Effects of cuproptosis and its application in inflammatory bowel disease (Review)

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Abstract. Inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease, is a common, recurring, chronic intestinal inflammatory illness that is considered to be impacted by the immune system, gut microbiota and genetic factors. Copper (Cu), a crucial metal ion in cuproptosis, contributes to IBD, with studies revealing that its dysregulation contributes to oxidative stress, intestinal inflammation, gut dysbiosis and disruption of barrier integrity. Additionally, cuproptosis-related genes have been implicated in the pathogenesis of IBD, characterized by defects in barrier integrity and enhanced immune responses. These genes have been identified as biomarkers of IBD, providing novel therapeutic strategies for exploring their treatment. The present review highlights the mechanism of cuproptosis and the role of Cu in IBD. The review also highlights the cuproptosis-related genes in the pathogenesis of IBD, as well as their applications as biomarkers for therapeutic purposes. These biomarkers may provide a reference for IBD for clinical decision-making. The primary challenge is the lack of standard clinical medications for treating IBD associated with cuproptosis-related genes. Consequently, researchers are employing molecular docking and other techniques to identify potential drugs aimed at these genes for therapeutic purposes.

Contents

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1. Introduction

A recently discovered type of cell death, known as cuproptosis, results from an excessive accumulation of copper (Cu) within cells (1). Through enzymatic activity and nuclear magnetic resonance analysis, Tsvetkov *et al* (2) discovered that elesclomol targets ferredoxin 1 (FDX1) and induces Cu-dependent cell death. Elesclomol and disulfiram are examples of Cu ionophores that raise intracellular Cu levels (3). This increase causes oxidative stress and consequent cell death, which may have consequences for cancer treatment (3). Additionally, Cu ionophores contribute to Cu toxicity and cell death by interfering with protein lipoylation and mitochondrial respiration (3). Cuproptosis is a Cu-dependent cell death that differs from the well-known programmed cell death (PCD) (4). Typical modes of PCD include ferroptosis, necroptosis, autophagy, pyroptosis, apoptosis and neutrophil extracellular traps (5). However, cuproptosis has unique molecular mechanisms and signaling pathways that differentiate it from other forms of cell death, such as apoptosis, necroptosis and ferroptosis (6).

Cuproptosis results from disruptions to Cu homeostasis, which is dependent on the Cu transporter (7). Inflammation, oxidative stress and apoptosis are among the pathogenic processes in which cuproptosis is now known to be involved (8). Attention has recently been drawn to the part that Cu and Cu-induced cell death play in the etiology of cancer (9). Due to its immense potential for cancer therapy, cuproptosis has attracted a lot of attention from cancer research communities (9). Cu-based therapy inhibits the growth of malignancies and may make it possible to treat tumors that are resistant to

chemotherapy (9). Cuproptosis is a highly investigated topic in the field of cancer research (8). In the setting of inflammatory bowel disease (IBD), cuproptosis has not been well studied (10). Additionally, numerous studies have now demonstrated that genes linked to cuproptosis are essential for the initiation, spread and prognosis of a wide range of malignancies, such as breast cancer, lung adenocarcinoma and uterine corpus endometrial carcinoma (11-14). Nevertheless, the precise function of genes linked to cuproptosis in ulcerative colitis (UC) (14) and Crohn's disease (CD) remains unclear. Current evidence indicates that these genes are involved in the pathophysiology of IBD (15). Despite this, limited clinical treatments target these genes in IBD, which justifies the search for new drugs that can cure IBD caused by cuproptosis-related genes. Consequently, the present review emphasizes the cuproptosis mechanism, related genes, their pathogenesis and their use as biomarkers for IBD, aiming to explore therapeutic strategies targeting these genes.

2. Mechanism of cuproptosis

The type of cell death known as cuproptosis was discovered in 2022 and depends on the precise delivery of Cu ions to lipoylated tricarboxylic acid (TCA) cycle proteins (16). A study by Huo *et al* (17) showed that the creation of the Cu ionophore elesclomol causes cuproptosis in cardiomyocytes, implying that Cu ions may be involved in cuproptosis. Solute carrier family 31 member 1 (SLC31A1) importers and ATPase Cu transporting β (ATP7B) exporters of Cu modulate intracellular Cu^{2+} levels to regulate cuproptosis (18). The first three metal-binding domains and the Cu chaperone antioxidant 1 Cu chaperone (ATOX1), which transports Cu to ATP7B, are essential for controlling ATP7B activity (19). Notably, excess Cu causes cuproptosis through the TCA cycle's Cu-dependent aberrant oligomerisation of lipoylation proteins and subsequent reduction in iron-sulphur cluster protein levels, leading to proteotoxic stress and, eventually, cellular death (7,16). During the TCA cycle, Cu binds to acyl-CoA synthetase, causing cuproptosis (20). In the formation of the pyruvate dehydrogenase (PDH) complex, FDX1 stimulates the lipoacylation of dihydrolipoyl transacetylase (DLAT) and inhibits iron-sulfur cluster proteins by converting Cu^{2+} to Cu^{+}, which results in cell death (7). Additionally, FDX1 interacts directly with lipoyl synthase (LIAS) to support its function in lipoylation of cellular proteins, which is necessary to keep cells viable in low-glucose environments (21). FDX1 is both a critical regulator of Cu ionophore-induced cell death and an upstream regulator of cellular protein lipoylation, a post-translational modification based on mitochondrial lipids that occurs spontaneously on four mitochondrial enzymes necessary for TCA cycle function (21).

In summary, the core regulatory axis of cuproptosis includes Cu increase, FDX1 stimulation, LIAS upregulation, and DLAT, as the executioner of cuproptosis. Elesclomol increases intracellular Cu levels (3), but FDX1 is a reductase that converts Cu^{2+} to a more hazardous Cu^{1+} (22). Furthermore, FDX1 directly interacts with LIAS to facilitate its role in cellular protein lipoylation (21). LIAS enhances the lipoylation of DLAT, thereby altering DLAT and facilitating Cu binding to it (23). Finally, DLAT conducts cuproptosis by aggregation and oligomerization. Proteotoxic stress-induced cuproptosis results from this, as well as the decrease in iron-sulfur cluster protein levels (23). Fig. 1 illustrates the pathways in more detail.

Possible regulatory mechanisms of cuproptosis in immune cells. Cu plays a vital role in immune function, and a lack of Cu can impair immune performance, making the body more susceptible to microbial infections (24). The metal can influence the activation of cells linked to innate immunity, such as macrophages and neutrophils, during bacterial infections, as well as the processes of leukocyte differentiation, maturation and migration (25,26). Furthermore, the presence of Cu within tumors has been shown to influence PD-L1 expression and tumor immune evasion (27). These indicate that Cu may play a role in regulating the immune system and its checkpoints. Consequently, this section will explore the potential modulatory effect of cuproptosis on immune cells and the checkpoints that govern them.

FDX1-lipoylation axis and metabolic rewiring. Cuproptosis, a new form of Cu-dependent cell death that relies on the precise delivery of Cu ions to lipoylated TCA cycle proteins and that is dependent on mitochondrial respiration regulation, is mediated by FDX1 (7,28,29). Cells that rely on mitochondrial respiration are more susceptible to the Cu ionophore elesclomol, which causes cuproptosis (30). More mitochondria and a higher rate of oxygen consumption are characteristics of M2-polarized macrophages (31). M2 macrophages often use glutamine to power the TCA cycle, in contrast to M1 macrophages, which rely on glycolysis (32). Therefore, M2 polarization is unaffected by glucose deprivation as long as oxidative phosphorylation (OXPHOS) and mitochondrial activity are maintained (33). As a result, inflammatory M1 macrophages exhibit decreased mitochondrial activity and increased glycolytic metabolism. On the other hand, anti-inflammatory M2 macrophages exhibit increased spare respiratory capacity and strong mitochondrial OXPHOS (31). Consequently, M2 macrophages (34), T cells in a resting state (35,36) and memory T cells (37) utilize OXPHOS. This suggests that these immune cells may exhibit increased sensitivity to the Cu ionophore elesclomol, which induces cell death through cuproptosis.

Transmembrane Cu flux mediators (SLC31A1 vs. ATP7A/B). i) SLC31A1 influx. The process of 'cuproptosis' is associated with SLC31A1, known as a Cu importer (38). Studies have shown that SLC31A1 exhibits higher expression in macrophages, chondrocytes and fibroblasts (39), in chronic apical periodontitis (40), and in CD (10). In CD, SLC31A1 is positively correlated with the relative abundance of resting natural killer (NK) cells and M1 macrophages (10). This shows that macrophages and NK cells expressing SLC31A1 may be susceptible to Cu-induced cell death.

ii) ATP7A and ATP7B efflux. ATP7A and ATP7B play a crucial role in regulating Cu levels in cells by facilitating the removal of excess Cu (41). Cu^{+} ions are transferred from delivery to acceptor proteins across the membrane via ATP7A/B without creating a free Cu^{+} gradient (42). Prior research demonstrated that bactericidal activity against a non-pathogenic strain of *Escherichia coli* was reduced when ATP7A expression was silenced in RAW264.7

