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*Review*

# Cuproptosis in Triple-Negative Breast Cancer: Current Insights, Limitations and Copper-Related Therapeutic Perspectives

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## Simple Summary

Triple-negative breast cancer is the most aggressive form of breast cancer, with limited treatment options and a high risk of treatment resistance and recurrence, creating an urgent clinical demand for novel therapeutic strategies. Cuproptosis is a recently discovered type of cell death that is triggered by copper and is closely linked to how tumor cells produce energy and maintain copper balance. A growing body of evidence suggests that this process may affect tumor growth, drug response, and the immune environment surrounding cancer cells. This review aims to explain how cuproptosis works, summarize its possible roles in triple-negative breast cancer, and discuss emerging treatment strategies that use copper-related cell death alone or in combination with current therapies. A better understanding of cuproptosis may help researchers identify new therapeutic targets, improve treatment combinations, and develop more effective strategies for patients with triple-negative breast cancer.

## Abstract

Cuproptosis, a recently identified form of copper-dependent regulated cell death, is closely associated with mitochondrial metabolism and copper homeostasis. Triple-negative breast cancer (TNBC) remains difficult to treat because of limited targeted therapeutic options and frequent therapeutic resistance. Emerging evidence suggests that cuproptosis-related pathways may influence TNBC progression, treatment response, and the tumor immune microenvironment. Preclinical studies further indicate that combining cuproptosis-targeting strategies with chemotherapy, targeted therapy, or immunotherapy may enhance antitumor efficacy. In this review, we summarize the molecular mechanisms of cuproptosis and its potential roles in TNBC progression, drug resistance, and immune regulation. We also discuss emerging therapeutic strategies targeting cuproptosis and their potential combination with existing treatments in TNBC. Finally, we highlight current challenges and future directions for the clinical translation of cuproptosis-based therapies in TNBC. Collectively, cuproptosis represents a promising but still evolving therapeutic vulnerability that requires further mechanistic and clinical validation.

**Keywords:** cuproptosis; triple-negative breast cancer; copper homeostasis; targeted therapy; immunotherapy; synergistic therapy

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## 1. Introduction

TNBC accounts for approximately 15–20% of all breast cancer cases and is characterized by aggressive biological behavior, high metastatic potential, early recurrence, and relatively poor prognosis [1,2]. TNBC is defined by an absence of estrogen receptor (ER) and progesterone receptor (PR) expression and a lack of human epidermal growth factor receptor 2 (HER2) overexpression or amplification. Multiple molecular classification systems have been proposed for TNBC. In the refined TNBCtype-4 framework, TNBC is divided into basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), and luminal androgen receptor (LAR) subtypes, whereas the previously described immunomodulatory and mesenchymal stem-like signatures were largely attributable to infiltrating immune and stromal cells [3]. This molecular heterogeneity poses substantial challenges for precision treatment. Chemotherapy remains a central component of TNBC management; however, the therapeutic landscape has expanded with immune checkpoint inhibitors, poly(ADP-ribose) polymerase (PARP) inhibitors for selected germline breast cancer susceptibility genes 1 and 2 (*BRCA1/2*)-mutated tumors, and antibody–drug conjugates [4–6]. Nevertheless, therapeutic resistance and the limited availability of broadly applicable molecular targets remain major clinical challenges. Therefore, exploring new pathogenic mechanisms and developing novel therapeutic strategies remain of considerable clinical significance.

Copper is an essential trace element involved in energy metabolism, redox regulation, deoxyribonucleic acid (DNA) repair, and cell signaling. Its intracellular homeostasis is maintained by a network of copper transporters and chaperones [7–9]. Copper dysregulation has been described across cancers, and reviews of hepatocellular carcinoma and B-Raf proto-oncogene, serine/threonine kinase (*BRAF*)-mutant melanoma illustrate its broader biological and therapeutic relevance [10–12]. Studies on copper suppression in melanoma focus on copper-dependent signaling and predate the discovery of cuproptosis [12]. In 2022, Tsvetkov et al. identified cuproptosis as a copper-dependent form of regulated cell death linked to mitochondrial metabolism [13]. In TNBC, copper concentrations have been reported to be higher in tumor tissues than in matched adjacent tissues [14]. Experimental studies have linked copper-handling and cuproptosis-related pathways to tumor progression, metabolic adaptation, drug response, and anti-tumor immunity [14–18].

This review examines the molecular mechanisms of cuproptosis and the evidence for copper-directed interventions in TNBC. We distinguish copper depletion from copper loading, assess disruption of copper trafficking as a separate approach, and identify findings derived from TNBC models, broader breast cancer cohorts, or other malignancies. This distinction is necessary because evidence for a copper-dependent tumor process does not by itself demonstrate cuproptosis or validate a treatment for TNBC.

## 2. Molecular Mechanisms of Cuproptosis

Cuproptosis is a copper-dependent form of regulated cell death that is closely associated with mitochondrial metabolism and protein lipoylation. Its induction requires intracellular copper accumulation and involves multiple interconnected processes, including copper transport and homeostasis, mitochondrial protein lipoylation, destabilization of iron–sulfur (Fe-S) cluster proteins, and proteotoxic stress [7,13]. Several molecular regulators, particularly ferredoxin 1 (FDX1) and components of the mitochondrial lipoylation machinery, influence cellular susceptibility to cuproptosis. Together, these processes form an interconnected regulatory network that determines the cellular response to copper overload [7,13,14] (Figure 1).

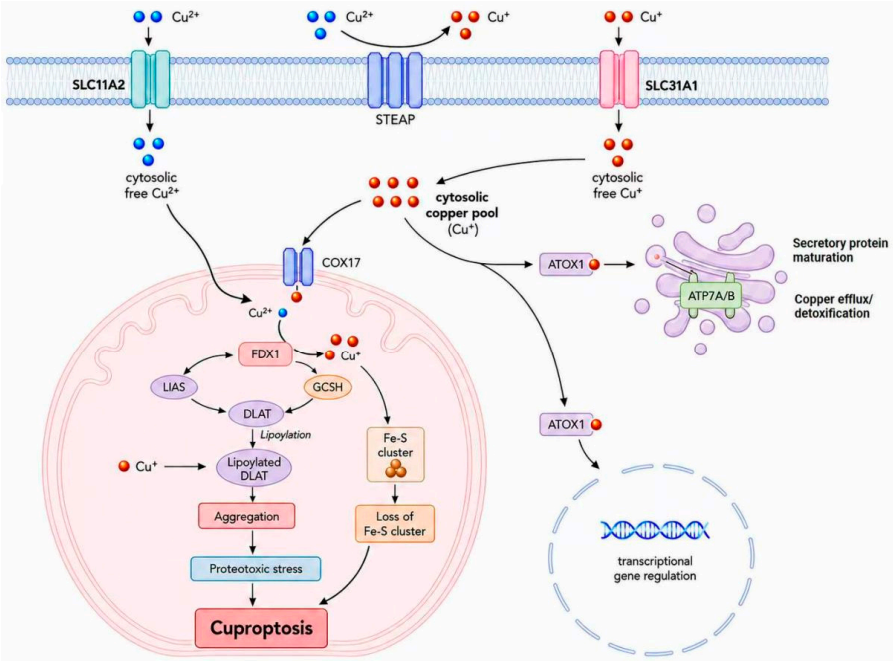


**Figure 1. Cellular mechanisms of cuproptosis.** Extracellular $Cu^{2+}$ must be reduced to $Cu^{+}$ before high-affinity uptake by copper transporter 1 (CTR1), whereas copper-transporting ATPase 1 (ATP7A) and copper-transporting ATPase 2 (ATP7B) mediate copper redistribution and export to maintain cellular copper homeostasis. Copper ionophores such as elesclomol can deliver $Cu^{2+}$ to mitochondria, where FDX1 promotes its reduction to $Cu^{+}$. $Cu^{+}$ binds lipoylated tricarboxylic acid (TCA) cycle proteins, particularly dihydrolipoamide S-acetyltransferase (DLAT) and other lipoylated enzymes such as dihydrolipoamide succinyltransferase (DLST), promoting aberrant protein aggregation. Loss of Fe–S cluster proteins and mitochondrial proteotoxic stress accompany this process and culminate in cuproptosis. Lipoic acid synthetase (LIAS) and lipoyltransferase 1 (LIPT1) support mitochondrial protein lipoylation and thereby influence cuproptosis sensitivity.

### *2.1. Copper Ion Transport and Homeostasis Regulation*

Intracellular copper homeostasis is maintained by a coordinated network of copper transporters and chaperones and represents an important determinant of cellular responses to copper overload [8,9]. CTR1 is a major copper importer, whereas the copper-transporting ATPases ATP7A and ATP7B mediate intracellular copper redistribution and efflux [8,9,19]. Altered expression of these transporters can modify intracellular copper availability and thereby influence susceptibility to copper-dependent cell death. Dysregulated copper metabolism has been reported in TNBC, including increased intracellular copper levels in experimental and clinical studies [14,15]. Altered copper uptake may contribute to tumor progression and therapeutic vulnerability, although the specific role of CTR1 in TNBC remains incompletely defined [14,15].

Copper chaperones, including ATOX1 and the copper chaperone for superoxide dismutase (CCS), further regulate intracellular copper trafficking by delivering copper to specific target proteins [8,9]. ATOX1 transfers copper to ATP7A/B, whereas CCS contributes to superoxide dismutase 1 (SOD1) maturation and redox regulation [8,9]. Alterations in these copper-handling pathways may affect cellular responses to copper stress; however, their specific roles in determining cuproptosis sensitivity and clinical outcome in TNBC remain incompletely defined.

### *2.2. Protein Lipoylation and Mitochondrial Vulnerability*

A defining feature of cuproptosis is its dependence on mitochondrial metabolism and protein lipoylation. Unlike apoptosis, ferroptosis, and necroptosis, cuproptosis does not primarily

depend on caspase activation, lipid peroxidation, or plasma-membrane rupture. Instead, copper directly interacts with lipoylated proteins of the mitochondrial TCA cycle [13,20].

Protein lipoylation is a conserved post-translational modification required for the activity of several mitochondrial enzyme complexes. Key lipoylated proteins include DLAT and DLST, while enzymes such as LIAS and LIPT1 regulate the generation and transfer of lipoic acid [13,21,22].

Tsvetkov et al. demonstrated that copper binds directly to lipoylated TCA-cycle proteins, particularly DLAT, promoting their abnormal oligomerization and aggregation and thereby inducing mitochondrial proteotoxic stress [13]. Because this process depends on mitochondrial respiration, cells with greater reliance on oxidative phosphorylation (OXPHOS) generally exhibit increased sensitivity to cuproptosis, whereas glycolysis-dominant cells tend to be less susceptible [7,13,20].

This metabolic dependency may have therapeutic implications, as certain drug-resistant or metabolically adaptive tumor-cell populations retain substantial mitochondrial respiratory activity. However, the extent to which this vulnerability can be selectively exploited in TNBC requires further validation [23–25].

### 2.3. Iron–Sulfur Cluster Destabilization and Proteotoxic Stress

Destabilization of iron–sulfur (Fe–S) cluster proteins is another characteristic associated with cuproptosis. Fe–S proteins participate in electron transport, enzymatic catalysis, DNA repair, and mitochondrial energy metabolism, and their maintenance is essential for normal mitochondrial function [26,27].

During cuproptosis, aggregation of lipoylated mitochondrial proteins is accompanied by a reduction in Fe–S cluster proteins [13]. The precise mechanisms responsible for this loss remain incompletely understood, but disruption of Fe–S protein homeostasis may contribute to mitochondrial dysfunction and proteotoxic stress. These changes can be accompanied by impaired respiration, redox imbalance, and accumulation of misfolded proteins, ultimately contributing to loss of cellular viability [20,26,27].

### 2.4. FDX1 as the Central Regulator of Cuproptosis

FDX1 has emerged as a key regulator of cuproptosis. FDX1 is a mitochondrial Fe–S protein involved in electron transfer, mitochondrial redox regulation, and several metabolic processes [7,13]. Genome-wide clustered regularly interspaced short palindromic repeats–CRISPR-associated protein 9 (CRISPR–Cas9) screening identified FDX1 as an important determinant of cellular sensitivity to copper-induced death, as loss of FDX1 markedly reduced the cytotoxic effects of copper ionophores [13].

Mechanistically, FDX1 contributes to cuproptosis by promoting the reduction of $Cu^{2+}$ to $Cu^{+}$ and by supporting mitochondrial protein lipoylation, thereby facilitating the interaction of copper with lipoylated TCA-cycle proteins [13,28]. These functions position FDX1 at the interface between copper metabolism and mitochondrial respiration.

FDX1 has therefore attracted interest as a potential biomarker for cuproptosis sensitivity [7,9,13,14]. Preclinical evidence from clear-cell renal cell carcinoma (ccRCC) further suggests that FDX1 may influence sensitivity to copper-ionophore treatment. Specifically, FDX1 overexpression enhanced elesclomol-induced cell killing in 786-O and 769-P cells [29]. This finding was obtained in cell-culture models and should not be interpreted as evidence of clinical predictive value. Although the same study also reported tumor-expression and survival analyses in ccRCC, it did not evaluate whether FDX1 predicts treatment benefit in patients receiving elesclomol or other copper-targeting therapies. Therefore, FDX1 remains a candidate biomarker, and its clinical predictive value has not been prospectively validated in TNBC or other malignancies.

### 2.5. Crosstalk Between Cuproptosis and Other Regulated Cell Death Pathways

Emerging evidence suggests that copper-dependent cell death may interact with other regulated cell death pathways, particularly ferroptosis, through shared disturbances in metal homeostasis, mitochondrial function, oxidative stress, and redox balance [7,28,30,31]. These mechanistic intersections provide a rationale for investigating combined metal-dependent cell death strategies, but they should not be interpreted as evidence that ferroptosis is a universal downstream event of canonical cuproptosis.

For example, alterations in glutathione metabolism, oxidative stress, and ferroptosis-related signaling have been reported in selected copper-based treatment models [28,30,31]. However, many of these observations were obtained under specific experimental conditions and cannot yet be considered universal downstream events of canonical cuproptosis. Further studies are required to distinguish direct mechanistic crosstalk from parallel cell death responses induced by copper overload or multifunctional therapeutic platforms.

### 2.6. Biochemical Mechanisms and Oxidative Stress

Copper can undergo redox cycling and interact with thiols, linking copper availability to glutathione (GSH) buffering and reactive oxygen species (ROS) production. Earlier elesclomol studies demonstrated mitochondrial copper accumulation and oxidative stress in cancer cells [32]. In TNBC models, inhibition of ATOX1/CCS-mediated copper trafficking with DCAC50 also increased oxidative stress and induced apoptosis [33]. Oxidative injury can therefore accompany and amplify copper toxicity, but its contribution depends on the agent, copper distribution, and cellular buffering capacity.

Canonical cuproptosis is defined by copper-dependent aggregation of lipoylated mitochondrial proteins and associated proteotoxic stress [13]. Increased ROS, mitochondrial injury, or antioxidant depletion alone does not establish this mechanism. Copper sequestration by GSH can reduce available copper. Experimental work on nuclear factor erythroid 2-related factor 2 (NRF2, encoded by *NFE2L2*) and solute carrier family 25 member 39 (SLC25A39) demonstrates a protective role for mitochondrial GSH in cuproptosis resistance [34]. Multifunctional formulations may combine lipoylation-dependent cell death with oxidative injury or chemodynamic effects [16,31,35]. Copper-chelation rescue, assessment of lipoylated-protein aggregation, and perturbation of FDX1 or the lipoylation machinery can help distinguish the contribution of cuproptosis from parallel cytotoxic processes.

### 2.7. Immunological Consequences of Cuproptosis

The potential relationship between cuproptosis and anti-tumor immunity has attracted increasing attention. Preclinical studies suggest that cuproptosis-associated cellular stress or death may influence the tumor immune microenvironment through the release or exposure of damage-associated molecular patterns (DAMPs) and activation of innate immune signaling pathways [17,36,37]. The interplay between cuproptosis and the TNBC immune microenvironment was investigated. DLAT expression was positively correlated with programmed death-ligand 1 (PD-L1) levels and the infiltration of cluster of differentiation 4-positive (CD4+) T cells, cluster of differentiation 8-positive (CD8+) T cells, and dendritic cells. Transcriptomic analysis of ES-Cu treated TNBC cells identified the upregulation of metal homeostasis and stress responsive genes, confirming the activation of copper overload mediated cuproptosis, while functional enrichment revealed robust enrichment of immune response and leukocyte activation pathways [16]. Collectively, cuproptosis induction not only directly eliminates TNBC cells but also remodels the tumor immune microenvironment by elevating PD-L1 expression and facilitating immune cell infiltration, thereby providing a solid theoretical basis for combining cuproptosis targeted therapy with immunotherapy [16].

Furthermore, recent nanomedicine studies indicate that simultaneous induction of cuproptosis and activation of the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway can significantly augment anti-tumor immunity and improve therapeutic efficacy in preclinical TNBC models. These observations raise the possibility that cuproptosis-inducing therapies could synergize with immune checkpoint blockade and other immunotherapeutic approaches [31,38–40]. More recently, a mechanistic study demonstrated reciprocal cuproptosis–immunity crosstalk: cuproptotic tumor cells promoted dendritic cell activation and CD8+ T-cell priming, whereas T-cell-derived interferon gamma (IFN-gamma) increased *FDX1* transcription and tumor cells' sensitivity to cuproptosis. Combining a cuproptosis inducer with PD-L1 blockade overcame checkpoint resistance in multiple preclinical models [17] (Figure 2).

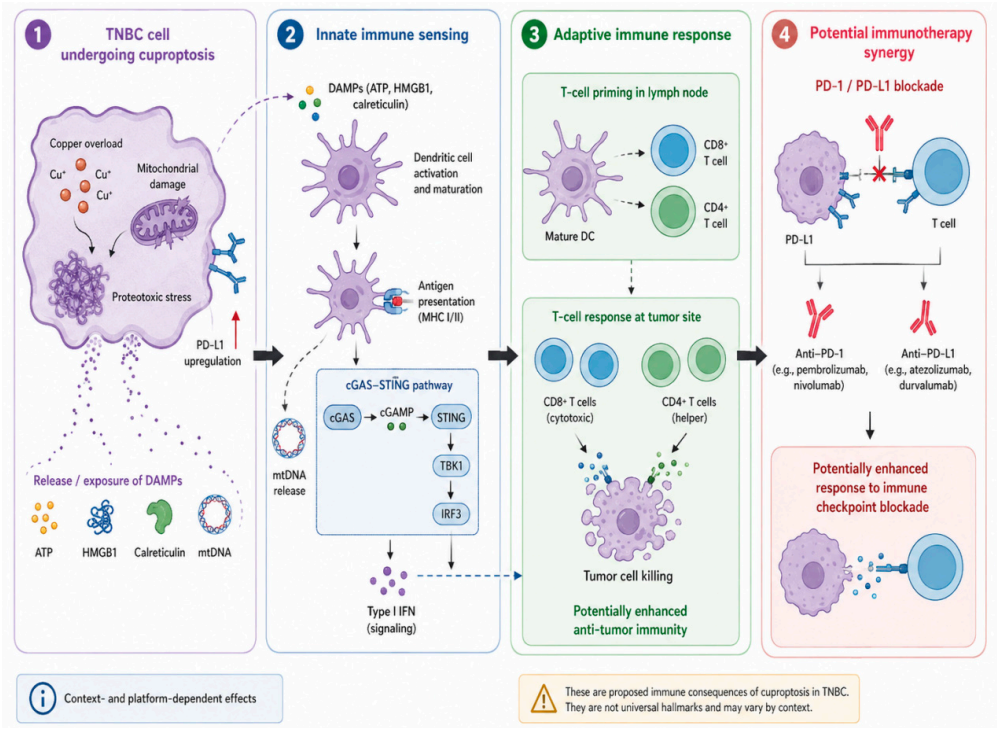


**Figure 2. Proposed immunological consequences of cuproptosis.** Preclinical studies suggest that cuproptosis-associated stress or cell death can be accompanied by exposure or release of DAMPs, including adenosine triphosphate (ATP), high mobility group box 1 (HMGB1) and calreticulin. In selected copper-based nanomedicine models, mitochondrial damage and mitochondrial DNA (mtDNA) release can activate cGAS–STING and type I interferon (IFN) signaling. These events may promote dendritic cell activation, T-cell priming and responsiveness to immune checkpoint blockade. These immune effects are context- and platform-dependent and should not be interpreted as universal hallmarks of cuproptosis.

## 3. Cuproptosis Landscape Across TNBC Molecular Subtypes

### *3.1. Molecular Heterogeneity of TNBC and Implications for Cuproptosis*

TNBC is increasingly recognized as a biologically heterogeneous disease rather than a single clinicopathological entity. Comprehensive transcriptomic and genomic analyses have identified multiple TNBC subtypes characterized by distinct molecular programs, metabolic dependencies, immune landscapes, and therapeutic vulnerabilities [2,3,41,42]. Serum copper levels have been reported as a potential prognostic biomarker in early-stage TNBC patients. Nomograms incorporating serum copper may provide a practical approach for individualized prognostic assessment [43]. Preclinical evidence suggests that copper fuels triple-negative breast cancer progression via six-transmembrane epithelial antigen of the prostate 3 (STEAP3)-dependent activation of cyclin-dependent kinase 16 (CDK16)-Janus

kinase 1 (JAK1) signaling cascade [44]. Another study showed that copper levels were markedly elevated in TNBC tissues relative to paired adjacent non-tumor tissues. Moreover, elevated copper abundance correlated with advanced tumor stages and unfavorable clinical outcomes among TNBC patients, while cancer cells harboring elevated intracellular copper concentrations displayed resistance to cuproptosis [14].

Tetrathiomolybdate (TTM), an orally available copper-chelating agent, has been investigated as a copper-depletion strategy in high-risk breast cancer. Importantly, this strategy has reached phase II clinical evaluation. In a phase II study, patients with stage II TNBC, stage III breast cancer, or stage IV disease with no evidence of disease (NED) received oral TTM to achieve sustained copper depletion [45]. The 2-year event-free survival (EFS) rates were 91% for patients with stage II–III disease and 67% for those with stage IV NED. Among patients with TNBC, EFS was 90% in the adjuvant cohort and 69% in the stage IV NED cohort at a median follow-up of 6.3 years [45]. A subsequent study of patients from this clinical program further linked TTM-associated copper depletion to collagen remodeling and immune changes in the pre-metastatic niche [46]. However, given the single-arm design and heterogeneous patient population, the therapeutic benefit of TTM and the potential preferential sensitivity of TNBC require confirmation in prospective randomized trials.

Disruption of intracellular copper trafficking provides an additional therapeutic approach. DCAC50 inhibits copper transfer mediated by ATOX1 and CCS, reshapes intracellular copper distribution, and induces oxidative stress and apoptosis with reduced angiogenesis in TNBC models [33]. This mechanism differs from systemic copper depletion with TTM. In head-and-neck cancer models, TTM suppressed angiogenesis and metastasis and promoted tumor necrosis [47]; these findings support copper-dependent microenvironmental biology in another malignancy and should not be interpreted as TNBC-specific clinical evidence. Notably, neither TTM nor DCAC50 functions by inducing cuproptosis. To date, no clinical trials targeting cuproptosis have been conducted in TNBC.

TNBC biological heterogeneity is particularly critical in shaping cuproptotic responsiveness, as cellular vulnerability to copper-dependent cell death is tightly governed by mitochondrial activity, oxidative metabolic status, and intracellular copper homeostasis. Given that these metabolic and copper handling traits vary drastically across TNBC molecular subtypes, distinct tumor subpopulations exhibit divergent sensitivities to cuproptosis induction [7,13,41,42].

Nevertheless, current evidence supporting subtype-specific cuproptosis susceptibility remains largely indirect. Most available observations are derived from metabolic profiling, transcriptomic analyses, and pan-cancer datasets, rather than from direct functional validation using TNBC-specific experimental models. Accordingly, the following discussion provides a conceptual mechanistic framework and hypothesis-generating perspective, rather than definitive biological conclusions [3,41,42]. The functional roles of cuproptosis across these TNBC subtypes remain to be verified by experimental evidence.

### 3.2. Basal-like TNBC: A Potential Cuproptosis-Sensitive Population

Basal-like TNBC is characterized by high proliferation, genomic instability, and frequent tumor protein p53 (*TP53*) mutations [41,42]. Although often considered glycolytic, some basal-like tumors retain active mitochondrial respiration and oxidative phosphorylation (OXPHOS) [23,25,41]. Because cuproptosis depends on mitochondrial respiration and lipoylated TCA-cycle proteins, OXPHOS-enriched basal-like TNBC may be more susceptible to cuproptosis, although direct subtype-specific evidence remains limited [7,13].

### 3.3. Mesenchymal TNBC: Metabolic Plasticity and Adaptive Resistance

Mesenchymal TNBC is characterized by epithelial-to-mesenchymal transition (EMT), invasiveness, stemness, and marked metabolic plasticity [2,41,42,48,49]. Its ability to switch

among glycolysis, oxidative phosphorylation, and other metabolic pathways may result in variable cuproptosis sensitivity: mitochondrial activity may increase susceptibility, whereas metabolic rewiring and antioxidant defenses may promote resistance [24,48,50]. Therefore, combining cuproptosis induction with inhibition of adaptive or antioxidant pathways may improve therapeutic efficacy.

### *3.4. Immune-Enriched TNBC and Immunological Consequences of Cuproptosis*

Immune-enriched TNBC shows abundant tumor-infiltrating lymphocytes, enhanced interferon signaling, and relatively greater responsiveness to immune checkpoint blockade [41,51,52]. Cuproptosis may promote anti-tumor immunity through DAMP release and activation of cGAS–STING/type I interferon signaling, thereby enhancing dendritic cell activation and T-cell responses [17,31,38–40]. These findings support further investigation of cuproptosis-inducing agents combined with immune checkpoint inhibitors.

### *3.5. Luminal Androgen Receptor (LAR) TNBC: A Distinct Metabolic Context*

LAR TNBC is characterized by androgen receptor signaling and luminal-like transcriptional features. Some LAR tumors exhibit enhanced lipid metabolism and mitochondrial oxidative activity, which may theoretically increase susceptibility to cuproptosis because this cell death pathway depends on mitochondrial respiration [3,13,24,53]. However, direct evidence demonstrating subtype-specific cuproptosis sensitivity in LAR TNBC remains limited. Therefore, LAR TNBC should currently be considered a potential, rather than established, cuproptosis-sensitive population. The potential cuproptosis sensitivity determined by molecular characteristics of distinct TNBC subtypes is summarized in Figure 3.

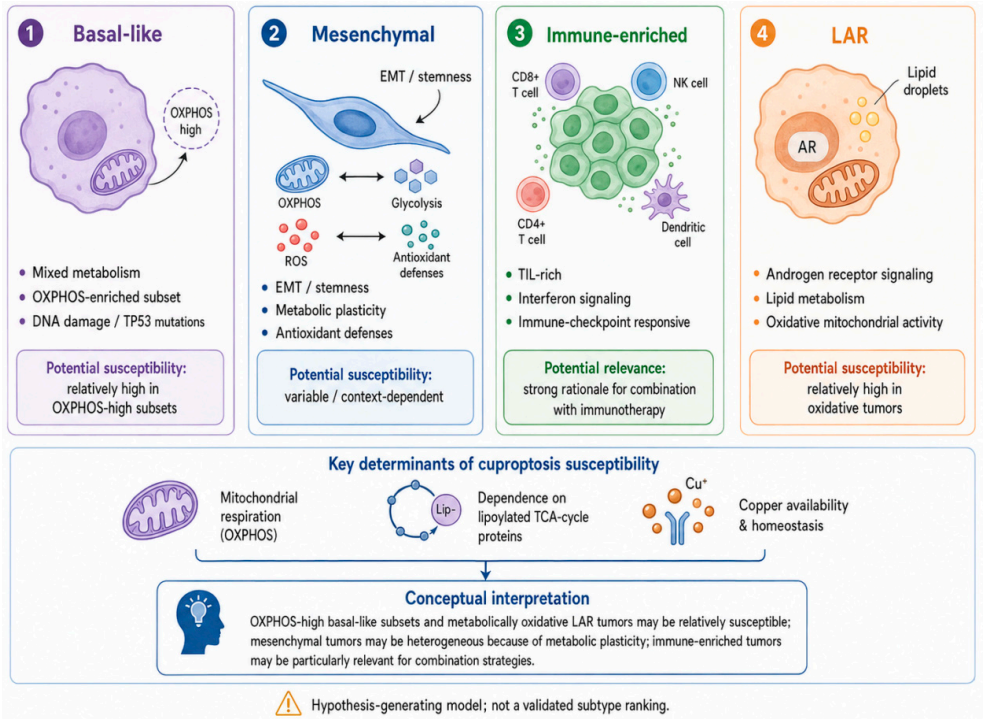


**Figure 3. Conceptual landscape of predicted cuproptosis susceptibility across TNBC molecular phenotypes.** This schematic is hypothesis-generating rather than a validated subtype ranking. Cuproptosis sensitivity is expected to track mitochondrial respiration and dependence on lipoylated TCA-cycle proteins more closely than TNBC subtype labels. OXPHOS-enriched basal-like subsets and metabolically oxidative LAR tumors may be relatively susceptible, whereas mesenchymal tumors may show heterogeneous responses because of metabolic plasticity.

### 3.6. Biomarkers of Cuproptosis in TNBC

Identifying reliable biomarkers remains a major challenge for the clinical translation of cuproptosis-based therapies. Several candidate molecules have been proposed, including FDX1, LIAS, LIPT1, DLAT, DLST, SLC31A1 (CTR1), ATP7A, and ATP7B [7,13,14,20]. Expression signatures derived from cuproptosis-related genes have shown prognostic associations in several cancer types, suggesting their potential value for molecular stratification. In breast cancer, a four-gene signature comprising NLR family pyrin domain containing 3 (*NLRP3*), *LIPT1*, pyruvate dehydrogenase E1 subunit alpha 1 (*PDHA1*), and *DLST* was associated with prognosis, immune infiltration, and tumor mutation burden in retrospective transcriptomic cohorts [54]. However, these findings were derived from breast cancer cohorts rather than prospective TNBC-specific studies, and prognostic associations should not be directly interpreted as predictors of therapeutic response.

Clinical correlative evidence is also beginning to emerge. Analysis of pretreatment tumor samples from patients enrolled in the phase II TTM trial found that higher cytoplasmic ATOX1 expression showed a trend toward better event-free survival in TNBC, suggesting that ATOX1 may have potential as a predictive biomarker for copper-depletion therapy; however, prospective validation is still required [55].

Among these candidates, FDX1 and DLAT have received particular attention in TNBC. FDX1 is a key regulator of cuproptosis, while recent studies also suggest that FDX1 may influence TNBC cell proliferation and anti-tumor immune responses [56]. DLAT is another core component of the cuproptosis pathway, and altered DLAT expression together with elevated copper abundance has been reported in TNBC [14,57]. Nevertheless, increased copper abundance or altered expression of individual cuproptosis-related proteins does not necessarily indicate greater sensitivity to cuproptosis, because TNBC cells may acquire adaptive resistance through signaling and metabolic reprogramming.

Bioinformatic studies have identified prognostic cuproptosis-related gene signatures in TNBC, while broader breast-cancer transcriptomic analyses have reported related prognostic signatures [54,58,59]. However, most of these findings are based on retrospective transcriptomic or bioinformatic analyses and have not yet been prospectively validated as predictive biomarkers of response to cuproptosis-targeted therapy. The lack of verified cuproptosis biomarkers restricts our ability to reliably evaluate the functional role of cuproptosis in TNBC pathogenesis and therapeutic response. This represents a major bottleneck and an important direction for future research. Future studies should therefore integrate copper abundance, copper transport, mitochondrial metabolic activity, protein lipoylation status, and resistance-associated signaling to more accurately identify TNBC populations that may benefit from copper-targeted interventions.

## 4. Therapeutic Strategies Targeting Cuproptosis in TNBC

### 4.1. Therapeutic Rationale for Targeting Cuproptosis in TNBC

The discovery of cuproptosis has generated considerable interest in exploiting copper-dependent cell death pathways for cancer therapy. Unlike conventional cytotoxic approaches that primarily target DNA replication or mitotic progression, cuproptosis-based therapies selectively disrupt mitochondrial metabolism and proteostasis. Because many TNBC tumors exhibit substantial metabolic plasticity and mitochondrial dependency, induction of cuproptosis may represent a promising strategy for selected TNBC subtypes [13,24,60]. Therapeutic strategies targeting cuproptosis discovered to date can be classified into four major categories: copper ionophores, copper-binding complexes, copper-based nanomedicines, and combination therapies designed to enhance cuproptotic sensitivity or exploit downstream immunological effects (Figure 4 and Table 1).

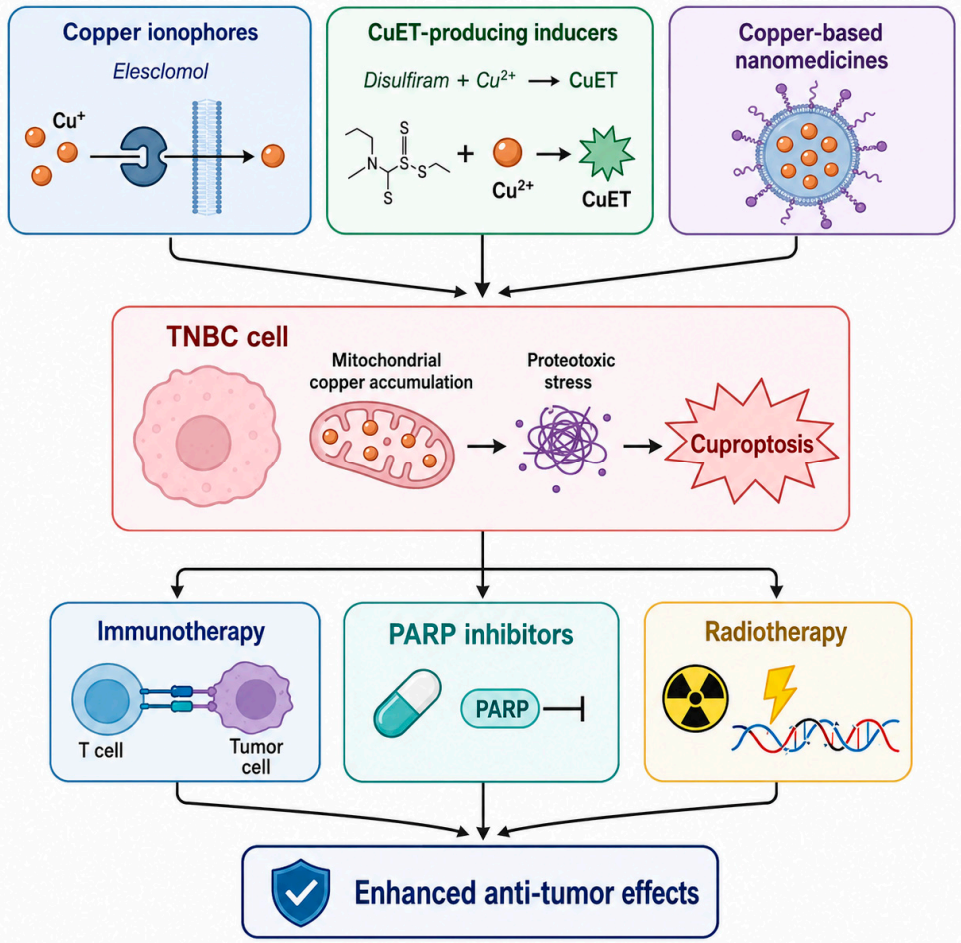


**Figure 4. Therapeutic strategies exploiting copper-dependent vulnerabilities and cuproptosis in TNBC.** Representative strategies include copper ionophores, CuET-producing agents, and copper-based nanomedicines, which promote copper accumulation, mitochondrial dysfunction, and proteotoxic stress. Combination with immunotherapy, PARP inhibitors, or radiotherapy may enhance anti-tumor efficacy, although current evidence is predominantly preclinical.

**Table 1.** Representative clinical and preclinical studies of copper-targeted therapeutic strategies in TNBC.

| Intervention | Population and Design | Main Observation | Evidence Boundary |
|---|---|---|---|
| TTM [45,46] | High-risk breast cancer including TNBC; single-arm phase II and same-program correlative follow-up | Copper depletion, tolerability, observed EFS, and microenvironmental changes | No concurrent control or proven survival benefit; copper depletion, not a clinical demonstration of cuproptosis. |
| DCAC50 [33] | TNBC cells and xenografts; preclinical | Disrupted chaperone-mediated copper trafficking; oxidative stress, apoptosis, and reduced angiogenesis | Distinct from systemic depletion; apoptosis findings do not establish canonical cuproptosis. |
| zinc pyrithione (ZnPT) [15] | TNBC cell and xenograft experiments | Copper-homeostasis disruption and cuproptosis-associated antitumor activity | No patient efficacy or validated subtype-selection rule. |
| MK-2206 + elesclomol–copper complex (ES–Cu) [14] | TNBC cells and animal models | Counteracted AKT serine/threonine kinase 1 (AKT1)–FDX1-associated cuproptosis resistance | Preclinical combination; FDX1 is not a validated clinical selection marker. |
| ES–Cu/glucose oxidase (GOx) hydrogel [16] | TNBC experimental models | Combined copper-associated killing, metabolic stress, and immune effects | Multifunctional platform; overall efficacy cannot be attributed to cuproptosis alone. |
| $Cu(L1)_2Cl$ [35] | TNBC experimental models | Cuproptosis-related effects combined with chemodynamic activity | Preclinical activity; clinical selectivity and benefit remain unproven. |

### 4.2. Copper Ionophores: Elesclomol as a Prototype Cuproptosis Inducer

Of the cuproptosis-inducing agents currently available, elesclomol remains the most extensively studied compound. Elesclomol is a small-molecule copper ionophore that forms a stable complex with extracellular copper and facilitates its transport into mitochondria [32,61]. Early studies demonstrated that elesclomol induces oxidative stress and apoptosis in cancer cells by promoting mitochondrial copper accumulation [32,61]. However, the core mechanism underlying its potent anti-tumor activity remained poorly defined until the formal identification of cuproptosis. Subsequent investigations revealed that elesclomol functions as a potent cuproptosis inducer by increasing intracellular copper availability and promoting copper-dependent aggregation of lipoylated mitochondrial proteins [13].

Preclinical evidence has validated that elesclomol selectively eliminates tumor cells with hyperactive oxidative phosphorylation. This metabolic dependency confers profound therapeutic specificity, as drug-resistant cancer stem cells (CSCs) predominantly rely on mitochondrial respiration rather than glycolysis to sustain self-renewal and malignant progression. Accordingly, elesclomol may hold the potential to deplete metabolically adaptive tumor subpopulations responsible for tumor relapse and therapeutic failure [25,62]. The combination of an AKT1 inhibitor with the elesclomol–$Cu^{2+}$ complex synergistically suppresses TNBC tumorigenesis by enhancing cuproptosis in vitro and in vivo [14]. Natural resorcylic acid lactones were recently identified as novel potent copper ionophores with the potential to trigger cuproptosis in TNBC [63].

Disulfiram, a long-established anti-alcoholism drug, has attracted substantial attention as a potential anti-cancer agent due to its ability to interact with copper and generate highly cytotoxic copper complexes [64,65]. In the presence of copper, disulfiram is rapidly converted into copper-containing metabolites, including copper bis(diethyldithiocarbamate) (CuET), which exert anti-tumor effects through multiple mechanisms. These include disruption of protein homeostasis, inhibition of proteasomal function, induction of oxidative stress, and interference with cancer stem cell maintenance [64,65]. Although disulfiram-induced cell death was initially considered distinct from cuproptosis, recent evidence suggests that copper accumulation and mitochondrial dysfunction may contribute substantially to its anti-tumor activity. Consequently, disulfiram serves as a representative example illustrating how clinically approved agents can be repurposed to exploit copper dependent vulnerabilities in cancer cells [60,64,65].

Copper ionophores and copper chelators such as TTM act through divergent mechanisms. Ionophores promote intracellular copper accumulation to initiate cuproptosis, while chelators deplete copper to block copper-dependent oncogenic functions and remodel the tumor microenvironment and metastatic niche to restrain tumor progression. At present, there are no established criteria based on TNBC molecular subtypes to guide the selection between these two therapeutic approaches.

### 4.3. Copper Complexes and Emerging Small-Molecule Cuproptosis Inducers

Beyond classical ionophores, numerous copper-containing complexes have demonstrated anti-cancer activity. Copper coordination compounds can induce mitochondrial dysfunction, oxidative stress, DNA damage, and proteotoxic stress through diverse mechanisms [66,67]. Recent studies have increasingly focused on developing compounds capable of selectively delivering copper to mitochondria. Such agents may enhance cuproptosis induction while minimizing systemic toxicity. Advances in medicinal chemistry have further enabled the engineering of copper responsive prodrugs, which achieve selective activation within the tumor microenvironment [35,66]. In preclinical TNBC models, a Cu(II)–dipyridophenazine complex has been reported to disrupt tricarboxylic acid cycle metabolism and enhance anti-tumor effects associated with cuproptosis and chemodynamic therapy [35].

Compounds that concurrently modulate copper transport, mitochondrial metabolism, and redox signaling are particularly promising. Since cuproptosis relies on the simultaneous occurrence of multiple molecular events, multitarget therapeutic strategies may exert superior efficacy compared with copper supplementation as a single intervention [18,30].

### 4.4. Copper-Based Nanomedicine

Nanotechnology has emerged as a powerful platform for improving the delivery and therapeutic index of anti-cancer agents. Nanoparticle systems can enhance tumor targeting, prolong circulation time, reduce off-target toxicity, and enable controlled drug release [68,69]. Copper-containing nanomaterials represent a particularly attractive strategy for cuproptosis induction: copper sulfide and copper peroxide nanoparticles and various copper-based hybrid systems have demonstrated potent anti-tumor activity in preclinical studies [31,70,71]. These nanoplatforms can generate localized copper accumulation within tumors, thereby reducing systemic exposure. Furthermore, many nanoparticle systems simultaneously induce oxidative stress, ferroptosis, immunogenic cell death, or photothermal effects, resulting in synergistic anti-tumor activity [31,35,70,71]. An increasing number of studies suggest that copper-containing nanomaterials can help overcome treatment resistance in preclinical TNBC models. In one study, an ultrasmall copper-doped hafnium oxide nanoradiosensitizer combined with brachytherapy overcame acquired radioresistance by inducing copper overload and cuproptosis [72]. Other copper-containing nanomaterials have enhanced responses to immunotherapy by triggering cuproptosis in mouse models [38–40]. Of particular interest, recent studies have developed multifunctional nanoparticles capable of inducing both ferroptosis and cuproptosis while simultaneously activating the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway. Such approaches have demonstrated enhanced immune activation and durable anti-tumor responses in experimental models [31]. Given the highly heterogeneous nature of TNBC, nanomedicine platforms may provide an effective means of integrating cuproptosis induction with personalized therapeutic strategies.

### 4.5. Combination Strategies with Immunotherapy

Recent evidence suggests that cuproptosis may augment anti-tumor immunity through the release of DAMPs, activation of antigen-presenting cells, and stimulation of innate immune signaling pathways. These immunological effects provide a strong rationale for combining cuproptosis-inducing agents with immune checkpoint inhibitors [17,36,37,71]. Mitochondrial stress generated during cuproptosis may enhance tumor antigen presentation and promote recruitment of cytotoxic T lymphocytes. In addition, activation of cGAS-STING signaling has been implicated in immune potentiation following copper-based nanotherapy [17,31,39].

Immune checkpoint blockade has significantly improved outcomes for selected patients with TNBC. Nevertheless, primary and acquired resistance remain major clinical challenges [4,52,73]. Recent preclinical evidence provides more direct support for combining cuproptosis induction with checkpoint blockade. A mechanistic study showed that cuproptosis can function as an immunogenic cell death program and that combining a cuproptosis inducer with PD-L1 blockade can overcome checkpoint resistance in multiple preclinical models [17]. In TNBC specifically, a nano-hydrogel system designed to enhance cuproptosis increased anti-tumor immune activation and synergized with anti-programmed cell death protein 1 (PD-1) therapy in preclinical models [38]. Clinical evidence for cuproptosis-inducing agents combined with immune checkpoint inhibitors is not yet available, and prospective clinical evaluation will be required.

### 4.6. Combination Strategies with PARP Inhibitors

PARP inhibitors are established therapeutic options for selected patients with HER2-negative breast cancer, including TNBC, who harbor germline *BRCA1* or *BRCA2* pathogenic variants [5]. However, resistance can emerge during treatment [74]. Conceptually, cuproptosis-based approaches may complement PARP inhibition, although direct experimental evidence supporting this combination in TNBC remains limited. Copper-induced mitochondrial dysfunction may increase oxidative stress, disrupt cellular energy homeostasis, and potentially intensify stress in DNA-repair-deficient tumors. These proposed interactions provide a rationale for future investigation but should currently be regarded as hypothesis-generating rather than clinically validated [18,74].

### 4.7. Combination Strategies with Radiotherapy

Radiotherapy remains a critical component of TNBC management, as radiation induces DNA damage, oxidative stress, and metabolic perturbations [75]. These effects provide a conceptual rationale for investigating combinations with cuproptosis-inducing strategies, but do not by themselves establish enhanced cuproptosis susceptibility.

Because mitochondrial respiration contributes substantially to radiation responses, simultaneous induction of cuproptosis may amplify metabolic stress beyond the threshold required for tumor cell survival. Furthermore, radiation-induced immunogenic effects may synergize with cuproptosis-associated immune activation [17,36,37]. More recently, direct preclinical evidence in acquired radioresistant TNBC showed that an ultrasmall copper-doped hafnium oxide nanoradiosensitizer combined with 192Ir brachytherapy triggered copper overload and cuproptosis, aggravated DNA damage, activated cGAS-STING signaling, and suppressed tumor growth and distant metastasis in murine models [72]. These findings strengthen the rationale for combining radiotherapy with cuproptosis induction, although clinical validation remains required.

### 4.8. Combination Strategies with Chemotherapy

Chemotherapy remains a central component of TNBC treatment, but primary and acquired chemoresistance remain major clinical challenges [2]. Recent studies indicate that copper homeostasis and cuproptosis-related pathways can influence chemotherapy response in cancer [76–78]. In breast cancer models, the copper ionophore ES-Cu reversed cisplatin resistance by promoting DLAT oligomerization, inducing cuproptosis, and increasing intracellular reactive oxygen species [78]. Separately, a screen of a Food and Drug Administration (FDA)-approved drug library identified zinc pyrithione (ZnPT) as a potential cuproptosis-inducing agent that suppresses TNBC progression by disrupting copper homeostasis and promoting DLAT oligomerization [15]. From a clinical treatment perspective, adding carboplatin to neoadjuvant chemotherapy in early-stage TNBC has been shown to increase pathological complete response and improve disease-free survival [79]. Together, these findings support further investigation of cuproptosis-targeted strategies for overcoming therapeutic resistance in TNBC, while clinical evidence for cuproptosis-directed combinations remains to be established.

## 5. Challenges for Clinical Translation

Despite encouraging preclinical findings, early clinical evidence has only just begun to emerge. A phase II clinical study of TTM-mediated copper depletion in high-risk breast cancer, including TNBC, demonstrated favorable tolerability and encouraging event-free survival [45,46]. Notably, this early phase II trial was single-arm, enrolled a heterogeneous high-risk breast cancer population without active disease, and lacked a parallel control group. The reported improvement in event-free survival represents only an observational

finding, and this preliminary evidence cannot be generalized to TNBC. Cuproptosis-related therapies have not yet entered clinical trials for triple-negative breast cancer. Several obstacles currently limit the clinical application of cuproptosis-targeting therapies, including uncertainty regarding optimal patient selection, potential systemic copper toxicity, and incomplete understanding of resistance mechanisms [7,18,28,30].

Several cuproptosis-related and copper-handling molecules, including FDX1, DLAT, DLST, LIAS, LIPT1, SLC31A1 (CTR1), ATP7A, and ATP7B, have been proposed as potential biomarkers for patient stratification [7,13,20,54,58,59]. However, these candidates have not yet been prospectively validated as predictors of therapeutic response. Future progress will therefore likely depend on biomarker-guided patient selection, development of tumor-selective copper delivery systems [68–72], and integration of multi-omics approaches to identify cuproptosis-sensitive tumor populations. Such advances may ultimately facilitate the incorporation of cuproptosis-targeted therapies into precision medicine frameworks for TNBC.

### *5.1. Biomarker Development for Patient Stratification*

One of the most significant barriers to the clinical translation of cuproptosis-targeted therapies is the lack of validated predictive biomarkers. Although cuproptosis has emerged as a promising therapeutic vulnerability, current evidence indicates that susceptibility to copper-induced cell death varies substantially among tumor types and even among molecular subgroups within the same type of cancer [7,13,20].

The dependence of cuproptosis on mitochondrial metabolism suggests that biomarkers reflecting oxidative phosphorylation activity may be particularly informative. Candidate biomarkers include the expression levels of FDX1, DLAT, DLST, LIAS, LIPT1, and other genes involved in mitochondrial protein lipoylation. Elevated expression of these molecules may indicate increased reliance on mitochondrial respiration and greater sensitivity to cuproptosis induction [13,20–22].

Copper transport machinery may represent an additional biomarker category. Expression levels of SLC31A1 (CTR1), ATP7A, ATP7B, and copper chaperones could influence intracellular copper accumulation and therapeutic responsiveness. In an exploratory analysis of tumor samples from 47 patients enrolled in a phase II tetrathiomolybdate (TTM) study, including 23 patients with TNBC, higher cytoplasmic ATOX1 expression showed a trend toward improved event-free survival in the TNBC subgroup; however, this difference was not statistically significant ($p = 0.45$) [55]. Integrating copper-transport and copper-chaperone signatures with metabolic biomarkers may improve patient selection for future clinical trials [8,9,60].

However, reliance on single-gene biomarkers is unlikely to adequately capture the complexity of cuproptosis biology. Future efforts should focus on multi-dimensional biomarker platforms integrating transcriptomic, proteomic, metabolomic, and spatial profiling data. Such approaches may facilitate the development of robust predictive models capable of identifying cuproptosis-sensitive TNBC populations [41,54,58,59].

### *5.2. Metabolic Heterogeneity and Dynamic Adaptation*

The remarkable metabolic plasticity of TNBC presents a major challenge for cuproptosis-based therapies. Because cuproptosis primarily targets mitochondrial respiration-dependent cells, therapeutic efficacy may be compromised by adaptive metabolic rewiring [24,48,80].

Cancer cells frequently switch between glycolysis and oxidative phosphorylation in response to environmental stress, nutrient availability, and therapeutic pressure. This metabolic flexibility may allow tumor cells to escape cuproptotic stress by reducing dependence on mitochondrial respiration and increasing glycolytic flux [24,48,80]. Furthermore,

metabolic heterogeneity exists not only among TNBC subtypes but also within individual tumors. Distinct cellular populations may coexist within the same lesion, including highly glycolytic cells, oxidative subpopulations, cancer stem cells, and therapy-resistant clones. Such heterogeneity may limit the efficacy of therapies targeting a single metabolic vulnerability [23,25,41].

Future therapeutic approaches will likely require real-time metabolic monitoring and adaptive treatment regimens that can respond to dynamic metabolic reprogramming within tumors.

### 5.3. Mechanisms of Resistance to Cuproptosis

Resistance represents an inevitable challenge for virtually all targeted therapies, and cuproptosis-inducing strategies are unlikely to be an exception. Although resistance mechanisms remain poorly characterized, several potential pathways have emerged from recent mechanistic studies [7,18,28,30].

One possible mechanism involves reduced intracellular copper accumulation through downregulation of copper uptake transporters or increased expression of copper efflux proteins. Alterations in SLC31A1, ATP7A, and ATP7B may significantly influence intracellular copper availability and diminish therapeutic efficacy [8,9,19]. Another mechanism may involve suppression of mitochondrial metabolism. Tumor cells that decrease oxidative phosphorylation and increase glycolytic dependency may become less susceptible to cuproptosis because of a reduced abundance of lipoylated mitochondrial proteins [7,13,20,23,24].

Additionally, enhanced antioxidant capacity may contribute to adaptive resistance. In particular, the *NFE2L2*-GSH-*SLC25A39* axis has been shown to increase mitochondrial glutathione availability and promote copper chelation, thereby reducing cuproptosis sensitivity [34]. More broadly, NRF2 coordinates cellular redox homeostasis and intermediary metabolism [81].

TNBC cells harboring elevated intracellular copper concentrations can display resistance to cuproptosis. Activated protein kinase B (AKT) is a critical determinant of cuproptosis resistance in TNBC cells, while AKT1-mediated FDX1 phosphorylation confers cuproptosis resistance, promotes TNBC progression, and enhances glycolysis. Combining an AKT inhibitor with a copper ionophore has been reported as a strategy to overcome cuproptosis resistance in TNBC models [14].

Understanding these resistance mechanisms will be essential for designing rational combination therapies capable of sustaining long-term therapeutic responses.

### 5.4. Safety Considerations and Copper Toxicity

Although induction of cuproptosis offers promising anti-tumor potential, systemic copper dysregulation may result in significant toxicity. Copper is essential for normal physiological functions, and excessive copper accumulation can damage the liver, nervous system, kidneys, and cardiovascular system [8–10,60]. The challenge of balancing therapeutic efficacy with systemic safety is particularly important in the context of copper ionophores and copper-based nanomedicines. Excessive copper exposure may induce off-target toxicity in healthy tissues with high mitochondrial activity [60,61,66].

Targeted delivery technologies may help address this challenge. Tumor-specific nanoparticles, stimulus-responsive drug delivery systems, and precision medicine approaches capable of selectively increasing copper concentrations within tumor tissues may improve therapeutic windows while minimizing adverse effects [68–70].

### 5.5. Integration with Precision Oncology

The future clinical success of cuproptosis-targeted therapies will likely depend on their integration into precision oncology frameworks rather than indiscriminate application across all TNBC patients. Similarly to the evolution of PARP inhibitors and immune

checkpoint blockade, patient selection will be essential for maximizing therapeutic benefit [5,52,73,74].

Future treatment algorithms may incorporate molecular subtype classification, cuproptosis-related gene signatures, metabolic phenotyping, and immune microenvironment assessment. Such approaches could facilitate the identification of patient populations most likely to benefit from copper-targeted interventions [3,41,42,51,54,58,59].

Artificial intelligence-assisted multi-omics analysis, single-cell sequencing, and spatial transcriptomics may further improve the precision of patient stratification and therapeutic decision-making. These technologies have the potential to reveal previously unrecognized cuproptosis-sensitive cellular states within heterogeneous TNBC tumors [41,54,58,59].

## 6. Discussion

The studies reviewed herein suggest that the therapeutic relevance of copper in TNBC depends on both tumor dependence on copper and susceptibility to copper-induced stress. These properties may coexist but do not necessarily correspond. Although mitochondrial respiration and protein lipoylation contribute to cuproptosis sensitivity [13,20], TNBC cells can tolerate elevated copper through adaptive mechanisms such as AKT1-mediated FDX1 phosphorylation [14]. Consequently, copper abundance alone is unlikely to identify responsive tumors. Its interpretation requires consideration of intracellular copper distribution, mitochondrial function, and resistance-associated signaling.

This biological complexity supports diverse copper-modulating approaches: copper depletion suppresses copper-dependent tumor-stromal functions, copper loading induces copper toxicity, and blockade of chaperone-mediated copper trafficking (e.g., DCAC50) causes oxidative stress and apoptosis in TNBC models [33,47]. These interventions do not act via cuproptosis. The TTM trial confirms the feasibility of copper depletion in high-risk patients including TNBC, though its single-arm design cannot validate treatment-related survival benefit [45,46]. Comparative studies are needed to identify optimal use cases for each strategy. In contrast, cuproptosis-activating therapies have not yet reached clinical testing in TNBC.

Patient selection is another unresolved issue. Retrospective cuproptosis-related gene signatures have identified prognostic associations [54,58,59], but these associations do not establish prediction of benefit from a particular intervention. Similarly, the exploratory ATOX1 analysis in TTM-treated patients provides a hypothesis for further investigation rather than a validated treatment-selection marker [55]. TNBC subtype labels may help organize biological heterogeneity. Functional measurements of respiration, protein lipoylation, and copper handling may complement subtype classification when evaluating treatment sensitivity. Future biomarker studies should link pretreatment measurements to responses to defined agents and distinguish prognostic effects from treatment-specific predictive value.

Interpretation of combination therapies also requires attention to their multiple mechanisms. Copper-containing hydrogels and coordination complexes can combine copper-associated toxicity with metabolic disruption, oxidative injury, and immune modulation [16,35]. Their overall anti-tumor activity therefore requires assessment of the contribution of each component. Appropriate controls, copper-chelation rescue, and genetic perturbation of FDX1 or the lipoylation machinery can strengthen mechanistic attribution. Preclinical findings involving immunotherapy and radiotherapy provide a basis for further development [17,31,38–40,72], while highlighting the need to assess how delivery systems and treatment schedules influence both tumor responses and normal-tissue toxicity.

This narrative review brings together evidence from heterogeneous experimental models, retrospective cohorts, and clinical copper-depletion studies. Differences in treatment

exposure, endpoints, and mechanistic assays limit direct comparisons across these studies. Progress will depend on reproducible assessments of copper-dependent vulnerabilities in patient-derived and immunocompetent models, followed by prospective evaluation of safety and treatment benefits. The registered randomized TTM study offers an opportunity to strengthen the clinical evidence for copper depletion [82]. In parallel, the development of cuproptosis-inducing agents requires evidence that their proposed mechanisms can be achieved safely and reproducibly in clinically relevant settings.

## 7. Conclusions and Perspectives

Copper homeostasis and cuproptosis provide a framework for understanding how copper can both support TNBC progression and create therapeutic vulnerabilities. The current evidence supports the investigation of copper depletion, disruption of copper trafficking, and copper loading as distinct treatment strategies. Their relevance depends on tumor biology and the mechanism of the intervention; currently, cuproptosis-inducing approaches remain predominantly at the preclinical stage.

The central translational question is whether these biological vulnerabilities can be used to achieve selective and durable tumor control in patients with TNBC. Addressing this question will require treatment-specific evidence linking tumor characteristics to therapeutic response. Copper-directed strategies represent a promising research direction, but their place in TNBC treatment remains to be defined.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| AKT | protein kinase B |
| AKT1 | AKT serine/threonine kinase 1 |
| AR | androgen receptor |
| ATOX1 | antioxidant 1 copper chaperone |
| ATP | adenosine triphosphate |
| ATP7A | copper-transporting ATPase 1 |
| ATP7B | copper-transporting ATPase 2 |
| BL1 | basal-like 1 |

| | |
|---|---|
| BL2 | basal-like 2 |
| BRAF | B-Raf proto-oncogene, serine/threonine kinase |
| BRCA1/2 | breast cancer susceptibility genes 1 and 2 |
| ccRCC | clear-cell renal cell carcinoma |
| CCS | copper chaperone for superoxide dismutase |
| CD4+ | cluster of differentiation 4-positive |
| CD8+ | cluster of differentiation 8-positive |
| CDK16 | cyclin-dependent kinase 16 |
| cGAMP | cyclic guanosine monophosphate–adenosine monophosphate |
| cGAS | cyclic GMP–AMP synthase |
| COX17 | cytochrome c oxidase copper chaperone |
| CRISPR–Cas9 | clustered regularly interspaced short palindromic repeats–CRISPR-associated protein 9 |
| CSCs | cancer stem cells |
| CTR1 | copper transporter 1 |
| CuET | bis(diethyldithiocarbamate)–copper complex |
| DAMPs | damage-associated molecular patterns |
| DC | dendritic cell |
| DCAC50 | copper-trafficking inhibitor (compound code) |
| DLAT | dihydrolipoamide S-acetyltransferase |
| DLST | dihydrolipoamide succinyltransferase |
| DNA | deoxyribonucleic acid |
| EFS | event-free survival |
| EMT | epithelial-to-mesenchymal transition |
| ER | estrogen receptor |
| ES–Cu | elesclomol–copper complex |
| FDA | Food and Drug Administration |
| FDX1 | ferredoxin 1 |
| Fe–S | iron–sulfur |
| GCSH | glycine cleavage system protein H |
| GOx | glucose oxidase |
| GSH | glutathione |
| HER2 | human epidermal growth factor receptor 2 |
| HMGB1 | high mobility group box 1 |
| IFN | interferon |
| IFN-gamma | interferon gamma |
| IRF3 | interferon regulatory factor 3 |
| JAK1 | Janus kinase 1 |
| LAR | luminal androgen receptor |
| LIAS | lipoic acid synthetase |
| LIPT1 | lipoyltransferase 1 |
| M | mesenchymal subtype |
| MHC | major histocompatibility complex |
| MK-2206 | AKT inhibitor (compound code) |
| mtDNA | mitochondrial DNA |
| NED | no evidence of disease |
| NFE2L2/NRF2 | nuclear factor erythroid 2-related factor 2 |
| NK | natural killer |
| NLRP3 | NLR family pyrin domain containing 3 |
| OXPHOS | oxidative phosphorylation |
| PARP | poly(ADP-ribose) polymerase |
| PD-1 | programmed cell death protein 1 |
| PD-L1 | programmed death-ligand 1 |
| PDHA1 | pyruvate dehydrogenase E1 subunit alpha 1 |
| PR | progesterone receptor |

| | |
|---|---|
| ROS | reactive oxygen species |
| SLC11A2 | solute carrier family 11 member 2 |
| SLC25A39 | solute carrier family 25 member 39 |
| SLC31A1 | solute carrier family 31 member 1 |
| SOD1 | superoxide dismutase 1 |
| STEAP | six-transmembrane epithelial antigen of the prostate |
| STEAP3 | six-transmembrane epithelial antigen of the prostate 3 |
| STING | stimulator of interferon genes |
| TBK1 | TANK-binding kinase 1 |
| TCA | tricarboxylic acid |
| TILs | tumor-infiltrating lymphocytes |
| TNBC | triple-negative breast cancer |
| TP53 | tumor protein p53 |
| TTM | tetrathiomolybdate |
| ZnPT | zinc pyrithione |

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