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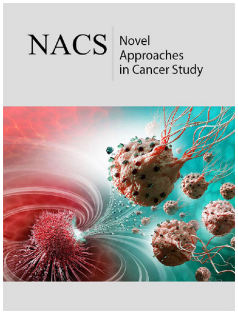

Cuproptosis in Colorectal Cancer: Mechanisms, Immunomodulation and Therapeutic Implications

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Abstract

Colorectal cancer (CRC) remains a significant global health challenge, necessitating the exploration of novel therapeutic strategies. Recent advancements in understanding regulated cell death (RCD) pathways have unveiled cuproptosis as a distinct form of RCD, triggered by copper accumulation and its direct binding to lipoylated proteins of the mitochondrial tricarboxylic acid (CAC) cycle. This review comprehensively synthesizes the current knowledge regarding cuproptosis, specifically focusing on its intricate mechanisms, its profound impact on the tumor microenvironment (TME) and immune responses, its utility as a prognostic and diagnostic biomarker, and the emerging therapeutic strategies leveraging cuproptosis in CRC. We delve into key molecular regulators such as FDX1, DLAT, and CDKN2A, elucidating their roles in modulating cuproptosis sensitivity and resistance. Furthermore, the immunogenic nature of cuproptosis, its interplay with other RCD pathways like ferroptosis, pyroptosis and disulfidptosis, and its influence on immune cell infiltration and function are thoroughly discussed. The review also highlights the development of cuproptosis-related gene and lncRNA signatures, as well as molecular subtyping, for predicting CRC prognosis and guiding personalized treatment. Finally, we explore innovative therapeutic approaches, including copper-based nanomaterials, small molecule modulators, and strategies targeting copper homeostasis, which hold immense promise for enhancing anti-tumor efficacy in CRC. This review underscores cuproptosis as a pivotal player in CRC pathophysiology and a compelling target for future therapeutic interventions.

Keywords: Cuproptosis; Colorectal cancer; Copper metabolism; Immunotherapy; Biomarkers; Targeted therapy; Tumor microenvironment; Regulated cell death

Introduction

Colorectal cancer (CRC) stands as one of the most prevalent and lethal malignancies worldwide, posing a substantial burden on global health systems. Despite significant advancements in diagnostic techniques and therapeutic modalities, including surgery, chemotherapy, radiotherapy and targeted therapies, the prognosis for advanced CRC patients remains challenging, often due to drug resistance, metastasis and an immunosuppressive tumor microenvironment (TME). Consequently, there is an urgent need to uncover novel mechanisms underlying CRC progression and identify innovative therapeutic targets.

The intricate interplay between cancer cells and their microenvironment, coupled with dysregulated cellular processes, underpins tumor development. Among these processes, regulated cell death (RCD) pathways have garnered considerable attention as critical

determinants of cancer cell fate and potential therapeutic vulnerabilities. Beyond conventional apoptosis, a diverse array of RCD mechanisms, including ferroptosis, pyroptosis and necroptosis, have been identified, each characterized by distinct molecular cascades and morphological features. The strategic induction of these RCD pathways represents a promising avenue for cancer therapy.

In recent years, a novel form of RCD, termed cuproptosis, has emerged, fundamentally reshaping our understanding of copper's role in cellular demise. Cuproptosis is distinct from other RCD pathways, being primarily triggered by the accumulation of copper ions, which directly bind to and induce the aggregation of lipoylated proteins within the mitochondrial tricarboxylic acid (CAC) cycle [1]. This copper-induced proteotoxic stress ultimately leads to cell death. The discovery of cuproptosis has opened new frontiers in cancer research, particularly given the well-established role of copper dyshomeostasis in various malignancies.

Copper, an essential trace element, is vital for numerous physiological processes, serving as a cofactor for enzymes involved in energy metabolism, antioxidant defense and angiogenesis. However, its cellular concentration must be tightly regulated, as both deficiency and excess can be detrimental. In the context of cancer, copper homeostasis is frequently perturbed, with many tumors exhibiting elevated copper levels, a phenomenon termed "cuproplasia" [2-4]. This copper accumulation can fuel tumor growth, angiogenesis, and metastasis, but paradoxically, it can also be exploited to induce cuproptosis, thereby offering a novel therapeutic window.

This comprehensive review aims to consolidate the burgeoning knowledge surrounding cuproptosis in the context of colorectal cancer. We will systematically delineate the molecular mechanisms governing cuproptosis induction and regulation, explore its multifaceted interactions with the CRC TME and immune system, discuss its potential as a prognostic and diagnostic biomarker, and highlight the innovative therapeutic strategies that harness cuproptosis to combat CRC. By synthesizing these diverse aspects, we seek to underscore the profound significance of cuproptosis as a critical determinant of CRC pathology and a promising target for future therapeutic interventions.

The Molecular Landscape of Cuproptosis

The discovery of cuproptosis has provided a novel perspective on how copper dysregulation can lead to cell death, distinct from other known RCD pathways. This section delves into the intricate molecular mechanisms underlying cuproptosis induction and the key regulators that govern its sensitivity and resistance in colorectal cancer.

Mechanism of Cuproptosis Induction

Cuproptosis is initiated by the intracellular accumulation of copper ions, which then directly bind to specific lipoylated proteins within the mitochondrial tricarboxylic acid (CAC) cycle [1]. This direct interaction is crucial for the execution of cuproptosis. The lipoylated proteins, primarily components of the pyruvate dehydrogenase complex (PDC) and α-ketoglutarate dehydrogenase complex (KGDHC), undergo aggregation upon copper binding. This aggregation leads to a cascade of events, including the loss of iron-sulfur cluster proteins, ultimately resulting in proteotoxic stress and mitochondrial dysfunction, culminating in cell death [1].

A central player in this process is Ferredoxin 1 (FDX1), which plays a critical role in reducing Cu^{2+} to Cu^{1+}, the more toxic form that drives cuproptosis. FDX1 is an essential enzyme for the lipoylation of mitochondrial enzymes, including DLAT (dihydrolipoamide S-acetyltransferase), a core component of the PDC. Therefore, FDX1 acts as a crucial upstream regulator, controlling both copper reduction and the lipoylation status of target proteins, thereby dictating cuproptosis sensitivity. For instance, the long non-coding RNA (lncRNA) PVT1 has been shown to transcriptionally activate FDX1, thereby promoting cuproptosis in CRC cells. Beyond its role in copper metabolism, FDX1 also regulates cuproptosis through the Hippo pathway, and its upregulation has been shown to inhibit CRC progression [5]. Conversely, hypoxia-induced autophagy can attenuate cuproptosis by reducing FDX1 levels, thereby promoting CRC progression and resistance to cuproptosis-inducing agents [6]. The importance of FDX1 extends to its ability to inhibit epithelial-mesenchymal transition (EMT), further suppressing CRC growth and progression [7].

Another key enzyme directly involved in the cuproptotic pathway is Dihydrolipoamide S-acetyltransferase (DLAT). DLAT is a core component of the PDC and is one of the primaries lipoylated proteins targeted by copper. Its accumulation and aggregation are hallmarks of cuproptosis. In hepatocellular carcinoma, DLAT has been identified as a cuproptosis-promoting factor and a molecular target for the cuproptosis inducer Elesclomol [8]. Low cuproptosis scores, often associated with reduced DLAT activity or expression, predict a favorable prognosis in some cancers, highlighting its prognostic significance [8]. In CRC, the BCL10 protein has been found to regulate DLAT expression via the NF-κB pathway, thereby influencing CRC cell sensitivity to cuproptosis [9].

The glycolytic enzyme Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) has also been implicated in cuproptosis. Certain compounds, such as 4-OI, promote cuproptosis by inhibiting GAPDH-mediated glycolysis [10]. This suggests a metabolic link, where inhibition of glycolysis can sensitize cells to copper-induced death.

ATP7A (ATPase Copper Transporting Alpha), a copper-transporting ATPase, plays a role in maintaining cellular copper homeostasis. While primarily studied in liver cancer, high ATP7A expression promotes tumor growth and its knockdown can induce cuproptosis, indicating its role in regulating intracellular copper levels and subsequent cuproptosis sensitivity [11].

Key Regulators of Cuproptosis in CRC

Beyond the core machinery, a complex network of genes, lncRNAs, and miRNAs modulate cuproptosis sensitivity and resistance in CRC. Understanding these regulators is crucial for identifying potential therapeutic targets and prognostic biomarkers.

A. **FDX1:** As discussed, FDX1 is a central regulator. Its transcriptional activation by lncRNA PVT1 promotes CRC cuproptosis. FDX1 also inhibits EMT, thereby suppressing CRC growth and progression [7]. The marine natural product CHC has been shown to induce CRC cell cuproptosis by specifically targeting FDX1 [12]. Conversely, hypoxia-induced autophagy can attenuate cuproptosis by downregulating FDX1, contributing to CRC progression [6].

B. **DLAT:** In addition to its direct role in the CAC cycle, DLAT's expression and activity are modulated by various factors. BCL10, through the NF-κB pathway, influences DLAT levels and thus CRC cuproptosis sensitivity [9]. DLAT, alongside CDKN2A, has been incorporated into prognostic models for CRC, highlighting its clinical relevance [13].

C. **CDKN2A (Cyclin Dependent Kinase Inhibitor 2A):** This tumor suppressor gene is frequently dysregulated in cancer. High expression of CDKN2A is observed in various tumors, correlating with poor prognosis and altered immune infiltration [14]. Importantly, CDKN2A has been shown to mediate cuproptosis resistance in CRC, primarily through its influence on glycolysis and copper homeostasis [15]. The lncRNA SNHG26 further exacerbates this resistance by degrading CDKN2A mRNA, thereby promoting CRC progression and facilitating CD8+ T cell immune evasion [16].

D. **HSPA8 (Heat Shock Protein Family A Member 8):** This chaperone protein plays a role in protein folding and stress response. Studies indicate a positive correlation between cuproptosis and disulfidptosis, another recently identified RCD pathway, with HSPA8 inhibiting CRC proliferation [17]. This suggests a complex interplay between different RCD mechanisms.

E. **TIGD1 (TIR Domain Containing 1):** TIGD1 has been identified as a novel gene regulating cuproptosis in CRC, indicating new avenues for understanding and targeting this pathway [18].

F. **P4HA1 (Prolyl 4-Hydroxylase Alpha 1):** Downregulation of P4HA1 has been shown to inhibit CRC growth and significantly enhance sensitivity to cuproptosis [19]. This suggests P4HA1 as a potential therapeutic target to sensitize CRC cells to cuproptosis.

G. **CEBPB (CCAAT Enhancer Binding Protein Beta):** CEBPB has been found to reduce CRC cuproptosis sensitivity through activation of the PI3K/AKT/mTOR signaling pathway [20]. This highlights a crucial survival pathway that can counteract cuproptosis induction.

H. **ACAD8 (Acyl-CoA Dehydrogenase Family Member 8):** Reduced expression of ACAD8 has been linked to the promotion of CRC metastasis [21]. While its direct role in cuproptosis requires further elucidation, its connection to CRC progression suggests potential indirect involvement.

I. **CALCOCO2 and HSPD1**: Curcumin, a natural compound, has been shown to induce oxidative stress and cuproptosis in CRC cells by downregulating CALCOCO2 and HSPD1, thereby inhibiting CRC progression [22]. This points to specific protein targets for cuproptosis induction.

J. **miR-653:** MicroRNAs also play regulatory roles. miR-653 has been shown to promote CRC proliferation by negatively regulating DLD (dihydrolipoamide dehydrogenase), an enzyme closely related to DLAT in the PDC [23]. This suggests that miRNAs can indirectly influence cuproptosis sensitivity by modulating key metabolic enzymes.

K. **SNHG7**: This lncRNA has been found to drive CRC progression by actively inhibiting cuproptosis, indicating its role as an oncogenic factor that confers resistance to copper-induced cell death [24].

L. **SLC31A1 (Solute Carrier Family 31 Member 1)**: As a copper transporter, SLC31A1 is crucial for cellular copper uptake. It has been identified as a potential biomarker and therapeutic target in various tumors [25]. In esophageal cancer, TRIM21 activates SLC31A1, leading to increased copper uptake and subsequent cuproptosis [26], suggesting a similar mechanism could be at play in CRC.

In summary, the molecular machinery of cuproptosis involves a delicate balance of copper uptake, reduction, and its interaction with lipoylated mitochondrial proteins. This process is tightly regulated by a diverse array of genes, lncRNAs, and miRNAs, many of which are dysregulated in CRC, offering multiple entry points for therapeutic intervention (Figure 1).

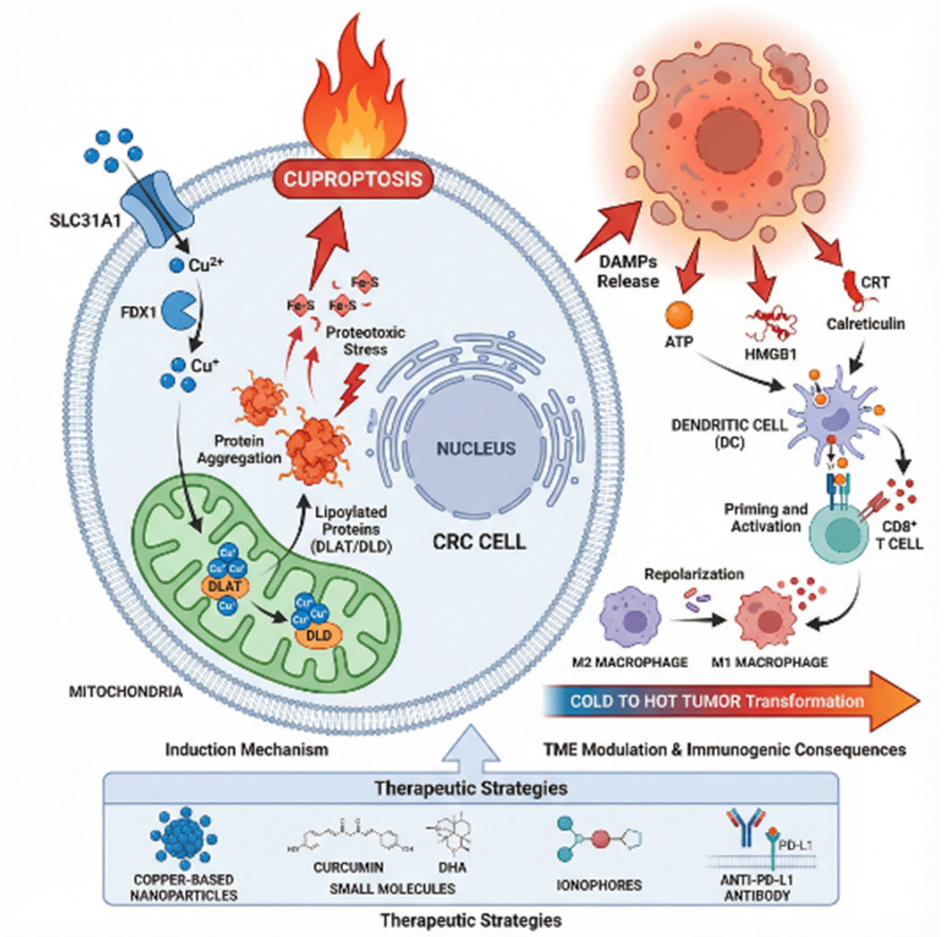

Figure 1: The mechanism and therapeutic implications of cuproptosis in colorectal cancer. This schematic illustrates the process of cuproptosis in colorectal cancer cells and its broader consequences. The pathway is initiated by the intracellular accumulation of copper ions, which, after reduction by FDX1, target mitochondrial lipoylated proteins (e.g., DLAT), leading to their aggregation, proteotoxic stress, and cell death. Cuproptosis also functions as an immunogenic cell death, releasing damage-associated molecular patterns that activate dendritic cells and cytotoxic T lymphocytes, and can modulate macrophage polarization, thereby reshaping the tumor microenvironment toward a more immunogenic state. These features highlight cuproptosis as a promising target for novel therapeutics, including copper-based nanomaterials and small molecule inducers, which may synergize with existing immunotherapies.

Cuproptosis and the Colorectal Cancer Tumor Microenvironment (TME)

The tumor microenvironment (TME) is a complex ecosystem comprising cancer cells, stromal cells, immune cells, extracellular matrix and signaling molecules. It profoundly influences tumor initiation, progression, metastasis and response to therapy. Emerging evidence highlights that cuproptosis is not merely a cell-autonomous event but significantly interacts with and reshapes the TME, particularly the immune landscape, in colorectal cancer.

Immunogenic Nature of Cuproptosis

A critical aspect of cuproptosis, distinguishing it from non-immunogenic forms of cell death, is its immunogenic potential. Cuproptosis has been recognized as an immunogenic cell death (ICD) pathway, capable of eliciting robust anti-tumor immune responses [27]. This immunogenicity stems from the induction of endoplasmic reticulum (ER) stress and the subsequent release of damage-associated molecular patterns (DAMPs) from dying cells. These DAMPs, such as ATP, HMGB1, and calreticulin, act as "danger signals" that alert and activate immune cells, particularly dendritic cells, leading to the priming and activation of cytotoxic T lymphocytes (CTLs). This activation of anti-tumor immunity is a highly desirable outcome in cancer therapy.

In the context of colorectal cancer, cuproptosis has been shown to influence the cytotoxicity of CD8+ T cells, particularly in microsatellite stable (MSS) colon cancer [28]. MSS CRC is often characterized by a "cold" TME with limited immune infiltration and poor response to immunotherapy. The ability of cuproptosis to enhance CD8+ T cell activity in this challenging subtype suggests its potential to convert immunologically "cold" tumors into "hot" ones, thereby improving immunotherapy efficacy.

Cuproptosis and Immune Evasion/Suppression

While cuproptosis can be immunogenic, its dysregulation or resistance can contribute to an immunosuppressive TME, facilitating immune evasion in CRC. Several studies have established a correlation between cuproptosis-related signatures and the immune landscape of various cancers, including CRC.

A low cuproptosis score has been consistently associated with a poor prognosis and an immunosuppressive TME in multiple cancers [29]. Specifically in CRC, a low cuproptosis score is predictive of poor prognosis and is closely linked to the TME and reduced efficacy of immunotherapy [30]. This suggests that tumors resistant to cuproptosis might foster an environment that actively suppresses anti-tumor immunity.

Molecular patterns associated with cuproptosis have been found to correlate with the immune microenvironment in CRC [31]. These patterns can influence the infiltration, activation, and polarization of various immune cell subsets. For instance, cuproptosis has been shown to downregulate GAL3ST4, which in turn inhibits the polarization of M2 macrophages [32]. M2 macrophages are pro-tumoral, promoting angiogenesis, immune suppression and tumor growth. By inhibiting M2 polarization, cuproptosis can shift the macrophage phenotype towards an anti-tumoral M1-like state, thereby enhancing anti-tumor immunity.

Conversely, certain factors can promote immune evasion by interfering with cuproptosis or related pathways. COX17, a copper chaperone, has been implicated in promoting immune evasion [33]. In contrast, DLAT, a key cuproptosis effector, has been shown to reverse T cell exhaustion and induce pyroptosis [33]. This highlights the complex and sometimes opposing roles of different molecules in shaping the immune response in the context of copper metabolism and cell death. Furthermore, the lncRNA SNHG26 promotes CRC progression and cuproptosis resistance and critically, it also contributes to CD8+ T cell immune evasion by degrading CDKN2A mRNA [16]. This mechanism directly links cuproptosis resistance to immune escape, underscoring the importance of targeting cuproptosis to overcome immune suppression.

Interplay with other Cell Death Pathways and Metabolism

The cellular response to stress and the execution of cell death are often interconnected, involving crosstalk between different RCD pathways. Cuproptosis is no exception, exhibiting complex relationships with other forms of RCD and metabolic processes, which collectively shape the fate of CRC cells and the TME (Figure 2).

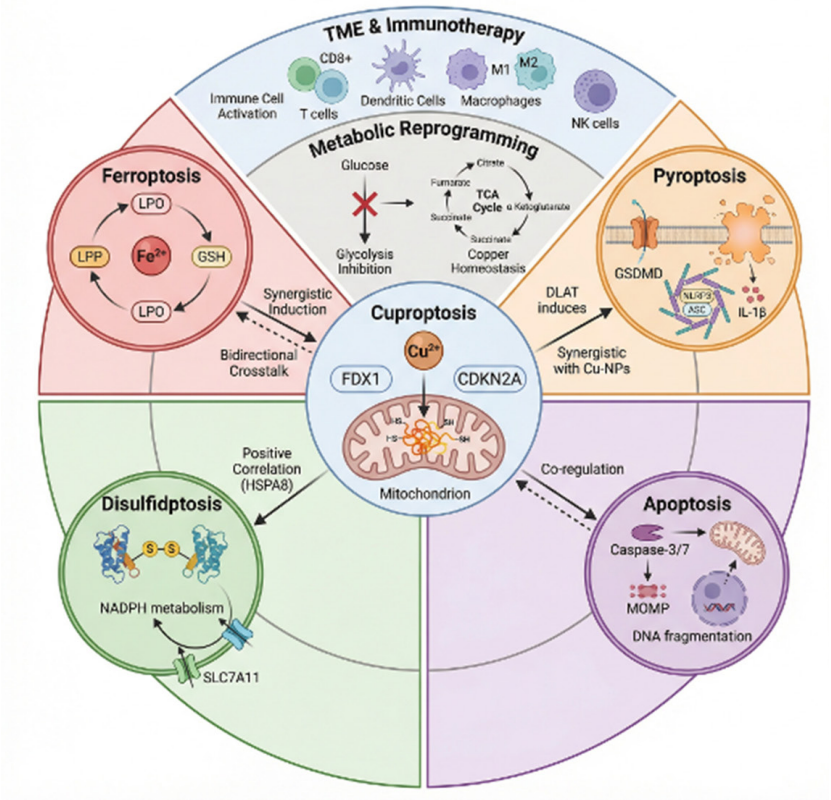

Figure 2: Crosstalk between cuproptosis and other regulated cell death (RCD) pathways in colorectal cancer. Cuproptosis interacts with multiple RCD pathways, influencing cancer cell fate and treatment responses. It synergizes with ferroptosis through shared inducers such as multifunctional nanoparticles; promotes pyroptosis via proteins like DLAT; correlates positively with disulfidptosis, potentially through HSPA8; and can be co-regulated with apoptosis. These interactions occur within a context of metabolic reprogramming and significantly shape the tumor immune landscape, offering opportunities for combination therapies targeting multiple cell death modalities.

a) **Disulfidptosis**: Cuproptosis has been found to be positively correlated with disulfidptosis, another recently identified RCD pathway [17]. However, it is also important to note that disulfidptosis and cuproptosis are distinct pathways, each with unique prognostic value in various cancers [34]. This suggests that while they may share some common triggers or downstream effects, their core mechanisms are different.

b) **Ferroptosis**: The interplay between cuproptosis and ferroptosis, an iron-dependent form of RCD, is also emerging. Cuproptosis and ferroptosis-related gene expression profiles have been shown to predict CRC patient prognosis and immunotherapy response [35]. This suggests that targeting both pathways simultaneously might offer synergistic therapeutic benefits. Multifunctional nanoparticles have been developed to synergistically treat CRC via cuproptosis, ferroptosis and apoptosis, highlighting the potential for multi-modal cell death induction [36].

c) **Pyroptosis**: Pyroptosis, a highly inflammatory form of RCD, also interacts with cuproptosis. Copper-based nanoparticles have been designed to regulate redox balance and inhibit glycolysis, synergistically enhancing both pyroptosis and cuproptosis for immunotherapy [37]. Furthermore, *in situ* sulfidation strategies have been developed to activate pyroptosis synergistically with cuproptosis for CRC immunotherapy [38]. The fact that DLAT can induce pyroptosis [33] further underscores the interconnectedness of these pathways.

d) **Apoptosis**: While distinct, cuproptosis can also synergize with apoptosis, the classical programmed cell death pathway. Natural small molecule hydrogels have been shown to inhibit CRC progression by regulating both cuproptosis and pan-apoptosis [39], indicating that inducing multiple RCD pathways can be a powerful anti-cancer strategy.

e) **Metabolic reprogramming**: Cancer cells are characterized by significant metabolic reprogramming, which can influence their sensitivity to RCD. Cuproptosis is intrinsically linked to mitochondrial metabolism, particularly the CAC cycle. Inhibition of glycolysis by compounds like 4-OI can promote cuproptosis [10]. Conversely, CDKN2A mediates cuproptosis resistance through its influence on glycolysis and copper homeostasis [15]. Hypoxia-induced autophagy attenuates cuproptosis via FDX1 downregulation, promoting CRC progression [6]. These findings highlight that targeting metabolic vulnerabilities can sensitize CRC cells to cuproptosis.

f) **Copper Metabolism and IBD**: The intricate relationship between copper metabolism and cuproptosis extends to inflammatory bowel disease (IBD) and CRC. Copper metabolism and cuproptosis exhibit dual regulatory roles in IBD and CRC, suggesting a complex interplay between inflammation, copper homeostasis and cancer development [40]. This connection is particularly relevant given that IBD is a risk factor for CRC.

In summary, cuproptosis plays a multifaceted role in the CRC TME, acting as an immunogenic cell death pathway that can activate anti-tumor immunity, while also being influenced by and interacting with various immune cells, other RCD pathways and metabolic reprogramming. Understanding these complex interactions is paramount for developing effective, TME-modulating therapeutic strategies for CRC.

Cuproptosis as a Prognostic and Diagnostic Biomarker in CRC

The identification of reliable biomarkers is crucial for early diagnosis, accurate prognosis prediction, and guiding personalized therapeutic decisions in colorectal cancer. Given the integral role of cuproptosis in CRC pathophysiology and its profound impact on the TME and treatment response, cuproptosis-related signatures have emerged as promising candidates for prognostic and diagnostic biomarkers.

Gene and LncRNA Signatures

Numerous studies have leveraged high-throughput sequencing data to identify cuproptosis-related gene and long non-coding RNA (lncRNA) signatures that hold significant prognostic and diagnostic value in CRC.

A. **LncRNA Models**: LncRNAs are non-protein-coding RNAs that play diverse regulatory roles in gene expression. Several lncRNA-based prognostic models related to cuproptosis have been developed for CRC. These include models based on 10 cuproptosis-related lncRNAs [41], lncRNA models predicting CRC prognosis and immunotherapy response [42], models for colon adenocarcinoma prognosis and diagnosis [43-45] and models based on four cuproptosis lncRNA features [46]. A comprehensive model based on 22 cuproptosis-related lncRNAs has also been constructed to predict CRC prognosis [47]. These models often integrate expression levels of multiple lncRNAs to generate a risk score, which can stratify patients into high- and low-risk groups with distinct survival outcomes. Similar lncRNA models have also been developed for other cancers, such as gastric cancer [48] and liver cancer [49], underscoring the broad applicability of this approach.

B. **Gene Signatures**: Beyond lncRNAs, specific cuproptosis-related gene features have been identified as prognostic indicators in CRC. These gene signatures can predict CRC prognosis and are often correlated with immune cell infiltration patterns within the TME [50-52]. Key cuproptosis effectors like DLAT and CDKN2A have been integrated into CRC prognostic models, which also show associations with the immune microenvironment [13]. The cuproptosis index model, derived from the expression of core cuproptosis genes, has been shown to accurately predict CRC patient prognosis [53].

C. **miRNA Features**: MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally. Cuproptosis-related miRNA features have been identified to predict CRC prognosis and sensitivity to immunotherapy. For example, miR-653, by negatively regulating DLD

(dihydrolipoamide dehydrogenase), promotes CRC proliferation, highlighting its role in modulating cuproptosis-related pathways and its potential as a biomarker [23].

Molecular Subtyping and Risk Models

The heterogeneity of CRC necessitates molecular subtyping to guide personalized treatment. Cuproptosis-related signatures contribute significantly to this endeavor by enabling the stratification of CRC patients into distinct molecular subtypes with varying clinical outcomes and therapeutic responses.

a) **Molecular subtyping**: Based on cuproptosis-related genes, distinct CRC molecular subtypes have been identified and corresponding prognostic prediction models have been constructed [54]. These subtypes often exhibit different immune landscapes and sensitivities to various therapies. For instance, a molecular subtyping approach based on both cuproptosis and hypoxia signatures has been proposed to guide personalized pan-cancer therapy, including immune and anti-fibrotic treatments [55].

b) **Risk models**: Cuproptosis-related gene molecular subtypes and risk models have been developed to predict CRC patients' responses to both immune checkpoint inhibitors and conventional chemotherapy [56]. This is particularly valuable for identifying patients who are likely to benefit from specific treatments, thereby avoiding ineffective therapies and associated toxicities. Multi-omics features, integrating genomic, transcriptomic and other data types related to cuproptosis, have also been employed to assess CRC prognosis and predict immunotherapy efficacy [57,58].

c) **TME Heterogeneity**: Cuproptosis modification patterns have been shown to correlate with the heterogeneity of the CRC tumor microenvironment [59]. This implies that cuproptosis-related signatures can provide insights into the complex cellular composition and functional states of the TME, which are critical determinants of therapeutic response.

d) **Recurrence prediction**: A model based on the negative correlation between cuproptosis and angiogenesis has been developed to predict CRC recurrence [60]. This offers a novel tool for identifying patients at high risk of relapse, allowing for more aggressive follow-up or adjuvant therapies.

e) **Interplay with other RCDs**: The combined analysis of cuproptosis and ferroptosis-related gene expression profiles has also proven effective in predicting CRC patient prognosis and immunotherapy response [35], suggesting that integrating multiple RCD pathways can enhance prognostic accuracy. Similarly, models incorporating both disulfidptosis and cuproptosis lncRNAs have been developed to predict colon cancer prognosis [61].

Clinical relevance

The clinical utility of cuproptosis-related biomarkers extends to various aspects of CRC patient management.

A. **Clinical status and immunotherapy**: Cuproptosis markers have been shown to influence CRC clinical status and predict responses to immunotherapy [62]. A low cuproptosis score, for example, is often associated with poor prognosis and is relevant to the TME and immunotherapy outcomes [30].

B. **Serum copper levels**: Changes in serum copper levels in CRC patients have been investigated through meta-analysis [63]. While not a direct measure of cuproptosis, systemic copper dysregulation can reflect the overall copper status in the body and potentially correlate with tumor copper levels, offering a less invasive diagnostic or prognostic indicator.

C. **Pan-cancer relevance**: Cuproptosis is a recognized cancer treatment target that has garnered significant attention in various cancer types [64]. This pan-cancer relevance suggests that findings from CRC studies on cuproptosis biomarkers may be translatable to other malignancies. For instance, DLAT has been identified as a key prognostic and immune biomarker across multiple cancer types [65].

In conclusion, cuproptosis-related gene, lncRNA, and miRNA signatures, as well as molecular subtyping and risk models, represent powerful tools for predicting CRC prognosis, stratifying patients for personalized treatment, and monitoring disease progression. These biomarkers offer valuable insights into the underlying biology of CRC and hold immense promise for improving patient outcomes.

Therapeutic Strategies Targeting Cuproptosis in CRC

The discovery of cuproptosis has opened a new therapeutic window for cancer treatment, particularly in colorectal cancer, where copper dyshomeostasis is prevalent. Strategies aimed at inducing or enhancing cuproptosis, either alone or in combination with other therapies, are actively being explored. These approaches primarily fall into three categories: copper-based nanomaterials and ionophores, small molecule modulators, and broader strategies targeting copper homeostasis.

Copper-Based Nanomaterials and Ionophores

Nanotechnology offers a versatile platform for delivering copper ions or copper-based compounds to tumor sites, enhancing their therapeutic efficacy while minimizing systemic toxicity.

a) **Enhanced immunotherapy**: Nanomaterials designed to target cuproptosis have shown promise in enhancing the immunotherapeutic efficacy in CRC [66]. These nanoparticles can selectively deliver copper to cancer cells, inducing cuproptosis and subsequently activating anti-tumor immune responses within the TME.

b) **Synergistic RCD induction**: Copper-based nanoparticles can regulate cellular redox balance and inhibit glycolysis, synergistically enhancing both pyroptosis and cuproptosis for immunotherapy [37]. This multi-modal RCD induction can overcome resistance mechanisms and achieve more robust

anti-tumor effects. Similarly, multifunctional nanoparticles have been developed to synergistically treat CRC via cuproptosis, ferroptosis and apoptosis, showcasing the potential of combining different RCD pathways [36].

c) **Targeted delivery and immunomodulation**: Mitochondria-targeting nanoparticles, such as Cu/TI, have been engineered to induce cuproptosis and concurrently downregulate PD-L1 expression, thereby enhancing the efficacy of immunotherapy [67]. This dual action addresses both tumor cell killing and immune checkpoint blockade. Self-assembled nanoreactors have also been developed to induce cuproptosis specifically for immunotherapy applications [68].

d) **Overcoming resistance and stemness**: Copper coordination nanoframeworks can enhance chemo-immunotherapy by inhibiting tumor stemness, a major contributor to drug resistance and recurrence [69]. The TPGS/P-C@Ce6 nanoplatform represents another innovative strategy, synergistically inducing cuproptosis and eliminating tumor stem cell characteristics [70]. Cu-PrIm nanozymes have been shown to induce apoptosis and cuproptosis, and importantly, degrade HIF-1α, thereby overcoming drug resistance in tumors [71].

e) **Combined modalities**: The integration of cuproptosis induction with other physical therapies is also being explored. A three-tier nanorocket strategy has been developed to induce CRC cuproptosis in conjunction with photothermal therapy, offering a powerful combinatorial approach [72]. Copper-based nanotherapeutics have also been shown to enhance the efficacy of cancer radiotherapy [73].

f) **Specific molecular targeting**: Nanohybrids specifically targeting CAD (carbamoyl phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase) have been designed to inhibit CRC by inducing cuproptosis [74]. This demonstrates the precision with which nanotechnology can be employed to target specific vulnerabilities. Furthermore, fibropeptide nanoparticles have been developed to block ATP7B, a copper efflux transporter, leading to "copper-free" cuproptosis by disrupting copper homeostasis [75].

g) ***In situ* activation**: *In situ* sulfidation is an innovative approach that activates pyroptosis synergistically with cuproptosis for CRC immunotherapy, showcasing the potential for localized and highly effective therapeutic interventions [38].

Small Molecule Modulators

Beyond nanomaterials, various small molecules have been identified or developed that can modulate cuproptosis, offering direct pharmacological interventions.

A. **Dihydroartemisinin (DHA)**: This artemisinin derivative has been shown to induce CRC cell cuproptosis by inhibiting LOXL2-mediated glycerophospholipid metabolism reprogramming [76]. This highlights a metabolic vulnerability that can be exploited to trigger cuproptosis.

B. **Curcumin**: This natural polyphenol acts as a copper ionophore, facilitating copper entry into cells and upregulating cuproptosis mediators [77]. Conversely, glutathione can inhibit this process, indicating the importance of redox balance. Curcumin also inhibits CRC by downregulating CALCOCO2 and HSPD1, leading to oxidative stress and cuproptosis [22].

C. **4-OI**: As mentioned earlier, 4-OI promotes cuproptosis by inhibiting GAPDH glycolysis [10], suggesting that targeting specific metabolic enzymes can induce cuproptosis.

D. **Natural small molecule hydrogels**: These innovative platforms can inhibit CRC progression by regulating both cuproptosis and pan-apoptosis, offering a multi-pronged approach to cell death induction [39].

E. **Targeting programmed cell death**: The development of small molecules specifically designed to target programmed cell death pathways, including cuproptosis, is a growing area of research for CRC treatment [78].

F. **Marine natural product CHC**: This compound has been shown to induce CRC cell cuproptosis by specifically targeting FDX1 [12], further validating FDX1 as a druggable target.

Targeting Anti-Aging Genes: Modulation of Sirtuin 1

Anti-aging genes play a central role in determining cell fate, metabolic regulation, and stress resistance. Among them, the class III histone deacetylase Sirtuin 1 (SIRT1) has been the most extensively studied. SIRT1 exerts its deacetylase activity in an NAD^+-dependent manner and is involved in the pathogenesis of various tumors, including colorectal cancer [79]. Accumulating evidence indicates that SIRT1 regulates key processes in CRC progression, such as apoptosis, autophagy, proliferation, migration, invasion, metastasis, oxidative stress, resistance to chemotherapy and radiotherapy, immune evasion and metabolic reprogramming [80]. Therefore, SIRT1 has emerged as a promising therapeutic target in CRC.

In the context of cuproptosis, the modulation of SIRT1 demonstrates dual potential. On the one hand, as a key sensor of cellular stress and metabolism, SIRT1 activity may influence mitochondrial function, energy metabolism and redox homeostasis, thereby indirectly regulating cellular sensitivity to copper ion accumulation and the acetylation status of key cuproptosis-related proteins (e.g., FDX1, DLAT). For instance, SIRT1-mediated metabolic reprogramming may alter the energy supply pattern of cancer cells, affecting their ability to cope with copper-induced mitochondrial proteotoxic stress. On the other hand, the role of SIRT1 in immune regulation [80] suggests that its inhibitors may synergize with cuproptosis inducers by disrupting tumor immune evasion mechanisms. As an immunogenic cell death modality, cuproptosis-induced release of tumor antigens and immune activation may combine with the improved immune microenvironment resulting from SIRT1 inhibition to jointly enhance anti-tumor immune responses.

Preclinical studies have shown promising prospects for SIRT1 inhibitors as monotherapy or in combination with chemotherapy, radiotherapy and immunotherapy in CRC [80]. For example, SIRT1 inhibitors may enhance the sensitivity of cancer cells to conventional chemotherapeutic agents by interfering with DNA repair capacity, inducing apoptosis, or senescence. Meanwhile, given the correlation between SIRT1 levels and metabolic diseases as well as neurodegenerative disorders, its potential as a plasma diagnostic biomarker warrants further exploration in CRC [81]. Integrating SIRT1 activity modulation into cuproptosis-targeted therapeutic strategies provides a new direction for developing more precise combination therapies. Future research should further elucidate the specific molecular mechanisms of SIRT1 in regulating cuproptosis in CRC and evaluate the application value of SIRT1 activators versus inhibitors in different CRC molecular subtypes and therapeutic contexts.

Targeting copper homeostasis

Given that cuproptosis is fundamentally driven by copper accumulation, strategies that manipulate cellular copper homeostasis represent a direct approach to inducing this form of RCD.

a) **Exploiting copper dyshomeostasis**: Colorectal cancer cells often exhibit dysregulated copper metabolism, with increased copper uptake and accumulation (cuproplasia) [3,4]. This inherent vulnerability can be exploited by administering copper-chelating agents (to reduce copper for specific contexts) or copper-ionophores (to increase intracellular copper to toxic levels), depending on the specific tumor's copper status and the desired outcome.

b) **Modulating copper transporters**: Targeting copper transporters like ATP7A [11] or SLC31A1 [25] can alter intracellular copper levels and thereby modulate cuproptosis sensitivity. Inhibiting copper efflux or enhancing copper influx could sensitize CRC cells to cuproptosis.

In summary, the therapeutic landscape for CRC is rapidly evolving with the integration of cuproptosis-targeting strategies. From sophisticated copper-based nanomaterials that offer precise delivery and synergistic RCD induction to small molecule modulators that directly interfere with cuproptosis pathways, and broader approaches that manipulate copper homeostasis, these innovations hold significant promise for improving the efficacy of CRC treatment.

Conclusion

The emergence of cuproptosis as a distinct form of regulated cell death has profoundly impacted our understanding of copper's role in cancer biology, particularly in colorectal cancer (CRC). This comprehensive review has highlighted the intricate molecular mechanisms governing cuproptosis, its multifaceted interactions with the tumor microenvironment (TME) and immune system, its utility as a prognostic and diagnostic biomarker, and the innovative therapeutic strategies leveraging this pathway in CRC.

We have elucidated that cuproptosis is triggered by copper accumulation, leading to the aggregation of lipoylated proteins in the mitochondrial tricarboxylic acid cycle, primarily mediated by key regulators such as FDX1 and DLAT [1,8]. The sensitivity to cuproptosis is finely tuned by a complex network of genes (e.g., CDKN2A, HSPA8, TIGD1), lncRNAs (e.g., PVT1, SNHG26, SNHG7), and miRNAs (e.g., miR-653), many of which are dysregulated in CRC, offering multiple points for therapeutic intervention [14,16-18,23,24].

Crucially, cuproptosis is not merely a cell-autonomous event but actively shapes the CRC TME. Its immunogenic nature, characterized by the induction of ER stress and DAMP release, can activate robust anti-tumor immunity, influencing CD8+ T cell cytotoxicity in MSS colon cancer [27,28]. Conversely, resistance to cuproptosis or its dysregulation can contribute to an immunosuppressive TME, often correlating with poor prognosis [29,30]. The intricate crosstalk between cuproptosis and other RCD pathways, such as ferroptosis, pyroptosis and disulfidptosis, as well as its links to metabolic reprogramming, further underscore its central role in determining CRC cell fate and immune responses [35,37,17,10].

The clinical relevance of cuproptosis is evident in its potential as a prognostic and diagnostic biomarker. Cuproptosis-related gene and lncRNA signatures, alongside molecular subtyping and risk models, have demonstrated significant predictive power for CRC prognosis, immune infiltration and response to immunotherapy [41,42,51,53,56]. These biomarkers offer valuable tools for patient stratification and guiding personalized treatment strategies.

The therapeutic landscape for CRC is being revolutionized by strategies that harness cuproptosis. Innovative approaches, including copper-based nanomaterials for targeted delivery and synergistic RCD induction (e.g., with pyroptosis, ferroptosis, or apoptosis) [66,37,36], hold immense promise for enhancing anti-tumor efficacy and overcoming resistance. Small molecule modulators like dihydroartemisinin and curcumin, which directly interfere with cuproptosis pathways, also represent compelling therapeutic avenues [76,77]. Furthermore, strategies that directly target copper homeostasis, exploiting the inherent copper dysregulation in CRC, offer a fundamental approach to inducing cuproptosis [3,4].

In conclusion, cuproptosis has emerged as a pivotal player in the pathophysiology of colorectal cancer, influencing cell death, immune responses and therapeutic outcomes. Its intricate mechanisms and widespread implications make it a compelling target for novel diagnostic and therapeutic interventions. Continued research into the precise molecular underpinnings of cuproptosis, its complex interactions within the TME and the development of highly specific and effective cuproptosis-modulating agents will be crucial for translating these exciting discoveries into tangible clinical benefits for CRC patients.

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Authors' Contributions

All authors contributed to the study conception and design. All authors declared no competing interests. Xinyue Jiang and Dengwang Chen: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing. (These authors contributed equally to this work.). Linna Wei, Dongmei Li and Zudi Meng: Supervision, Project administration, Resources, Writing - Review & Editing.

Ethics Approval and Consent to Participate

Not applicable.

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Competing Interests

The authors declare that they have no competing interests.

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