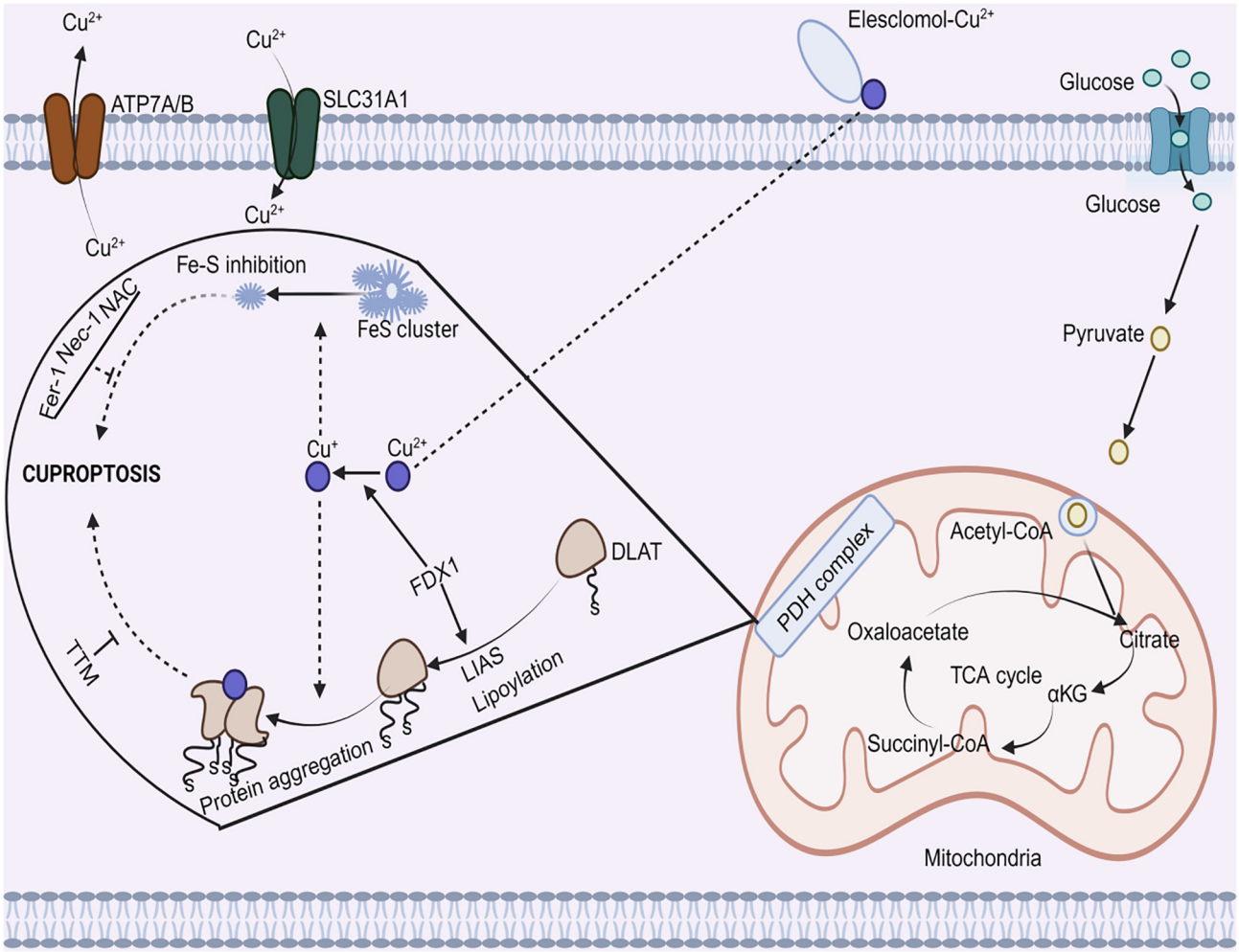

Figure 1. Cuproptosis route. Excess Cu^+ causes cuproptosis in the TCA cycle. Fer-1, Nec-1 and NAC do not inhibit cuproptosis, however, TTM does. Created using BioRender.com. αKG, α ketoglutarate; Cu^+, copper ion; DLAT, dihydrolipoyl transacetylase; Fer-1, ferrostatin-1; Fe-S, iron-sulfur; LIAS, lipoyl synthase; NAC, N-acetyl cysteine; Nec-1, necrostatin-1; TTM, tetrathiomolybdate; ATP7A/B, ATPase Cu transporting α/β; SLC31A1, solute carrier family 31 member 1; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid; FDX1, ferredoxin 1.

macrophage-like cells (43). Additionally, in comparison to macrophages separated from wild-type mice, primary macrophages isolated from ATP7AlysMcre (mice with the ATP7A gene specifically deleted) showed reduced Cu transport into phagosomal compartments and a lower capacity to kill *Salmonella enterica* serovar Typhimurium (44). These findings suggest that increased ATP7A expression in macrophages may enhance Cu transport into phagosomes, thereby helping to fight infection. This suggests that extracting more Cu from macrophage cytosol may help prevent cuproptosis in these cells by inhibiting mitochondrial Cu entry.

Glutathione (GSH) and intracellular Cu buffering. i) The GSH-cuproptosis brake. GSH chelates Cu to prevent cuproptosis (45,46). By contrast, cell cuproptosis is enhanced when GSH concentration is decreased (46). Cu chelators, such as tetrathiomolybdate (TTM), can be used to lessen cuproptosis (47). ROS produced by activated T cells activate the GSH response, which is required to buffer the increasing ROS and prevent cellular damage (48). GSH controls metabolic activity, which is crucial for T-cell effector functions (48). Since GSH inhibits cuproptosis by chelating Cu, the loss of the antioxidant GSH may likely perpetuate cuproptosis in cells, including T cells.

p53-glycolytic switch. OXPHOS is a critical component of mitochondrial respiration and is responsible for cuproptosis, a recently discovered mechanism of cell death (49). Cells with high OXPHOS capacity are more prone to cuproptosis (50). Notably, in cancer cells, the tumor suppressor p53 is an essential metabolic regulator that prevents glycolysis and promotes a metabolic shift towards OXPHOS (51). Furthermore, this tumor suppressor may be involved in cuproptosis, as p53 regulates the production of iron-sulfur clusters and the Cu chelator GSH, both of which are required for cuproptosis (51). Thus, by inhibiting glycolysis and promoting the switch to mitochondrial metabolism, p53 may make cells more vulnerable to cuproptosis (30). High levels of glycolysis flux via the pentose phosphate pathway and an increase in some Krebs cycle intermediates, such as succinate, citrate and itaconic acid, are characteristics of M1 macrophage metabolism (32). However, M2 macrophages have high levels of OXPHOS and fatty acid oxidation in their metabolism (52,53). As a result, immune cells most likely undergo cuproptosis as they transition from glycolysis to OXPHOS. Anti-inflammatory macrophages (M2 subtype) may undergo cuproptosis via p53 glycolytic switch to the OXPHOS phase compared with M1 macrophages.

Crosstalk with immune checkpoints and the microenvironment. Programmed death ligand 1 (PDL1) has been recognized as the ligand for the immunological suppressive receptor programmed death 1 protein (PD1). PDL1 may suppress T-cell responses by triggering apoptosis when it binds to PD1 on active T cells. PD-L1 is therefore considered a therapeutic target for malignant tumors, as it promotes immune evasion and contributes to tumor growth (54). PD-L1 expression in cancer cells is affected by Cu levels within the tumor. A study found that Cu-chelators significantly inhibited neuroblastoma tumor growth, improved survival rates in mice, and increased the number of $CD8^+$ T cells and NK cells infiltrating the tumors (27). This suggests that Cu may increase tumor immune evasion by increasing PDL1 expression, which inhibits T-cell and NK responses while facilitating tumor growth. High T-cell infiltration, elevated interferon-γ signaling, PD-L1 expression and a high tumor mutational burden are characteristics of immune-inflamed tumors, commonly referred to as 'hot tumors' (55) and immune checkpoint inhibitors (ICIs) typically have a greater effect on tumors with an inflammatory nature (56,57). Conversely, cold tumors also contain immunosuppressive cell populations, such as myeloid-derived suppressor cells, regulatory T cells and tumor-associated macrophages (55), and ICI monotherapy is rarely effective for treating 'cold tumors' (56).

Possible regulatory mechanisms of cuproptosis on gut microbiota. The intestinal microbiota contributes significantly to immune homeostasis. Numerous immune-related inflammatory disorders, such as systemic lupus erythematosus, rheumatoid arthritis, diabetes and IBD, have been linked to changes in the gut microbiota and its metabolites (58). An unregulated immunological response to dysbiosis of the gut microbiome is one cause of IBD (59). The effects of Cu oxide (CuO) nanoparticles (NPs) on the intestinal microbiota and their metabolite levels have been shown to mediate their intestinal immunotoxicity (60). Additionally, CuO NPs can strongly activate the FDX1-LIAS-DLAT cuproptosis pathway and penetrate mitochondria, damaging their structure. Intestinal homeostasis is disrupted, and the gut microbiota is altered by a decrease in Firmicutes and Fusobacteria, and an increase in Proteobacteria and Actinobacteria (61). CuO has also been shown to raise Proteobacteria levels while lowering those of Bacteroidetes and Firmicutes (62). These findings imply that cuproptosis may alter the gut microbiota and intestinal homeostasis, potentially leading to dysbiosis and unregulated immune responses.

3. Key features between cuproptosis and ferroptosis, apoptosis, pyroptosis and necroptosis

Cuproptosis is a type of cell death triggered by excessive Cu accumulation within cells (1), and key regulatory genes include negative regulators [glutaminase (GLS), cyclin-dependent kinase inhibitor 2A (CDKN2A) and metal regulatory transcription factor 1] and positive regulators [FDX1, LIAS, lipoyltransferase 1, dihydrolipoamide dehydrogenase (DLD), DLAT, pyruvate dehydrogenase E1 subunit α1 (PDHA1) and pyruvate dehydrogenase E1 subunit β (PDHB)] (63,64), whilst ferroptosis, which is a non-apoptotic cell death that is iron-dependent, involves a deficiency in GSH or glutathione peroxidase 4 (GPX4) (65,66). The expression levels of GPX4 (67), FDX1, LIAS, DLAT, PDHA1 and DLD (15,68) in the inflamed gut are all decreased. Also, necroptosis is driven by receptor-interacting protein kinase 1 (RIPK1), RIPK3 and mixed lineage kinase domain-like protein (MLKL), leading to cell expansion, membrane disintegration, leakage of intracellular content and cell death, along with inflammation (69). Deficiency in caspase-8 leads to activation of RIPK3 and MLKL (70,71). In the inflamed gut, RIPK3 and MLKL levels are increased when caspase-8 is reduced or deficient (70). Conversely, adaptor proteins such as TNF receptor-associated death domain protein (TRADD) and Fas-associated death domain protein, along with caspase-8 and caspase-10, are essential for apoptosis signaling through death receptors. Within the inflamed gut environment, the expression of Fas and Fas ligand (72), which are part of the extrinsic route, is increased, while in the intrinsic route of apoptosis, the expression of BAX and caspase 3 is increased (73). Pyroptosis is an inflammatory cell death triggered by inflammasomes; it degrades gasdermin D (GSDMD) and activates cytokines such as IL-1β and IL-18 (74,75). The pyroptosis effector is GSDMD (76). In the inflamed gut environment, GSDMD, as well as other markers of pyroptosis, such as NOD-like receptor family pyrin domain-containing 3 (NLRP3), IL-1β and caspase-1, are increased (77).

To summarize, in terms of core elements, cuproptosis depends on Cu ions, ferroptosis on iron, apoptosis on death receptors and caspase 8, necroptosis on RIPK1, RIPK3 and MLKL in the absence of caspase 8, and pyroptosis on GSDMD. Furthermore, cuproptosis does not require caspases but relies on lipoylation proteins, whereas apoptosis and pyroptosis require caspases. The morphological alterations in cuproptosis, as well as the genes involved, differ from other cell death processes. This suggests that therapeutic approaches for other types of cell death, such as ferroptosis, necroptosis, pyroptosis and apoptosis, may differ from cuprotosis due to distinct cell death pathways.

Although Table I (7,16,69,78-97) highlights the key differences between cuproptosis and other forms of cell death, there are also key overlapping features among them. Cuproptosis and ferroptosis, for example, share a link to GSH depletion. Notably, when comparing ferroptosis and cuproptosis, GSH works at the crossover point of the regulation network (98). Therefore, GSH depletion may lead to cuproptosis and ferroptosis. Additionally, the cystine-glutamate antiporter xCT allows free cystine to enter cells; however, plasma GSH-disulfide may be the primary source of cystine in the body (99). Reduced cystine and glutamine levels interfere with GSH synthesis in acute myeloid cells, which causes glutathione peroxidase-4 (GPX4), a cofactor that keeps lipid peroxidation homeostasis, to malfunction (100). Thus, blocking the cystine-glutamate antiporter xCT (SLC7A11/SLC3A2) may diminish GSH and GPX4 and, in the presence of elevated Cu levels, might lead to cuproptosis and ferroptosis. Additionally, SLC31A1 downregulation and mitochondrial Cu depletion in cardiac fibrosis (CF) are associated with lower Cu concentrations (101). SLC31A1 deficiency specific to fibroblasts increases mitochondrial Cu depletion, increases glycolysis, stimulates fibroblast proliferation and causes CF (104). This suggests that SLC31A1

Table I. Key differences between cuproptosis, ferroptosis, apoptosis, pyroptosis, and necroptosis.

Parameter	Cuproptosis	Ferroptosis	Apoptosis	Pyroptosis	Necroptosis	(Refs.)
Trigger(s)	Cu^{2+} buildup	-Iron buildup -GSH-GPX4 failure -Excessive peroxidation of lipids	Either extrinsically by death signals from the outside of the cell or intrinsically through mitochondrial membrane permeabilization	-Damage-associated molecular patterns -Pathogen-associated molecular patterns	-Virus sensors -Pattern-recognizing receptors -Death receptor activation with caspase-8 deficiency	(16,78-84)
Key executioners	Lipoylation of DLAT	-Fe^{2+}, -GPX4 failure -PUFAs	Caspase 3, 6, 7	-GSDMD -Caspase 1, 4, 5, 11	-RIPK-1, 3 -MLKL	(7,16,79, 82,83,85)
Mechanism	Excess Cu causes cuproptosis, a process in which the TCA cycle's Cu-dependent aberrant oligomerization of lipoylation proteins reduces iron-sulfur cluster protein levels, resulting in proteotoxic stress and cell death.	When the GPX4 function is inhibited, lipid peroxidation occurs, and ferroptosis may be induced.	Both extrinsic and intrinsic mechanisms of apoptosis activate a family of proteases known as caspases, which are responsible for the final cell death during the execution process of apoptosis.	The last step of pyroptosis requires the cleavage of GSDMD at D275 (numbering after human GSDMD) into N- and C-termini by caspase 1 in the canonical pathway and caspase 4/5/11 (caspase 4/5 in humans, caspase 11 in mice) in the noncanonical pathway. Upon cleavage, the N-terminus of GSDMD forms a transmembrane pore that releases cytokines such as IL-1β and IL-18 and disturbs the regulation of ions and water, eventually resulting in strong inflammation and cell death	The stimuli stimulate RIPK3 via RHIM-containing proteins. RIPK3 binds and phosphorylates MLKL, resulting in alterations in cell shape.	(7,81,82, 84,86,87)
Morphological features	-Cell membrane rupture -Mitochondrial shrinkage -Mitochondrial stress	-Condensed density of the mitochondrial membrane in smaller-than-normal mitochondria -Diminished or absent mitochondrial cristae -Disruption of the outer membrane of the mitochondria	-Condensation of the nucleus and cytoplasm. -Cell fragmentation into well-preserved, membrane-bound fragments	-Ballooning morphology of cells -Breakdown of the cell/plasma membrane and the production of inflammatory mediators such as HMGB1, IL-1β and IL-18	-Cell expansion and rupture of the cell/plasma membrane -Intracellular content leakage -Cell death and the creation of inflammation	(69,84, 88-92)

Table I. Continued.

Parameter	Cuproptosis	Ferroptosis	Apoptosis	Pyroptosis	Necroptosis	(Refs.)
Inflammatory profile	Yes/immunogenic reaction	Yes	No (silent)	Yes	Yes	(91, 93-96)
Caspase dependency	No	No	Yes	Yes	No	(84,93,97)

Cu, copper; DLAT, dihydrolipoyl transacetylase; GPX4, glutathione peroxidase-4; GSH, gluthatione; IL, interleukin; PUFA, polyunsaturated fatty acids; TCA, tricarboxylic acid; HMGB1, high mobility group protein B1; Fe^{2+}, ferrous iron; RIPK, receptor-interacting protein kinase; MLKL, mixed lineage kinase domain-like protein; GSDMD, gasdermin D; RHIM, RIPK homology interaction motif.

upregulation may increase mitochondrial Cu accumulation, leading to cuproptosis. Lysine demethylase 5B (KDM5B) is activated by intracellular α-ketoglutarate buildup caused by SLC31A1-mediated cuproptosis (102). Activated KDM5B, in particular, demethylates H3K4me3 marks at the promoter of the ferroptosis regulator ferritin heavy chain 1 (FTH1), inhibiting transcription and making keratinocytes more susceptible to ferroptotic cell death, thereby increasing inflammatory tissue damage (102). These results demonstrate a basic pathogenic SLC31A1/KDM5B/FTH1 molecular axis that connects cuproptosis and dysregulated Cu metabolism to the execution of ferroptosis (102). Thus, cuproptosis and ferroptosis could overlap or intersect via SLC31A1, GSH depletion and the cystine-glutamate antiporter xCT (SLC7A11/SLC3A2).

Cuproptosis can also overlap with apoptosis in terms of mitochondrial damage. One of the roles of cytochrome *c* in living cells is to catalyze lipid peroxidation in the inner mitochondrial membrane, which triggers apoptosis (103). According to a previous study, Cu buildup in cardiomyocyte mitochondria causes mitochondrial damage, and exposure to cytochrome *c* causes apoptosis, further damaging the heart (104). Additionally, mitochondrial damage has been identified as a characteristic of cuproptosis (105). This implies that mitochondrial damage may occur in both cuproptosis and apoptosis. Furthermore, cuproptosis can coexist with apoptosis by producing ROS. Oxidative stress refers to elevated intracellular ROS levels that harm proteins, lipids and DNA (106). Overproduction of ROS overwhelms the cells' antioxidant defenses, resulting in either cell death or functional damage (107). Cu ionophores that increase intracellular Cu levels include disulfiram and elesclomol. This rise results in oxidative stress, which leads to cell death (3). This implies that ROS may overlap with the cuproptosis and apoptosis pathways. Finally, p53 activities may also overlap with cuproptosis and apoptosis. For instance, Cu buildup results in apoptosis, which appears to be mediated by p53 activation and DNA damage (108). At physiological concentrations, Cu can directly interact with p53 and prevent it from binding DNA (109), but high Cu levels in hepatocytes result in increased p53 mRNA and apoptotic cell death (110). p53 regulates a variety of metabolic pathways to help cells maintain metabolic homeostasis and adapt to stress (111). In Fanconi anemia hematopoietic stem cells, p53 inactivation inhibits the switch from glycolysis to OXPHOS (112), implying that p53 activation may stimulate this switch. Given that OXPHOS is an essential component of cuproptosis (46), p53 may play a role in regulating cuproptosis (51).

Cuproptosis and pyroptosis may overlap via the NLRP3 pathway. Cu exposure causes NLRP3-dependent cellular pyroptosis, which promotes inflammatory reactions and neurotoxicity (113). Cu has been shown to mediate macrophage pyroptosis and participate in the control of the inflammatory response through the NLRP3 inflammatory vesicle-initiation pathway (114). In a mouse model of acute inflammation that was pretreated with the Cu chelator TTM, serum caspase-1-dependent cellular factors were decreased, but caspase-1-independent cellular factors were unaffected (114,115). Dong *et al* (116) demonstrated that NLRP3, cleaved caspase-1, apoptosis-associated speck-like protein containing a CARD and IL-1β protein levels increased in a

time-dependent manner when $CuCl_2$ and lipopolysaccharide were administered to primary microglia in non-mutant control mice. $CuCl_2$ exposure has been indicated to trigger NLRP3 activation-mediated inflammation and the resultant neurotoxicity in microglia (116). Additionally, hepatocyte toxicity is mediated by caspase-1-dependent cellular pyroptosis, which is triggered by excessive Cu exposure. CuSO-treated hepatocytes cocultured with N-acetylcysteine exhibited increased expression of the caspase-1 protein and mRNA levels of genes linked to Cu^{2+}-induced pyroptosis. Treatment with the caspase-1 inhibitor Z-YVAD-FMK reduced Cu^{2+}-induced increases in lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase activities, mitochondrial membrane potential and apoptotic activity. These findings suggest a link and signaling pathway interaction between pyroptosis and apoptosis caused by Cu exposure (116,117).

Cuproptosis and necroptosis may overlap due to the activation of the necroptosome. When cells are exposed to high levels of Cu, they allow MLKL infiltration and increase MLKL levels, triggering the formation of necroptosomes. This causes MLKL to translocate to the nucleus, where it regulates NF-kB transcriptional activity and provides components for MLKL pore assembly. Cu overload also activates downstream tumor necrosis factor (TNF)/TNF receptor regulators, such as cellular inhibitor of apoptosis 1/TRADD/RIPK1/TNF-receptor-associated factor-2 complexes that control NF-κB essential modulator (NEMO) and TAK1-binding protein 2/3 protein levels and inhibitor of NF-κBα activity, which in turn affects NF-κB transcription. Additionally, the linear ubiquitin chain assembly complex ligates linear chains to NEMO after being drawn to the activated TNF receptor complex by identifying ubiquitin chains produced by other E3 ubiquitin ligases. When the ubiquitin binding in ABIN and NEMO structural domain of NEMO in another IκB kinase (IKK) complex identifies the linear chains attached to NEMO, the IKK complex dimerizes, IKK2 is autophosphorylated and NF-κB is activated (118).

4. Cuproptosis is a unique type of cell death distinct from other forms

Cell death entails signaling pathways and molecularly specified effector processes (119), including necroptosis (120), apoptosis (121), ferroptosis (122,123) and pyroptosis (124,125). According to previous studies, elesclomol causes ROS-dependent apoptosis in cells (126-128). However, neither the cleavage of caspase 3 nor its activation, which is indicative of apoptosis, occurred in elesclomol-induced cell death (129). Similarly, when the two main apoptotic effectors, BAX and BAK1, were removed or cells were co-treated with pan-caspase inhibitors (Z-VAD-FMK and Boc-D-FMK), the ability of elesclomol to kill cells was preserved, demonstrating once again that Cu-induced cell death is distinct from apoptosis (16). Additionally, Cu ionophore-induced cell death was not prevented by treatment with inhibitors of other recognized cell death pathways, such as ferroptosis (ferrostatin-1), necroptosis (necrostatin-1) or oxidative stress (N-acetyl cysteine), indicating a process different from established cell death routes (16). As a result, treatment for cuproptosis-induced IBD may differ from other types of controlled cell death.

5. IBD overview

A long-term and recurrent inflammatory condition of the gut is known as IBD (130), with the two main types being CD and UC (131). Depending on the type, location and intensity of the ailment, symptoms may include diarrhea, bleeding, abdominal pain, fever and weight loss (132). It is considered that a patient's immune system, gut microbiota and genetic composition all significantly influence IBD (133). IBD is a prevalent ailment in Europe and America, and its incidence rate is increasing in Asia due to dietary changes (134). Although colorectal cancer (CRC) cases have been less common recently, patients with IBD are at a higher risk of developing CRC (135). The complications of IBD include a toxic megacolon (136), strictures (137), intestinal fibrosis (138), fistulas, abscesses and colitis-associated neoplasia (139). Balloon dilatation of strictures has been replaced by endoscopic stricturotomy, strictureplasty, stenting, fistulotomy, sinusotomy and neoplasia ablation as the methods for treating complications (139). These endoscopic procedures have made it possible to treat certain complications using minimally invasive procedures (139). Additionally, extra-intestinal manifestations (EIMs) of IBD are linked to intestinal activity and can negatively impact quality of life (140). EIMs usually impact the skin, joints and eyes, while the kidneys, liver and pancreas are less frequently affected (140). Studies have shown the efficacy of aminosalicylates (141,142), corticosteroids (143-145), immunomodulators (146-148), small molecule inhibitors (149,150) and biologics (151-155) in treating IBD.

6. Role of Cu in IBD

Cu levels in patients with IBD. Cu levels in patients with IBD have been reported to vary in studies. According to certain studies, Cu levels are higher in IBD groups than in healthy control groups (156-159), while other studies have reported a deficiency in patients with IBD (160,161). Notably, Makevic *et al* (162) found that the terminal ileums and cecums of patients with IBD have lower Cu levels than those of controls; however, serum Cu level increased in CD. In another study, Skalny *et al* (163) also found higher Cu/Zn ratios and lower serum Zn levels in children with attention deficit/hyperactivity disorder than in controls. Common risk factors for Cu deficiency include foregut surgery, dietary deficiency, enteropathies with malabsorption, prolonged intravenous nutrition (total parenteral nutrition) (164) and Zn overload (165). Conversely, an increase in Cu in patients with IBD may be due to systemic inflammation (161). The Cu levels in IBD are summarized in Table II.

Dual roles of Cu

Beneficial roles. i) Antioxidant defense. A family of enzymes called superoxide dismutases (SODs) contains Cu and plays a role in the metabolism of ROS by converting superoxide anion radicals into hydrogen peroxide and oxygen (166). The Cu ion that is active in redox reactions drives catalysis. In most cases, SODs have a zinc (Zn) ion at the active site, which enhances Cu catalytic processes and preserves protein structure (166). The periplasm of bacteria and almost every organelle in a human cell contains these bimetallic Cu,

Table II. Summary of Cu levels in inflammatory bowel disease.

Authors, year	Cu levels	Sample	(Refs.)
Schneider *et al*, 2020	Decreased	Serum	(161)
Xing *et al*, 2021	Increased	Serum	(156)
Ritland *et al*, 1979	Increased in UC, normal in CD	Liver	(157)
Mohammadi *et al*, 2017	Increased	Serum	(158)
Piątek-Guziewicz *et al*, 2021	Increased	Serum	(159)
Kamel *et al*, 2024	Decreased	Serum or whole blood	(160)
Makevic *et al*, 2023	Increased in CD Decreased	Serum Intestinal mucosa	(162)

Cu, copper; CD, Crohn's disease; UC, ulcerative colitis.

Zn-SODs. Nevertheless, a novel class of SODs that contain Cu and do not require Zn has just surfaced (166). The body's antioxidant defense against oxidative stress is based on metalloenzymes known as SOD (167). Therefore, SOD supplementation may activate the body's natural antioxidant system to counteract excess free radicals and be applied in pathological situations (167). Studies have shown decreased SOD levels in IBD (168), collagen-induced arthritis (169) and cognitive impairment after mild acute ischemic stroke (170), implying that increased SOD may mitigate several diseases. A recent study found that mice with colitis exhibited fewer symptoms when SOD mimics Mn1 and Mn1C were injected into lactic acid bacteria (171). Additionally, Cu ion-luteolin nanocomplexes have been shown to enhance anti-inflammatory and antioxidant effects of cells by regulating the NF-κB signaling pathway and the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 oxidative stress pathway, increasing SOD activity/content, and reducing intestinal inflammation (172). Other nanocomposites composed of Cu and carbon have shown promise in increasing antioxidant defenses, hence decreasing intestinal inflammation (173). These studies show that Cu may enhance antioxidant defenses to curb intestinal inflammation.

ii) Regulation of inflammation and gut microbiota in intestinal health. Numerous biological functions, including Cu transport, have been linked to Cu metabolism MURR1 domain-containing 1 (COMMD1) (174). COMMD1 selectively binds with NF-κB components to suppress their transcriptional activity (175,176). Colon inflammation has been linked to the NF-κB pathway (177,178). COMMD1, a negative regulator of NF-κB, regulates intestinal inflammation and prevents colitis-associated cancer, according to genetic research on mice and humans (179). Prolonged NF-κB activation leads to intestinal epithelial cell death and upregulation of proinflammatory cytokines, resulting in mucosal inflammation and barrier breakdown (180). As a result, COMMD1, a Cu transporter, may modulate inflammation. Li *et al* (181) found that circulating leukocytes and colon biopsy specimens from patients with IBD had lower levels of COMMD1 expression; thus, myeloid cells expressing COMMD1 exhibited anti-inflammatory properties, and the pathophysiology of IBD may involve reduced COMMD1 expression or function.

Cu has been shown to enhance the stability and accumulation of hypoxia-inducible factor 1α (HIF-1α) (182). The transcriptional control of anti-inflammatory or cellular responses to hypoxia is mediated by the master regulator HIF-1α (183). A study found that after infection with *Citrobacter rodentium*, transgenic mice with selective inactivation of the HIF-1α gene in innate retinoic acid receptor-related orphan receptor-γt-positive cells experienced more severe colitis, primarily since they could not upregulate IL-22 (184). Additionally, HIF-1α-mediated stimulation of type 1 innate lymphoid cells prevents elevated inflammation and fibrosis during persistent gut injury, even though it is detrimental during acute colitis (185). Hence, the ability of Cu to enhance HIF-1α may help regulate inflammation in the colon. Other studies suggest that HIF-1α expression is linked to reduced colon inflammation (186,187).

In addition to regulating inflammation, Cu has been shown to improve intestinal barrier function, support bacterial populations and reduce intestinal damage. For instance, Li *et al* (188) found that Cu/Zn-montmorillonite administration reduced the potentially harmful bacteria (*Streptococcus* and *Pseudomonas*) in the colon of weaned pigs, increased the relative abundance of core bacteria (*Lactococcus* and *Bacillus*) at the genus level, and elevated expression levels of tight junction proteins [zonula occludens-1 (ZO-1) and claudin-1]. Similarly, Jiao *et al* also (189) found that in weaned pigs, dietary Cu/Zn-Mt enhanced barrier function, reduced intestinal inflammation and affected the toll-like receptor 4-myeloid differentiation primary response 88 and transforming growth factor-β1 signaling pathways, thereby decreasing LPS-induced intestinal damage. Dietary Cu deficiency is associated with colonic injury, and these alterations occur together with disruption of the intestinal barrier, inflammatory response activation and dysbiosis of the gut microbiota (190)

iii) Iron regulation. Ceruloplasmin (CP) is a ferroxidase found in the blood plasma of mammals. This protein, which belongs to the multiCu oxidase family, carries >95% of the Cu present in plasma (191). Iron homeostasis is dependent on CP, and abnormal activity of this protein results in iron accumulation (192). CP is considered to have evolved from cupredoxin, a multi-Cu blue protein with three mononuclear and trinuclear Cu binding sites (193). Ferrous iron is oxidized to ferric iron

by multiCu ferroxidases (194). Iron insufficiency is correlated with low vitamin D levels in IBD. By decreasing hepcidin and increasing CP, vitamin D may improve intestinal iron absorption and treat iron insufficiency (195). Additionally, in a previous study, ferroxidase CP expression was highly increased in Caco-2 cells by 1,25(OH)D (195). Baykalir *et al* (196) also found that lycopene helps prevent colitis by increasing SOD activity, CP and iron levels. IBD-related iron deficiency and anemia are frequently treated with intravenous iron, which can cause hypophosphatemia (197), implying that iron may be required to treat anemia. This suggests that increased CP may improve iron sufficiency and absorption.

iv) Other beneficial roles: Connective tissue formation. A cuproenzyme called protein-lysine 6-oxidase is necessary for the enzymatic cross-linking of collagen and elastin, which stabilizes extracellular matrices (198). Also, Cu-dependent monoamine oxidases known as lysyl oxidases (LOXs) are essential for the remodeling of the extracellular matrix (199). Other biological roles of the LOX and LOX-like proteins include tumor suppression, cellular senescence, and the regulation of development and growth (199). To stabilize the crosslinks between collagen and/or elastin during the development or remodeling of the extracellular matrix, Cu-dependent LOX proteins catalyze the oxidation of lysine residues within these fibrous proteins (200).

v) Other beneficial roles: Neurotransmitter synthesis and central nervous system function. The Cu-containing enzyme dopamine β-hydroxylase (DBH) is crucial for preserving the balance between the two neurotransmitters, dopamine and noradrenaline, within cells (201). DBH is an oxygenase that contains Cu and uses molecular oxygen ascorbate as a cofactor to catalyze the hydroxylation of the β-carbon of a broad range of phenylethylamine derivatives (202). DBH is found in immunocytes as well as the catecholaminergic neuron system, and it contributes to the immunological responses of vertebrates (203). Numerous neuropsychiatric disorders are linked to DBH functional polymorphisms, which also affect serum DBH protein levels and DBH enzymatic activity (201).

vi) Other beneficial roles: Melanin production. Tyrosinases are abundant in nature. These Cu-containing oxidases, along with hemocyanins and catechol oxidases, belong to the type 3 Cu protein family (204). In 2011, Matoba *et al* (205) presented a chemical mechanism that uses a metallochaperone, caddie, to help move two Cu ions to the catalytic core of tyrosinase. The pigmentation of mammalian skin and hair is a result of tyrosinases, which are essential enzymes in the production of melanin (204). Two other enzymes, known as tyrosinase-related proteins, also play a role in the pathway (204).

Detrimental roles. i) Oxidative stress. Oxidative stress has a significant impact on IBD, as chronic inflammation in the gut produces an excess of ROS, causing oxidative stress (206). Numerous lines of evidence indicate that oxidative stress results from excess ROS or reduced antioxidant activity, and that IBD is associated with this imbalance (206). According to previous studies, exposure to Cu/Cu sulphate causes oxidative stress, apoptosis and a decline in antioxidant function, which can result in lung lesions and dysfunction (207), hepatic apoptosis (208) and spermatogenesis disorders (209). These results suggest that Cu may cause oxidative stress. Additionally, Cu ion carriers have been shown in studies to block anti-apoptotic NF-κB signaling, generate ROS and activate pro-apoptotic signaling pathways, including the c-Jun N-terminal kinase and mitogen-activated protein kinase pathways (210,211). Moreover, Cu complex nanoparticles exhibit stimulus-responsive Cu complex discharge, which causes mitochondrial dysfunction and promotes lipoylated DLAT aggregation, ultimately resulting in cuproptosis (212). Diseases such as IBD and cancer are marked by alterations in mitochondrial function and the activation of the unfolded protein response (213). A bioenergetic crisis occurs when mitochondrial function is impaired. This impairment weakens the epithelial barrier, increasing the risk of cuproptosis, reducing the production of secretory barrier factors, and hindering the repair process following injury (214-216). As a result, using pharmaceuticals or natural agents to combat oxidative stress may aid in the prevention of IBD.

ii) Impact of Cu on inflammation, intestinal integrity and gut microbiota. Results from animal models have shown that the gut microbiota plays a variety of context-specific roles in health and disease, from pro-inflammatory to protective. Furthermore, data from these experimental models indicate that while gut bacteria frequently trigger immunological stimulation, persistent inflammation also influences the gut microbiota, leading to dysbiosis (217). Cu has been demonstrated in studies to decrease barrier function, affect gut flora and trigger inflammatory reactions. For instance, Liao *et al* (218) found that excessive Cu resulted in decreased expression of tight junction proteins (ZO-1, quinoline, claudin-1 and junctional adhesion molecule-1), increased inflammatory cytokines and increased levels of *Streptococcus*, *unidentified_Enterobacteriaceae* and *unidentified_Muribaculaceae,* but decreased levels of *Lactobacillus* and *Methanobrevibacter*. Also, Ma *et al* (219) found that early-life exposure to both Cu and florfenicol leads to visceral damage, inflammatory responses and alterations in the gut microbiota associated with disease and energy intake. Notably, at the phylum level, exposure to Cu only increased *Bacteroidetes* levels, while decreasing *Spirochaetae*, *Actinobacteria* and *Verrucomicrobia* levels when compared with the control group. In another study, exposure to Cu was shown to decrease *Lactobacillus*, *Bifidobacteria* and *Romboutsia* levels, and alter the ratio of *Firmicutes* to *Bacteroidetes* and the abundance of bacteria linked to intestinal inflammation and fat metabolism, suggesting that prolonged Cu exposure weakens the gut barrier and elevates permeability due to gut microbial disorders, which may trigger an inflammatory reaction (220). These findings suggest that Cu may cause impaired barrier integrity, intestinal dysbiosis and inflammation. These findings may support the dual involvement of Cu in IBD. Fig. 2 shows the dual roles of Cu in IBD.

7. Cuproptosis-related genes in IBD pathogenesis

Preclinical studies. Genetic factors play an important role in IBD. Notably, preclinical studies have demonstrated that downregulation of cuproptosis-related genes contributes to the development of IBD by damaging the intestinal epithelium, reducing junctional protein expression and increasing inflammatory cell infiltration (15,68,221). Additionally, these processes lead to a reduction in colon length, increased weight

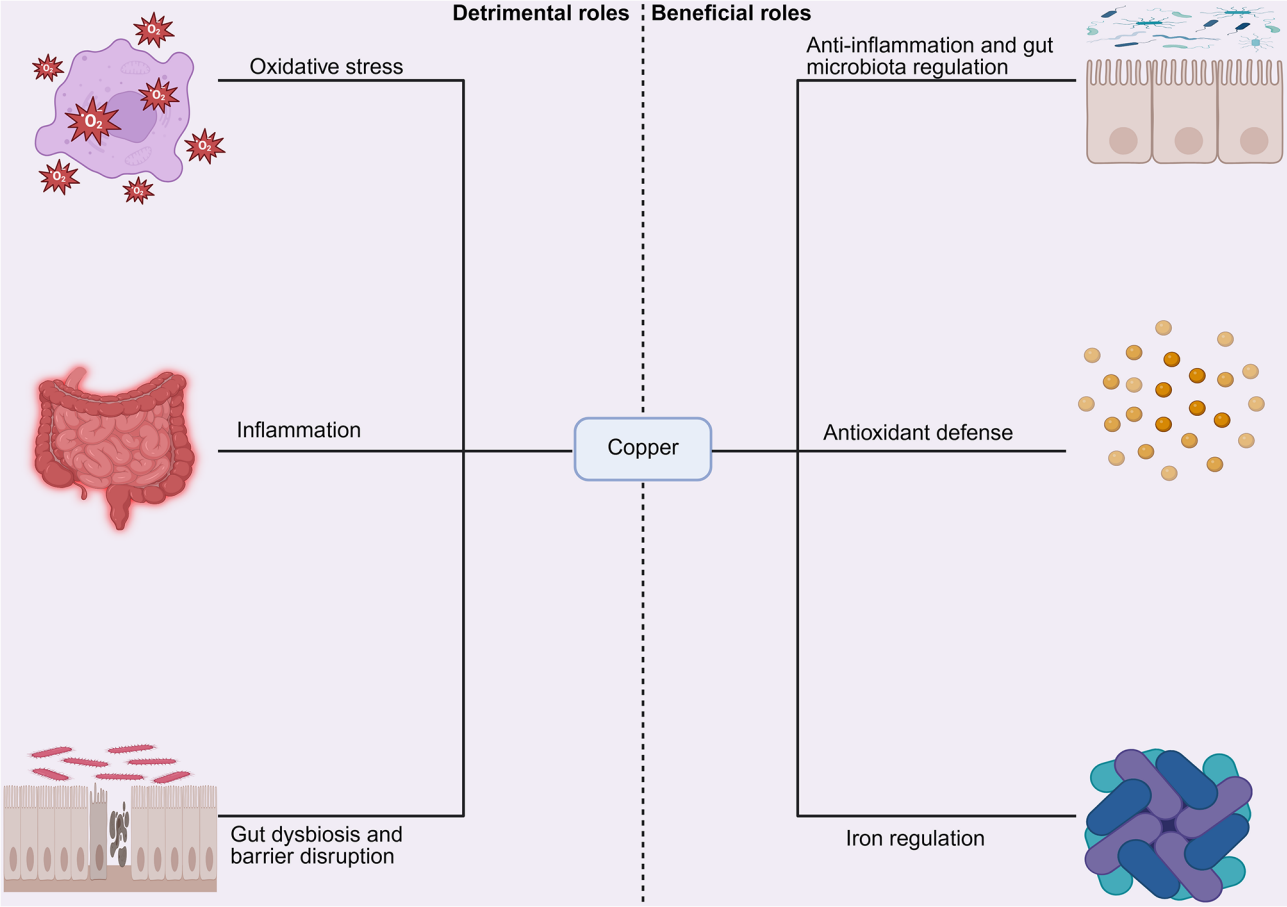

Figure 2. Dual roles of Cu in IBD. Cu plays a beneficial role in IBD, contributing to antioxidant defense, regulating inflammation and managing iron levels, while also having detrimental effects such as inducing oxidative stress, promoting gut dysbiosis, disrupting barriers and activating the intestinal immune system. Created using BioRender.com. CU, copper; IBD, inflammatory bowel disease.

loss and a higher disease activity index, all of which are characteristic signs of IBD (15,68,221). Emerging evidence suggests that in DSS-induced colitis, levels of FDX1, DLAT, dihydrolipoamide branched chain transacylase E2 (DBT), LIAS, DLD and PDHA1 are markedly lower than in the control group (15,68,221). These findings suggest that genes related to cuproptosis may be involved in the pathophysiology of IBD. Notably, these genes are downregulated in IBD. As a result, drugs that upregulate these genes may prevent IBD in tandem with Cu chelation agents. As shown previously, systemic inflammation can lead to increased Cu levels (161). Therefore, to prevent cuproptosis-induced IBD, this Cu must be removed to prevent excess Cu, which may trigger cuproptosis by the conversion of Cu^{2+} to Cu^{+} by FDX1. Additionally, safely increasing the cuproptosis-related genes helps transition from the glycolytic phase to mitochondrial OXPHOS, which is associated with M2 macrophage polarization. M2 macrophages have been shown to reduce inflammation, restore intestinal tissue, interact with the gut microbiota and prevent IBD (222,223). Thus, the combination of Cu chelation agents and upregulation (safely) of critical cuproptosis genes may effectively prevent cuproptosis-induced IBD. Increasing these cuproptosis genes could lead to the functional activation of the PDH complex (16). The first and most crucial enzyme in the conversion of pyruvate into acetyl-CoA, which enters the TCA cycle to generate ATP and electron donors, is PDH (224). Additionally, when the PDHA1 gene is overexpressed, PDH activity rises, improving mitochondrial OXPHOS and ATP production (225). According to one study, tight junction proteins are disrupted by ATP deficiency (226), implying that the assembly of the PDH complex and its increased activity may provide energy via ATP for the repair of the mucosal barrier by increasing tight junction proteins. Fig. 3 depicts the role of cuproptosis-related genes in preclinical studies of IBD.

Clinical studies involving cuproptosis-related genes, immune infiltration and biomarkers. Bioinformatics and machine learning techniques have revealed that cuproptosis-related genes show differential expression in IBD. Moreover, these genes are associated with immune cell infiltration and can act as biomarkers for IBD. For instance, a study identified the hub genes associated with cuproptosis in active UC, including sulfatase modifying factor 1 (SUMF1), metallothionein 1G (MT1G), antioxidant 1 Cu chaperone (ATOX1), ATP7B, FDX1 and LIAS, with corresponding area under the curve values of 0.877, 0.864, 0.823, 0.803, 0.799 and 0.752, respectively (227). The genes displayed reduced expression, except for ATOXI, which displayed elevated expression in active UC (227). The study found that SUMF1, MT1G, ATP7B, FDX1 and LIAS showed a marked positive association with $CD8^{+}$ T cell infiltration, whereas ATOX1 had

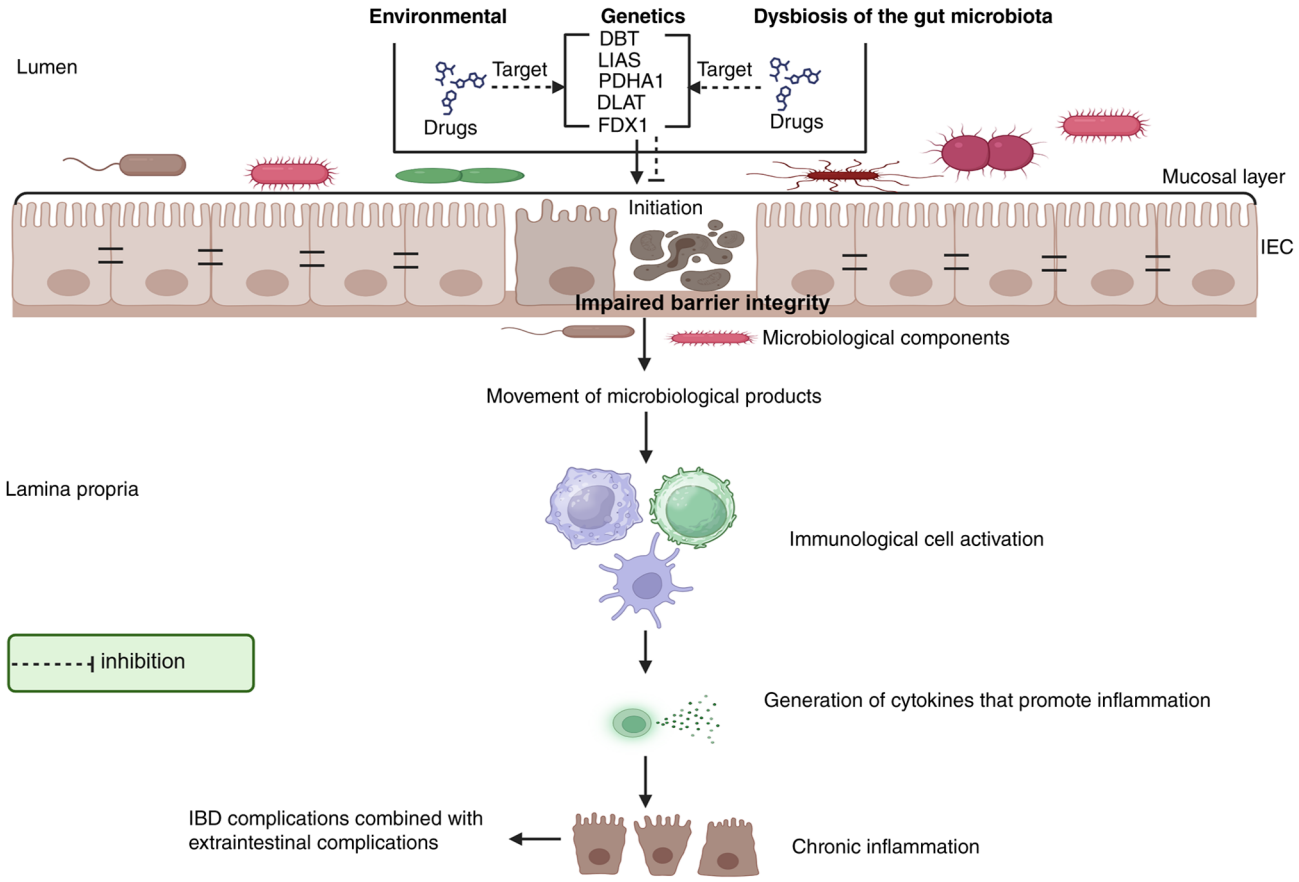

Figure 3. Role of cuproptosis-related genes in the pathogenesis and potential therapeutic targets in IBD. Cuproptosis-related genes are downregulated in preclinical studies, compromising the gut integrity. This causes increased immune cell infiltration and the generation of pro-inflammatory cytokines, which exacerbate the illness (chronic inflammation) and lead to IBD and extraintestinal problems. Molecular docking techniques have been used to identify potential drugs that target specific cuproptosis-related genes for IBD remission. These prevent barrier disruption, immunological reactions, the generations of cytokines, chronic inflammation and IBD complications. Created using BioRender.com. IBD, inflammatory bowel disease; DBT, dihydrolipoamide branched chain transacylase E2; LIAS, lipoyl synthase; PDHA1, pyruvate dehydrogenase E1 subunit α1; DLAT, dihydrolipoyl transacetylase; FDX1, ferredoxin 1; IEC, intestinal epithelial cell.

a marked negative link (227). Other studies have also found cuproptosis genes, including PDHA1, PDHB, LIAS, FDX1, DLD, DLAT, ATP7B and DBT (68), metallothionein 1M, β-secretase 1, ATP binding cassette subfamily B member 6, GLS, FDX1, PDHA1 and LIAS (228), DBT, LIAS, PDHA1 and DLAT (221), and DLD, DLAT, PDHB and DBT (10), respectively, which serve as diagnostic markers for IBD. These genes have been shown to correlate with immune cell infiltrations such as macrophages and neutrophils, activated CD4 and CD8 T cells, and T17 cells. It is noteworthy that while these cuproptosis genes are differentially expressed in IBD, comparable observations have also been made in its complications, such as CRC, which can be exploited for diagnostic purposes (229,230). Table III shows that the expression of key cuproptosis-related genes (positive regulators: FDX1, LIAS, PDHA1 and DLAT) was downregulated in IBD and CRC, which is consistent with preclinical investigations in IBD models. The negative regulators (such as CDKN2A) were increased in CRC. However, GLS (a negative regulator) was downregulated in IBD but elevated in CRC. Other associated genes were either upregulated or downregulated. These results suggest that the core regulatory genes involved in cuproptosis (FDX1, LIAS and DLAT) are downregulated in IBD.

Summary of potential biomarkers from other diseases. Table IV (11-13,231-237) summarizes the potential indicators of cuproptosis-related genes in different illnesses, including sepsis-induced myocardial dysfunction, diabetic nephropathy, atherosclerosis, acute myeloid leukemia, sarcopenia, hepatic ischemia and reperfusion injury, lung adenocarcinoma, severe community-acquired pneumonia, breast cancer and uterine corpus endometrial carcinoma.

8. Therapeutic applications of cuproptosis in IBD

Chelation therapy is the preferred method of treatment for Cu overload or poisoning (238). Cu chelators have been used at the cellular and organismal levels to study Cu acquisition, distribution and disposition (239). One of the most effective ways to maintain physiological Cu concentrations is by using Cu-chelating agents (240). Tetrathiomolybdate™, trientine (triethylenetetramine dihydrochloride), 5,7-dichloro-2[(dimethylamino)methyl]quinoline-8-ol, 2,3-dimercaptosuccinic acid and D-penicillamine [(S)-2-amino-3-mercapto-3-methylbutanoic acid] are the primary Cu-chelating agents (240). Numerous chelating medications have been shown to alter Cu levels by various processes. Specifically, tetrathiomolybdate encourages Cu biliary

Table III. Summary of potential biomarkers of cuproptosis-related genes in IBD and related CRC.

Authors, year	Cuproptosis gene	Condition	Diagnosis	Parameter/AUC	Prognostic	Parameter	(Refs.)
Zou *et al*, 2023	↓SUMF1, ↓MT1G, ↑ATOX1, ↓ATP7B, ↓FDX1, ↓LIAS	UC	√	0.877, 0.864, 0.823, 0.803, 0.799, 0.752	-	-	(227)
Huang *et al*, 2022	↓FDX1, ↓LIAS, ↓DLAT	UC, DSS-induced UC	√	0.889	-	-	(68)
Chen *et al*, 2022	↓DBT, ↓LIAS ↓PDHA1, ↓DLAT	DSS-induced UC, IBD	√	0.743	-	-	(221)
Yuan *et al*, 2022	↓MT1TM, ↑BACE1, ↑ABCB6, ↓GLS, ↓FDX1, ↓PDHA1, ↓LIAS	CD	√	0.759, 0.720, 0.649, 0.730, 0.631, 0.685, 0.678	-	-	(228)
Shi *et al*, 2025	↓DLD	IBD + MDD	√	-	-	-	(10)
Wu *et al*, 2022	↑CDKN2A, ↓DLAT	CRC	-	-	√	OS (HR, 1.14); OS (HR, 0.53)	(229)
Du *et al*, 2022	↑CDKN2A, ↑GLS, ↓DLAT	CRC	-	-	√	0.616, 0.681, and 0.677 in the 1st, 3rd and 5th years, respectively	(230)

CD, Crohn's disease; CRC, colorectal cancer; DSS, dextran sulfate sodium; HR, hazard ratio; IBD, inflammatory bowel disease; MDD, major depressive disorder; OS, overall survival; AUC, area under the curve; HR, hazard ratio; UC, ulcerative colitis; DBT, dihydrolipoamide branched chain transacylase E2; LIAS, lipoyl synthase; PDHA1, pyruvate dehydrogenase E1 subunit α1; DLAT, dihydrolipoyl transacetylase; FDX1, ferredoxin 1; SUMF1, sulfatase modifying factor 1; MT1G, metallothionein 1G; ATOX1, antioxidant 1 Cu chaperone; ATP7B, ATPase Cu transporting β; MT1TM, metallothionein 1M; BACE1, β-secretase 1; ABCB6, ATP binding cassette subfamily B member 6; GLS, glutaminase; DLD, dihydrolipoamide dehydrogenase; CDKN2A, cyclin-dependent kinase inhibitor 2A.

excretion, whereas penicillamine, trientine and dimercaptosuccinic acid produce complexes that are eliminated in the urine (240). As a result, using medications to help regulate Cu levels in IBD may help alleviate cuproptosis. Preclinical studies have shown that Cu chelators TM (241), TM + cetuximab (242) and disulfiram + oxaliplatin (243) can be used in treating breast cancer, head and neck carcinoma, and CRC, respectively. Additionally, other clinical trials or studies have also shown that trientine plus carboplatin and pegylated liposomal doxorubicin (244), bis-choline tetrathiomolybdate or trientine tetrahydrochloride (245,246), D-penicillamine with Cu sulfate (247), and TM combined with irinotecan, 5-fluorouracil and leucovorin (248) can be used to treat relapse of epithelial ovarian, tubal and peritoneal cancer, Wilson disease, glioblastoma multiforme and metastatic CRC, respectively. Nonetheless, research into Cu chelators and ionophores in the treatment of IBD is ongoing, and there is no concrete evidence that Cu chelators can control Cu levels in IBD. Notably, differentially expressed cuproptosis-related genes have been shown to contribute to the etiology of IBD. As a result, drugs that target these genes using molecular approaches may prevent IBD. For example, molecular docking and other techniques have been used to identify potential medications targeting cuproptosis genes in IBD and provide therapeutic benefit (10,68,221,227). These prospective medication breakthroughs could help prevent IBD in the future.

Potential cuproptosis-related gene drug discoveries

Methotrexate (MTX). The synthetic folic acid analog methotrexate is prized for its anti-inflammatory and anti-proliferative qualities. MTX is frequently used to treat steroid-recalcitrant inflammatory diseases and is regarded as one of the first immune-modifying drugs (249). Intracellular metabolites of MTX, known as MTX polyglutamates, play a crucial role in the efficacy of the drug and influence its toxicity (250). The most important enzyme in the cuproptosis-regulatory pathway is FDX1. Chen *et al* (221) used computational simulation to study the molecular interactions between FDX1 and IBD medications. Based on molecular

Table IV. Summary of potential biomarkers of cuproptosis-related genes in other conditions.

Authors, year	Cuproptosis-related genes	Condition	Diagnosis	Parameter/AUC	Prognostic	Parameter/AUC	(Refs.)
Shi *et al*, 2025	↓PDHB	Sepsis-induced myocardial dysfunction	√	0.995, 0.960, 0.864, 0.984 (AUC values from different data sets)	-	-	(231)
Chen *et al*, 2024	↑FSTL1, ↑CX3CR1, ↑AGR2	Diabetic nephropathy	√	0.911, 0.935, 0.922	-	-	(232)
Chen *et al*, 2023	↑SLC31A1, ↑SLC31A2, ↓SOD1	Atherosclerosis	√	0.800, 0.779, and 0.798 respectively (for one data set), 0.736, 0.838 and 0.848 respectively (for another data set)	-	-	(233)
Li and Kan, 2024	↑MTF1, ↑LIPT1	Acute myeloid leukemia	√	-	√	0.953, 0.795	(234)
Zhu *et al*, 2023	↓PDHA1, ↓DLAT, ↓PDHB, ↓NDUFC1	Sarcopenia	√	0.83, 0.87 and 0.64 for validation	-	-	(235)
Xiao *et al*, 2024	↑NLRP3, ↓ATP7B, ↑NFE2L2	Hepatic ischemia and reperfusion injury	√	0.832, 0.904 for validation	-	-	(236)
Li *et al*, 2024	↑DBT, ↑DLAT	Lung adenocarcinoma	-	-	√	Poor prognosis (DLAT: HR, 6.103; DBT: HR, 4.985)	(11)
Chen *et al*, 2023	↓GCSH, ↓LIPT1, ↑DLD	Severe community-acquired pneumonia	√	0.8359, 0.8724, 0.9566	-	-	(237)
Jiang *et al*, 2022	↑CDKN2A, ↑PDHA1, ↓MTF1, ↓DLD, ↓LIPT1, ↓FDX1	Breast cancer	-	-	√	HR, 1.22 (poor OS); HR, 1.39 (poor OS); HR, 0.65 (better OS)[a]; HR, 0.65 (better OS)[a]; HR, 0.37 (better OS)[a]	(12)

Table IV. Continued.

Authors, year	Cuproptosis-related genes	Condition	Diagnosis	Parameter/ AUC	Prognostic	Parameter/ AUC	(Refs.)
Chen, 2022	↑CDKN2A, ↓GLS ↓LIPT1	Uterine corpus endometrial carcinoma	-	-	√	HR, 3.58 (poor prognosis); HR, 3.23 (poor prognosis)[b]; HR, 1.95 (poor prognosis)[b]	(13)

[a]Improved survival when increased, [b]poor prognosis when increased. AUC, area under the receiver operating characteristic curve; HR, hazard ratio; OS, overall survival; DBT, dihydrolipoamide branched chain transacylase E2; PDHA1, pyruvate dehydrogenase E1 subunit α1; DLAT, dihydrolipoyl transacetylase; FDX1, ferredoxin 1; ATP7B, ATPase Cu transporting β; GLS, glutaminase; DLD, dihydrolipoamide dehydrogenase; CDKN2A, cyclin-dependent kinase inhibitor 2A; PDHB, pyruvate dehydrogenase E1 subunit β; FSTL1, follistatin-like-1; CX3CR1, C-X3-C motif chemokine receptor 1; AGR2, anterior gradient-2; SLC31A1/2, solute carrier family 31 member 1/2; SOD1, superoxide dismutase 1; MTF1, metal regulatory transcription factor 1; LIPT1, lipoyltransferase 1; NDUFC1, NADH:ubiquinone oxidoreductase subunit C1; NLRP3, NOD-like receptor family pyrin domain-containing 3; NFE2L2, nuclear factor, erythroid derived 2, like 2; GCSH, glycine cleavage system protein H.

docking studies, they discovered that MTX had the highest affinity for binding to the primary chain of significant regulators linked to cuproptosis when compared to other drugs. MTX had the highest binding potential among IBD drugs, including olsalazine, prednisone and tofacitinib; thus, it could be used as a target for cuproptosis genes to treat IBD. With its growing use in clinical practice, MTX, a folic acid antagonist, is one of the most commonly administered medications (251). However, due to its numerous side effects, which include bone marrow suppression, hepatic or renal dysfunction, gastrointestinal distress, mucocutaneous injury and neurotoxicity, the use of the medication needs to be monitored (251). The toxicity typically happens quickly and results in difficult-to-manage advanced renal failure, sepsis and severe neutropenia (251).

Barasertib and NTP-TAE684. Barasertib, a selective inhibitor of Aurora B kinase, serves as the prodrug for barasertib-hydroxy-quinazoline pyrazole anilide. This compound has shown early effectiveness against acute myeloid leukemia in clinical settings (252), inhibits T47D breast cancer cell lines resistant to fulvestrant (253) and influences the migration of hepatocellular carcinoma cells (254). It has recently been demonstrated that NTP-TAE684 and barasertib can target cuproptosis-related genes for therapeutic purposes in IBD. Barasertib and NTP-TAE684, which target DLAT, have been predicted to be the most effective drugs based on molecular docking and molecular dynamics simulation analyses. Additionally, Barasertib and NTP-TAE684 are the leading compounds with the most promise for treating MDD and IBD, providing fresh insights for treatment strategies in these intricate and crippling conditions, based on thorough molecular dynamics models using DLAT as the therapeutic target (10).

Golimumab, infliximab and vedolizumab. TNF antagonists have completely transformed the treatment of IBD. The first biological drugs used to cause and sustain remission in UC were infliximab and adalimumab (255). The transgenic anti-TNF monoclonal antibody known as golimumab mainly works by identifying and neutralizing TNF to stop inflammation (256). Research has demonstrated that golimumab helps patients with UC experience clinical remission and mucosal repair (257,258). Additionally, research has demonstrated that infliximab, an anti-tumor necrosis factor agent, can be used to treat IBD, albeit response rates have varied (152,259,260). Another anti-integrin monoclonal antibody effective for CD and UC is vedolizumab (261), and research (262-265) indicates that it is safe and effective in treating IBD. It is worth noting that golimumab, vedolizumab and infliximab have been shown to target cuproptosis-related genes associated with IBD, which improves outcomes. In patients with active UC, golimumab responders alleviate defective intestinal mucosal cuproptosis by controlling hub differentially expressed cuproptosis genes (227). In a previous study, golimumab injections improved SUMF1, MT1G, FDX1, ATP7B and LIAS levels while decreasing ATOX1 in patients with active UC, thereby promoting colonic mucosal healing (227). Similarly, infliximab therapy increased the expression of SUMF1, MT1G, FDX1 and LIAS in the colonic mucosa of patients with active UC while downregulating ATOX1 (227). Additionally, the differentially expressed cuproptosis genes exhibited expression patterns similar to those of golimumab after vedolizumab treatment (227). These findings suggest that drugs may modulate genes associated with cuproptosis, reduce inflammation and reduce colonic mucosal damage.

Other drugs. Antibiotics (latamoxef and clindamycin) (266), tricyclic antidepressants (clomipramine) (267), sulfonylureas (glibenclamide) (268), organic acid/metabolite

(pyruvic acid) (269), corticosteroids (medrysone) (270), metabolic cofactor (flavin adenine dinucleotide) (271), vitinoin and caspan have been identified to target cuproptosis genes for IBD management. Therapeutics that target cuproptosis, a unique mechanism of Cu-induced cell death, are an emerging field. As a result, therapeutic compounds targeting cuproptosis-related genes have been investigated. According to the expected results, the target agents of cuproptosis-related genes may include latamoxef (PDHA1, FDX1, DBT, DLAT and LIAS), vitinoin (PDHA1, DBT, PDHB and DLD), clomipramine (DBT and LIAS), chlorzoxazone (PDHA1, FDX1, DLAT and DLD), glibenclamide (PDHA1, FDX1, DLAT and DLD), pyruvic acid (LIAS and DLD), clindamycin (PDHA1, FDX1, DLAT and LIAS), medrysone (FDX1, DLAT and LIAS), flavin adenine dinucleotide (DLD) and caspan (ATP7B, DLAT and DBT) (68). Fig. 3 depicts the potential role of prospective pharmacological agents targeting cuproptosis-related genes in IBD.

Potential drugs targeting cuproptosis-related genes from other studies. Other studies have discovered that cuproptosis-related genes can be targeted for therapeutic benefit. According to one study, PDHB expression, a gene linked to cuproptosis, was lower in patients with sepsis-induced myocardial dysfunction than in controls. Using immunohistochemistry, similar findings were discovered in sepsis-induced myocardial dysfunction animal models (231). Additionally, drug-gene interaction analysis was used to suggest prospective gene-targeting drugs. Using molecular docking, it was found that PDHB exhibits strong binding activity with ferric ammonium citrate, oxidopamine, imatinib, cube root extract, deferoxamine and vinblastine (231). Furthermore, Zhu *et al* (235) found that four genes associated with cuproptosis, PDHA1, DLAT, PDHB and NADH:ubiquinone oxidoreductase subunit C1 (NDUFC1), may serve as diagnostic indicators for sarcopenia, and that metformin shows great promise as a treatment for the condition. While no possible medications were found for the other three genes (PDHA1, DLAT and PDHB), metformin hydrochloride was identified as the therapeutic medication for NDUFC1 (235). Another study found that the occurrence and immune infiltration of septic cardiomyopathy are linked to the cuproptosis-related gene PDHB (272). However, rhodioloside, adenosine and pyruvic acid were predicted to be targets and to bind to PDHB (272). Therefore, these results suggest that possible medications that target genes linked to cuproptosis may be useful in treating a variety of illnesses, including IBD.

9. Limitations and future directions

Cuproptosis is a recently discovered type of cell death that warrants further investigation. Studies have reported increased Cu levels in IBD, while others have found lower Cu levels in the same condition. As a result, more research is needed to determine the specific pathways by which dysregulated Cu contributes to the pathogenesis of IBD. Moreover, the availability of Cu-targeting medications for IBD is currently limited. Notably, Cu has been shown to play a dual role in IBD, having both beneficial and harmful effects, which complicates the targeting of Cu ions as a therapeutic approach.

According to the present review, the majority of cuproptosis-related genes have a role in IBD pathogenesis. However, most of these genes were found via bioinformatic analyses or public databases. Additionally, the complicated regulatory mechanisms of cuproptosis in IBD were also observed. The clinical and experimental data on cuproptosis in IBD are extremely scarce. A lack of raw sequencing data, which could lead to selection bias, and smaller sample sizes were also seen (10,68,227,228). Therefore, these findings provide additional clinical or experimental validation of cuproptosis-related gene expression levels in IBD pathogenesis. In addition, larger sample sizes are required for clinical investigations and well-designed prospective studies. Further research is needed to clarify the underlying mechanisms of cuproptosis genes in IBD. Also, prospective studies on cuproptosis dynamics during the transition from chronic inflammation to colitis-associated cancer are recommended. The use of molecular docking/methods, more IBD medications, natural products, stem cells and nanoparticles should be explored to target cuproptosis-related genes for therapeutic purposes. When it comes to natural products, stem cells and nanoparticles, these can help reduce the side effects of some IBD medications.

10. Conclusion

IBD is a chronic inflammatory disorder characterized by recurrent episodes and includes conditions such as UC and CD. Research has shown that IBD is associated with imbalances in Cu levels; while some studies indicate that Cu levels increase in patients with IBD, others report a decrease. Cu plays a complex role in IBD, complicating the development of effective therapeutic strategies. Recent studies have identified several cuproptosis-related genes that can serve as biomarkers in diagnosing and predicting the progression of IBD. These genes have also been linked to increased infiltration of immune cells. In response, emerging therapeutic approaches aim to regulate these cuproptosis-related genes. Researchers are exploring novel drugs through molecular docking and other methods to target these genes for treatment.

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Availability of data and materials

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Authors' contributions

LC, FAA and FM conceptualized the study. Funding acquisition and editing was performed by JG. BP and BW edited and reviewed the manuscript. LC and FAA wrote the original draft. FM reviewed and edited the manuscript. All authors have read and agreed to the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhang C, Huang T and Li L: Targeting cuproptosis for cancer therapy: Mechanistic insights and clinical perspectives. J Hematol Oncol 17: 68, 2024.
2. Tsvetkov P, Detappe A, Cai K, Keys HR, Brune Z, Ying W, Thiru P, Reidy M, Kugener G, Rossen J, *et al*: Mitochondrial metabolism promotes adaptation to proteotoxic stress. Nat Chem Biol 15: 681-689, 2019.
3. Springer C, Humayun D and Skouta R: Cuproptosis: Unraveling the mechanisms of copper-induced cell death and its implication in cancer therapy. Cancers (Basel) 16: 647, 2024.
4. Jawed R and Bhatti H: Cuproptosis in lung cancer: Therapeutic options and prognostic models. Apoptosis 29: 1393-1398, 2024.
5. Wang M, Wang Z, Li Z, Qu Y, Zhao J, Wang L, Zhou X, Xu Z, Zhang D, Jiang P, *et al*: Targeting programmed cell death in inflammatory bowel disease through natural products: New insights from molecular mechanisms to targeted therapies. Phytother Res 39: 1776-1807, 2025.
6. Cong Y, Li N, Zhang Z, Shang Y and Zhao H: Cuproptosis: Molecular mechanisms, cancer prognosis, and therapeutic applications. J Transl Med 23: 104, 2025.
7. Wang D, Tian Z, Zhang P, Zhen L, Meng Q, Sun B, Xu X, Jia T and Li S: The molecular mechanisms of cuproptosis and its relevance to cardiovascular disease. Biomed Pharmacother 163: 114830, 2023.
8. Wang M, Zheng L, Ma S, Lin R, Li J and Yang S: Cuproptosis: Emerging biomarkers and potential therapeutics in cancers. Front Oncol 13: 1288504, 2023.
9. Wang Y, Chen Y, Zhang J, Yang Y, Fleishman JS, Wang Y, Wang J, Chen J, Li Y and Wang H: Cuproptosis: A novel therapeutic target for overcoming cancer drug resistance. Drug Resist Updat 72: 101018, 2024.
10. Shi J, Wu Q, Sang M and Mao L: Common regulatory mechanisms mediated by cuproptosis genes in inflammatory bowel disease and major depressive disorder. Genes (Basel) 16: 339, 2025.
11. Li R, Tong R, Zhang JL, Zhang Z, Deng M and Hou G: Comprehensive molecular analyses of cuproptosis-related genes with regard to prognosis, immune landscape, and response to immune checkpoint blockers in lung adenocarcinoma. J Cancer Res Clin Oncol 150: 246, 2024.
12. Jiang B, Zhu H, Feng W, Wan Z, Qi X, He R, Xie L and Li Y: Database mining detected a cuproptosis-related prognostic signature and a related regulatory axis in breast cancer. Dis Markers 2022: 9004830, 2022.
13. Chen Y: Identification and validation of cuproptosis-related prognostic signature and associated regulatory axis in uterine corpus endometrial carcinoma. Front Genet 13: 912037, 2022.
14. Wang Z, Wang Y, Yan J, Wei Y, Zhang Y, Wang X and Leng X: Analysis of cuproptosis-related genes in Ulcerative colitis and immunological characterization based on machine learning. Front Med (Lausanne) 10: 1115500, 2023.
15. Yang C, Wang W, Li S, Qiao Z, Ma X, Yang M, Zhang J, Cao L, Yao S, Yang Z and Wang W: Identification of cuproptosis hub genes contributing to the immune microenvironment in ulcerative colitis using bioinformatic analysis and experimental verification. Front Immunol 14: 1113385, 2023.
16. Tsvetkov P, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, Rossen J, Joesch-Cohen L, Humeidi R, Spangler RD, *et al*: Copper induces cell death by targeting lipoylated TCA cycle proteins. Science 375: 1254-1261, 2022.
17. Huo S, Wang Q, Shi W, Peng L, Jiang Y, Zhu M, Guo J, Peng D, Wang M, Men L, *et al*: ATF3/SPI1/SLC31A1 signaling promotes cuproptosis induced by advanced glycosylation end products in diabetic myocardial injury. Int J Mol Sci 24: 1667, 2023.
18. Panda SP and Kesharwani A: Micronutrients/miRs/ATP networking in mitochondria: Clinical intervention with ferroptosis, cuproptosis, and calcium burden. Mitochondrion 71: 1-16, 2023.
19. Corey HY, Yang N, Bothe J, Tonelli M, Nokhrin S, Dolgova NV, Braiterman L, Lutsenko S and Dmitriev OY: The metal chaperone Atox1 regulates the activity of the human copper transporter ATP7B by modulating domain dynamics. J Biol Chem 292: 18169-18177, 2017.
20. Fan H, Wang K, Zhao X, Song B, Yao T, Liu T, Gao G, Lu W and Liu C: Emerging insights into cuproptosis and copper metabolism: Implications for age-related diseases and potential therapeutic strategies. Front Aging Neurosci 16: 1335122, 2024.
21. Dreishpoon MB, Bick NR, Petrova B, Warui DM, Cameron A, Booker SJ, Kanarek N, Golub TR and Tsvetkov P: FDX1 regulates cellular protein lipoylation through direct binding to LIAS. J Biol Chem 299: 105046, 2023.
22. Kahlson MA and Dixon SJ: Copper-induced cell death. Science 375: 1231-1232, 2022.
23. Li K, Wu L, Wang H, Fu Z, Gao J, Liu X, Fan Y, Qin X, Ni D, Wang J and Xie D: Apoptosis and cuproptosis Co-activated Copper-based metal-organic frameworks for cancer therapy. J Nanobiotechnology 22: 546, 2024.
24. Muñoz C, Rios E, Olivos J, Brunser O and Olivares M: Iron, copper and immunocompetence. Br J Nutr 98 (Suppl 1): S24-S28, 2007.
25. Djoko KY, Cheryl-lynn YO, Walker MJ and McEwan AG: The role of copper and zinc toxicity in innate immune defense against bacterial pathogens. J Biol Chem 290: 18954-18961, 2015.
26. Festa RA and Thiele DJ: Copper at the front line of the host-pathogen battle. PLoS Pathog 8: e1002887, 2012.
27. Voli F, Valli E, Lerra L, Kimpton K, Saletta F, Giorgi FM, Mercatelli D, Rouaen JRC, Shen S, Murray JE, *et al*: Intratumoral copper modulates PD-L1 expression and influences tumor immune evasion. Cancer Res 80: 4129-4144, 2020.
28. Zu H, Wu Y, Meng H, Cheng X, Wang Y, Zhang LW and Wang Y: Tumor metabolism aiming $Cu_{2-x}S$ nanoagents mediate photothermal-derived cuproptosis and immune activation. ACS Nano 18: 23941-23957, 2024.
29. Li X, Dai Z, Liu J, Sun Z, Li N, Jiao G and Cao H: Characterization of the functional effects of ferredoxin 1 as a cuproptosis biomarker in cancer. Front Genet 13: 969856, 2022.
30. Jiao Y, Wang H, Zhu M, Liu T, Li Y, Yang S, Zhang M and Zhang L: Copper-induced cell death mechanisms and their role in the tumor microenvironment. Front Cell Death 4: 1628470, 2025.
31. Van den Bossche J, Baardman J and de Winther MPJ: Metabolic characterization of polarized M1 and M2 bone marrow-derived macrophages using real-time extracellular flux analysis. J Vis Exp 28: 53424, 2015.
32. Jha AK, Huang SCC, Sergushichev A, Lampropoulou V, Ivanova Y, Loginicheva E, Chmielewski K, Stewart KM, Ashall J, Everts B, *et al*: Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization. Immunity 42: 419-430, 2015.
33. Wang F, Zhang S, Vuckovic I, Jeon R, Lerman A, Folmes CD, Dzeja PP and Herrmann J: Glycolytic stimulation is not a requirement for M2 macrophage differentiation. Cell Metab 28: 463-475.e4, 2018.
34. O'Neill LA, Kishton RJ and Rathmell J: A guide to immunometabolism for immunologists. Nat Rev Immunol 16: 553-565, 2016.
35. