and approximately 70% of patients experience a relapse within 2 years [26]. The ineffectiveness of postoperative treatment for ovarian cancer is predominantly attributed to the resistance of ovarian cancer cells to chemotherapy drugs, and the mechanism of platinum resistance is the outcome of multiple factors and multiple pathways.

3.1 Dysregulation of Drug Influx and Efflux Systems

A widely recognized mechanism underlying platinum resistance is the dysregulation of influx and efflux of platinum salts in tumor cells. Specifically, CTR1 functions as the primary channel mediating cisplatin entry into cells. Accumulating evidence has demonstrated that platinum-resistant ovarian cancer cells exhibit either downregulated CTR1 expression or functional loss of CTR1, both of which directly contribute to reduced drug uptake [27]. Notably, loss of CTR1 function—essentially shutting down the major route for platinum entry into cells—represents the primary and critical step leading to decreased intracellular platinum accumulation. Copper transporter 2 (CTR2) is primarily localized to the membranes of organelles, including lysosomes and vesicles. When expressed on the cell membrane, CTR2 functions similarly to CTR1 in mediating copper uptake. In the context of cisplatin resistance, CTR2 plays a negative regulatory role. Specifically, it has demonstrated that knockdown of CTR2 expression in tumor cells increases cisplatin uptake and elevates the levels of cisplatin-DNA adducts [28]. Consistent with this, a clinical study revealed a slight increase in CTR2 expression in ovarian cancer patients with chemoresistance, accompanied by a significant elevation in the CTR2/CTR1 ratio; notably, all these patients exhibited a poor prognosis [29]. Collectively, these findings further confirm the pro-resistance role of CTR2 in cisplatin-resistant ovarian cancer.

The key mediators of the drug efflux system are ATP7A and ATP7B. Studies have demonstrated that both platinum-based chemotherapeutic agents and copper ions are soft Lewis acids, which allows copper transporters to recognize and bind platinum drugs, thereby mediating their transmembrane transport [30]. Under physiological conditions, ATP7A is primarily localized to the Golgi apparatus, where it facilitates the loading of copper ions into copper-dependent enzymes. When intracellular copper levels rise, ATP7A redistributes to the plasma membrane to pump excess copper out of the cell. ATP7B is predominantly expressed in the liver; it loads copper into ceruloplasmin within the Golgi apparatus and regulates systemic copper homeostasis via the biliary excretion pathway [16]. Under continuous cisplatin exposure, acquired drug-resistant tumor cells redistribute ATP7A/B from the Golgi apparatus to peripheral vesicular structures [31]. ATP7A sequesters cisplatin that has entered the cytoplasm into the lumens of these vesicles, thereby achieving intravesicular sequestration of the drug, while ATP7B is more involved in mediating cisplatin efflux [32]. From this, we identified that this process is not merely a simple transmembrane efflux, but also a functional compartmentalized sequestration. This prevents cisplatin from diffusing effectively in the cytoplasm and, more importantly, hinders its access to target sites in the cell nucleus, thereby significantly reducing the chance of forming lethal platinum-DNA adducts with nuclear DNA and ultimately leading to the loss of cytotoxicity and treatment failure.

3.2 DNA Damage Repair

The primary mechanism of action of platinum-based drugs involves the formation of intra- and interstrand cross-links with cancer cell DNA. These crosslinks secondarily give rise to severe forms of DNA damage, most notably double-strand breaks, which are highly cytotoxic and strongly suppress cellular survival. Such lesions severely disrupt essential processes, including DNA replication and gene transcription. As DNA damage accumulates progressively, cells activate intrinsic apoptotic signaling pathways, ultimately leading to tumor cell death [33]. However, cancer cells can counteract this process by enhancing their DNA damage repair capacity, which constitutes one of the core mechanisms underlying cisplatin resistance. The most prominent of these mechanisms is repair via the nucleotide excision repair (NER) pathway [34]. Studies have demonstrated that cells with NER overexpression exhibit reduced sensitivity to cisplatin [35]. As a core regulatory protein in DNA repair, high excision repair cross-complementation group 1 (ERCC1) expression was identified in a clinical study to be significantly associated with cisplatin resistance and

disease progression in patients with ovarian cancer [36]. Additionally, functional defects in the mismatch repair (MMR) system also play a crucial role in cisplatin resistance. A functional MMR system can recognize cisplatin-induced DNA damage and initiate apoptotic signaling. In contrast, silencing or mutation of genes such as mutl homolog 1(MLH1) and muts homolog 2(MSH2) can lead to MMR deficiency, resulting in unrecognized DNA damage, failure to initiate apoptotic signaling, and subsequent cell survival and proliferation under conditions of genomic instability, ultimately contributing to the development of drug resistance [37].

3.3 Oxidative Stress and Metabolic Reprogramming

Oxidative stress serves as a key mechanism underlying cisplatin-mediated cancer cell killing. Within cells, cisplatin triggers excessive mitochondrial production of reactive oxygen species (ROS), which inflict DNA damage and ultimately induce apoptosis. However, tumor cells can develop resistance to cisplatin by counteracting oxidative stress—chiefly through strengthening antioxidant defenses and rewiring cellular metabolism. Glutathione (GSH) is the primary antioxidant in human cells and plays an indispensable role in maintaining cellular redox homeostasis. The thiol group within GSH can directly scavenge reactive oxygen species (ROS). As such, elevated GSH levels not only shield normal cells from ROS-induced damage but also render tumor cells resistant to exogenous oxidative stress, thereby markedly attenuating the tumoricidal effects mediated by cisplatin-generated ROS [38]. Meanwhile, cisplatin exposure also triggers profound alterations in cellular metabolism. Specifically, cells shift their primary mode of energy production from glycolysis toward increased reliance on oxidative phosphorylation (OXPHOS). While OXPHOS itself can drive ROS generation, drug-resistant cells mitigate this effect by activating nuclear regulators such as PGC-1α, which promotes mitochondrial DNA replication and transcription. This adaptive response prevents excessive ROS accumulation and reinforces cellular antioxidant capacity [39]. Parallel observations have been made in drug-resistant breast cancer cells, whose survival and progression are highly dependent on OXPHOS; notably, pharmacological inhibition of OXPHOS elevates ROS levels and suppresses tumor growth [40]. Mitochondria lie at the core of this adaptive process. Studies in platinum-resistant ovarian cancer cells have demonstrated that downregulation of mitochondrial transcription factor A (TFAM) leads to suppressed OXPHOS activity and enhanced glycolysis, whereas TFAM overexpression restores mitochondrial function and resensitizes cells to platinum-based therapy [41]. Accordingly, targeting the oxidative stress balance and reversing metabolic adaptations to restore drug susceptibility in cancer cells has emerged as a promising strategy to overcome chemoresistance.

3.4 Tumor Microenvironment

The tumor microenvironment plays an indispensable role in the initiation, progression, metastatic spread, and development of cisplatin resistance in ovarian cancer. Unlike many malignancies that disseminate primarily through hematogenous routes, ovarian cancer metastasis occurs primarily within the peritoneal cavity, with a distinct predilection for colonizing the omentum—a tissue rich in adipocytes. As documented in the literature, adipocytes within the omentum release large quantities of fatty acids, which are readily taken up by adjacent cancer cells. These fatty acids serve as critical energy substrates and key biosynthetic building blocks for membrane biogenesis, thereby sustaining rapid cell growth, sustained proliferation, and the gradual acquisition of a drug-resistant phenotype [42]. Complementing these observations, experimental studies have further revealed that mitochondrial elongation factor 2 contributes significantly to ovarian cancer progression by driving the biosynthesis of fatty acids and cholesterol, ultimately enhancing cancer cell growth and metastatic potential [43]. It has been found that cancer cells derived from metastatic lesions of ovarian cancer patients exhibit higher levels of polyunsaturated fatty

acyl (PUFA)-lipids than those derived from primary tumors [44]. This profound reprogramming of lipid metabolism is now recognized as a key adaptive mechanism closely associated with the development of chemoresistance. In a study by Carmi et al., soluble growth factors enriched in ovarian cancer ascites were found to promote cisplatin resistance in ovarian cancer cells [45]. Functionally, ascites acts as a critical fluid medium that enables widespread dissemination of tumor cells across the entire peritoneal cavity. Beyond facilitating metastasis, the unique biochemical and cellular composition of the ascites microenvironment also contributes directly to disease progression, the emergence of drug resistance, and ultimately poor clinical outcomes in patients with ovarian cancer.

4 Intrinsic Association between Cuproptosis and Cisplatin Resistance

Cisplatin is a widely utilized chemotherapeutic agent for ovarian cancer (OC), and its efficacy is profoundly challenged due to the prevalent occurrence of drug resistance. Mechanistically, both platinum-based drugs and copper ions are classified as soft Lewis acids, a chemical characteristic that enables copper transporters to recognize and bind platinum compounds, thereby mediating their transmembrane transport [30]. Consequently, the copper homeostasis machinery and the recently elucidated cuproptosis pathway are intrinsically and complexly linked with cisplatin resistance in ovarian cancer.

4.1 Shared Transporter and Chaperone System

The copper homeostasis network relies on the following key players: the CTR1 copper uptake transporter, the ATOX1 copper chaperone, and the copper-transporting ATPases ATP7A and ATP7B. All of these collectively orchestrate cellular uptake, intracellular distribution, and cellular efflux. As shown in Fig. 2, copper and cisplatin share a transporter and chaperone system.

CTR1 is the primary protein responsible for cellular copper uptake. Intracellular Cu levels regulate its expression and function. A high internal Cu concentration triggers CTR1 internalization and degradation, thereby reducing further copper absorption [46]. Notably, seminal studies that date back two decades established that CTR1 is not only critical for copper influx but also serves as the primary entry channel for cisplatin into the cell [47]. *In vitro* evidence in ovarian cancer (OC) cells has indicated that downregulation of the zinc-finger transcription factor ZNF711 leads to reduced expression of CTR1, which in turn decreases cisplatin uptake and consequently confers cisplatin resistance in ovarian cancer cells [48].

Conversely, Ginsenoside Rg6 has been shown to reverse cisplatin resistance in OC by augmenting CTR1 expression and function [49]. Theoretically, the OC cell mechanism of CTR1 downregulation that contributes to cisplatin resistance might inadvertently reduce its sensitivity to copper death. This strongly suggests that the enhancement of CTR1 expression could be a viable strategy to simultaneously induce cuproptosis and overcome cisplatin resistance.

Studies have found that high levels of ATOX1 are associated with cisplatin resistance. During intracellular trafficking, ATOX1 binds Cu^{+} via its CXXC metal-binding motif. This causes the transference of the ion to ATP7A/B to prevent an accumulation of toxic free copper and facilitate copper efflux. Concurrently, ATOX1 can also directly bind cisplatin through its CXXC motif, and this contributes to cisplatin resistance. This implies a competitive relationship between copper and cisplatin when binding to ATOX1 [31]. Additional research has revealed that ATOX1 is not only involved in intracellular copper transport but also functions as a transcription factor that enters the nucleus to promote cell proliferation [50].

Copper efflux plays a pivotal role in copper homeostasis maintenance, and ATP7A and ATP7B serve as the core regulators and key antagonists of copper death. Research has indicated that ATP7A/B protein expression levels are significantly higher in cisplatin-resistant cells compared to cisplatin-sensitive cells [51].

Therefore, ATP7A/B can be considered a well-defined driver of cisplatin resistance in tumor cells. *In vitro* experiments have confirmed that ATP7A protein expression upregulation induces cisplatin resistance in ovarian cancer cells, whereas silencing ATP7A reverses this resistance [52]. ATP7B acts as a critical mediator of both drug resistance and immune evasion. ATP7B protein expression upregulation can inhibit copper death and activate the HIF-1/PD-L1 pathway. This promotes the progression of non-small cell lung cancer cells [53]. The lysosomal gene transcription factor, EB (TFEB), has also been shown to influence cisplatin resistance in ovarian cancer cells by regulating ATP7B expression [54]. Epigallocatechin gallate (EGCG) has been shown to downregulate MTF1 expression, thereby impeding the transcriptional regulation of ATP7B. This promotes copper accumulation within tumors and enhances the organism's susceptibility to copper [22]. Based on the above evidence, we conclude that the inhibition of ATP7A and ATP7B expression could theoretically achieve a dual effect of impeding copper efflux to induce copper death and simultaneously increasing the intracellular cisplatin accumulation to reverse cisplatin resistance. This makes them highly attractive therapeutic targets in ovarian cancer treatment.

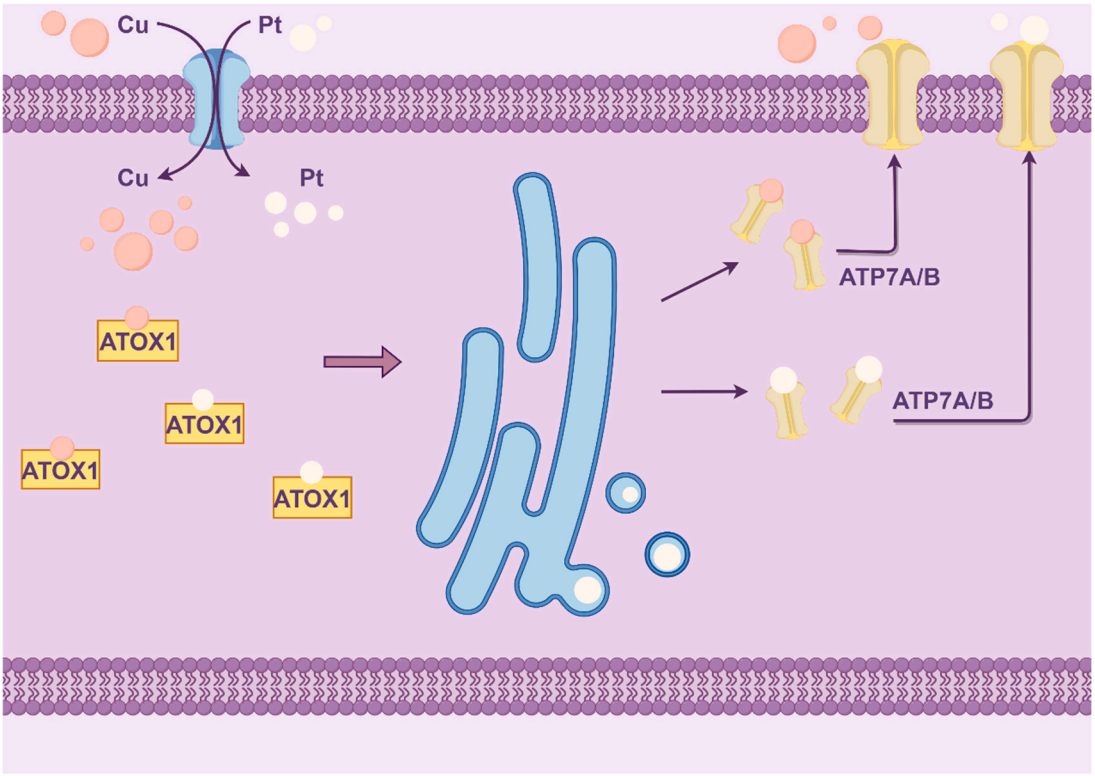

Figure 2: CTR1 transports copper and platinum into the cell. After ATOX1 binds to these metals, the ATOX1-metal complex is transferred to ATP7A/B, which facilitates their excretion. Under continuous cisplatin exposure, cytoplasmic cisplatin is not only sequestered within vesicles, resulting in intracellular drug sequestration, but its excretion is also enhanced.

4.2 Metabolic Reprogramming and Copper Homeostasis Dysregulation

Cisplatin resistance in tumor cells is an active adaptive process, whereby cancer cells alter their metabolic pathways to support rapid proliferation. Studies have shown that metabolic reprogramming in tumor cells is a key factor in cisplatin resistance [55]. Tumor cells not only enhance glycolysis to some extent but also upregulate the tricarboxylic acid (TCA) cycle and oxidative phosphorylation levels to defend against cisplatin [56]. This not only provides substantial ATP for DNA repair and drug efflux but also supplies precursors for the synthesis of amino acids and nucleotides. The TCA cycle activity elevation

implies that proteins, such as DLAT, may be overexpressed in cisplatin-resistant cells, and their critical lipoylation levels are also maintained at a high state. This provides a potential foundation for the occurrence of copper death. Experimental data have indicated that cisplatin-resistant ovarian cancer cells exhibit higher basal oxygen consumption rates (OCR), elevated mitochondrial membrane potential (MMP), and significantly increased mitochondrial mass [57]. The mitochondria have been shown to participate in chemoresistance to cisplatin in human ovarian cancer cells [58]. This suggests that copper metabolism and distribution may be altered in cisplatin-resistant cells. Additionally, hypoxic conditions within the tumor microenvironment favor the existence of copper in the Cu^+ form. Therefore, when sufficient Cu^+ accumulates intracellularly, copper-lipoylated protein complexes can form in large quantities and trigger copper death. Based on the above analysis, we observed that the adaptive changes made by the cancer cells to resist cisplatin simultaneously disrupted the intracellular copper homeostasis to some extent. This result also provides a new perspective to overcome cisplatin resistance in ovarian cancer.

5 Therapeutic

The aforementioned findings underscore the intrinsic connection between cuproptosis and cisplatin resistance. The findings suggest that an active and precise induction of a cuproptosis program could be a promising therapeutic strategy to reverse chemoresistance.

5.1 Copper Ionophores

The induction of cuproptosis has emerged as a highly promising novel strategy to overcome cisplatin resistance in OC. In addition, the small molecular compound, Elesclomol, plays an indispensable and central role. This drug was initially classified as an oxidative stress inducer, and its precise mechanism of action became clear with the proposal of the cuproptosis concept [59]. The drug is a highly efficient and specific copper ionophore [60]. Elesclomol forms a stable, electrically neutral complex with copper ions in the extracellular space and enters cells via passive diffusion, ultimately delivering and releasing copper ions within the mitochondria. This leads to a burst accumulation of copper ions inside the cell, particularly within this metabolic hub [61].

This precise copper ion delivery behavior directly triggers the core molecular events of cuproptosis. The high concentration of copper ions within the mitochondria directly targets lipoylated enzymes during the TCA cycle, including dihydrolipoamide S-acetyltransferase. The irreversible binding of copper to the lipoyl moiety causes oligomerization and functional loss of these critical metabolic proteins. This triggers lethal proteotoxic stress [62]. Importantly, this process strictly depends on FDX1, a key protein in the cuproptosis pathway that acts as an upstream regulator of both reductase activity and protein lipoylation. In addition, it is necessary for Elesclomol-induced toxicity [63]. Therefore, Elesclomol-driven cell death is a novel form of cell death caused by metabolic catastrophe, and it is independent of the apoptotic signaling pathway.

It is this unique mechanism that enables Elesclomol to demonstrate significant potential to reverse cisplatin resistance in OC. First, it can effectively circumvent classical cisplatin resistance mechanisms caused by upregulation of anti-apoptotic proteins or defects in apoptotic pathways [64]. Second, OC cells that exhibit cisplatin resistance often undergo metabolic reprogramming [65], and their active mitochondrial respiratory metabolism conversely constitutes a “metabolic vulnerability” to cuproptosis. The resistant cells that survive cisplatin pressure due to heightened metabolism may be more sensitive to Elesclomol-mediated cuproptosis, creating a “synthetic lethal” effect [66]. Finally, the synergistic effect of Elesclomol and cisplatin has been confirmed by preclinical studies. The collapse of the TCA cycle due to cuproptosis and the ensuing

energy and biosynthetic crises severely impair the DNA damage repair capacity of cancer cells, thereby re-sensitizing them to the toxic effects of cisplatin [8,67].

Furthermore, disulfiram is a newly identified effective copper ionophore that has been shown in experimental studies to significantly reduce the survival rate of human ovarian cancer cells. When combined with copper gluconate, it led to a reduced expression of ferredoxin 1 and a loss of Fe-S cluster proteins (biomarkers of copper toxicity), more effectively inhibiting ovarian cancer growth [68].

In summary, copper ionophores precisely deliver copper ions to the mitochondria and specifically activate the cuproptosis pathway. This provides a powerful new tool to overcome cisplatin resistance in OC that is mediated by apoptosis resistance and metabolic adaptation. Hence, this is an important research direction in this therapeutic field.

5.2 Copper-Based Nanomaterials

In addition to small-molecule copper ionophores such as Elesclomol, copper-based nanomaterials (NMs) based on nanotechnology provide a more versatile and precise platform for the targeted induction of cuproptosis. The use of NMs are new frontier in overcoming cisplatin resistance in OC. Copper-based NMs (e.g., copper-based metal-organic frameworks (Cu-MOFs), copper sulfide nanoparticles (CuS NPs), and copper oxide nanoparticles (CuO NPs)) themselves act as substantial "copper reservoirs". They can achieve a controlled degradation via weak acidity, a high glutathione concentration characteristic of the tumor microenvironment [69], or external stimuli (e.g., near-infrared light [70]). Hence, they can release large amounts of copper ions within the cytoplasm or the mitochondria of cancer cells. This "on-demand" release characteristic not only significantly enhances treatment specificity and reduces systemic toxicity but also mimics and amplifies the cuproptosis-inducing effect of Elesclomol. This specifically causes the aberrant aggregation of lipoylated TCA cycle proteins and the destabilization of iron-sulfur cluster proteins within the mitochondria, triggering lethal proteotoxic stress [70].

Owing to their unique physicochemical properties and the enhanced permeability and retention (EPR) effect, copper-based NMs can achieve selective accumulation at tumor sites and efficiently trigger cuproptosis through multiple synergistic mechanisms while simultaneously reversing drug resistance. First, the released copper ions can undergo Fenton-like or Haber–Weiss reactions within the cell and convert overexpressed hydrogen peroxide into highly toxic hydroxyl radicals. This leads to oxidative stress damage and contributes to cuproptosis [71]. This oxidative stress not only directly damages cellular structures but also forms a positive feedback loop with the cuproptosis pathway, accelerating cellular collapse. Second, CuS NPs possess an excellent photothermal conversion efficiency. They generate localized hyperthermia under near-infrared light irradiation, and this directly kills cancer cells and accelerates copper ion release and cellular metabolic rates. These processes combine to "heat up" and amplify the cuproptosis effect [72]. Hyperthermia can also disrupt the mitochondrial membrane potential, further exacerbating mitochondrial dysfunction [73]. Furthermore, through co-loading or combination drug delivery, nanomaterials can co-deliver cisplatin and cuproptosis inducers to resistant cells. They therefore can act synergistically at both the DNA damage and metabolic crisis levels. This overwhelms cancer cell repair mechanisms, thereby restoring their cisplatin sensitivity to [74].

In summary, copper-based nanomaterials enable spatiotemporally controllable induction of cuproptosis in tumor cells by acting as intelligent "copper ion bombs". Further exploration is required regarding their biosafety, scalable production, and *in vivo* targeting efficiency; however, copper-based nanomaterials undoubtedly represent one of the most promising and translatable strategies to harness the emerging concept of cuproptosis to combat chemoresistance.

5.3 Indirect Regulation of Cuproptosis and Combination Therapeutic Strategies

Unlike copper ionophores and copper-based nanomaterials, which directly deliver copper into cells, the indirect regulatory strategy involves creating conditions for the eventual induction of cuproptosis by interfering with intracellular proteins or metabolic pathways related to copper homeostasis. We note that (-)-epigallocatechin-3-gallate (EGCG) has previously been shown to enhance CTR1 expression in ovarian cancer cells and xenograft mouse models by inhibiting cisplatin-induced CTR1 degradation. Concurrently, the combination of EGCG and cisplatin increases the accumulation of cisplatin and cisplatin-DNA adducts, thereby enhancing the sensitivity of ovarian cancer cells to cisplatin [75]. Additionally, AMP-activated protein kinase (AMPK) has been found to increase CTR1 protein stability through phosphorylation; as an AMPK agonist, metformin can effectively upregulate CTR1 expression and promote copper uptake [76]. In a preclinical study of 15 patients with advanced epithelial ovarian cancer requiring neoadjuvant or palliative care, combining metformin with platinum-based therapy increased the area under the plasma concentration-time curve (AUC) of platinum agents by 22% and decreased their clearance rate by 28%. These findings suggest that metformin may enhance platinum drug exposure, supporting our proposal that the combination of metformin and platinum-based agents is feasible, safe, and tolerable for the treatment of advanced epithelial ovarian cancer [77].

To date, numerous studies have confirmed that high ATP7B expression is one of the key mechanisms underlying cisplatin resistance in ovarian cancer. Specifically, copper sulfate has been shown to inhibit ATP7B expression, thereby reducing platinum efflux and enhancing cisplatin efficacy [78]. Using synthetic lethality screening, Mariniello, M demonstrated that tranilast, telmisartan, and amphotericin B enhance cisplatin toxicity and induce death in cisplatin-resistant ovarian cancer cells. While the exact mechanism remains unclear, experimental data show that tranilast reduces ATOX1 expression in drug-resistant tumor cells without impacting ATOX1 levels in hepatocytes, altering ATP7B transport function, or increasing cisplatin toxicity [79]. As we noted earlier, ATP7B plays a critical role in maintaining copper homeostasis. Thus, tranilast may mitigate the risk of treatment-related side effects and adverse events.

FDX1 is a key regulator of cuproptosis; however, excessive cuproptosis activation disrupts the intracellular microenvironment, leading to damage and downregulation of proteins such as FDX1 [80]. As an anti-alcoholism drug, studies have shown that Disulfiram (DSF) induces ovarian cancer cell death by downregulating Bcl-2 and upregulating Bax. When DSF is combined with copper (DSF/Cu), cancer cells exhibit hallmark cuproptotic events, including decreased FDX1 expression and loss of Fe-S cluster proteins. These effects were further validated in a mouse xenograft model using SKOV-3 cells, where DSF/Cu significantly reduced tumor volume and improved mouse survival [69].

In recent years, studies have identified Metallothionein 2A (MT2A) as a novel key copper-storing protein regulated by HIF-1α. MT2A chelates free copper ions, preventing their intracellular accumulation to levels sufficient to trigger cuproptosis. The HIF-1α inhibitor PX-478 downregulates MT2A expression, thereby releasing chelated copper ions. This effect effectively enhances the sensitivity of solid tumors to both cuproptosis and cisplatin. Furthermore, the strategy of combining PX-478 with copper ions or copper carriers has demonstrated potent, low-toxicity antitumor effects in multiple orthotopic tumor models [81].

Compared with direct cuproptosis-targeting strategies such as copper-based nanomaterials, indirect regulatory and combination therapeutic strategies do not directly introduce large amounts of exogenous copper, avoiding the risk of systemic copper overload and potentially offering superior systemic safety.

6 Outlook

OC continues to exhibit high mortality and recurrence rates [82]. Cuproptosis is a novel conceptual direction to address cisplatin resistance. Nevertheless, the clinical translation of cuproptosis-based therapies faces several obstacles. It is a rapidly growing research area, but the molecular intricacies of cuproptosis are not yet fully elucidated. Moreover, copper is an essential trace element, and the achievement of tumor-selective cell death induction while averting systemic toxicity remains a significant hurdle. Modulation of the expression of copper homeostasis proteins in cisplatin-resistant cells could theoretically promote intracellular copper accumulation and cuproptosis, but available evidence also indicates that CTR1 downregulation and ATP7A/B upregulation in such cells can reduce cisplatin accumulation, but it may concurrently lower copper levels as an adaptive resistance mechanism against cuproptosis. Thus, numerous intrinsic links and paradoxes between cuproptosis and cisplatin resistance require further clarification. This review highlighted important directions for future investigations. Our understanding of cuproptosis will deepen and advance in nanomaterials research, and targeting cuproptosis in tumor cells holds promise to become an integral component of therapeutic regimens for cisplatin-resistant OC. This direction may offer new and effective options for patients who have experienced chemotherapy failure and ultimately contribute to improved clinical outcomes.

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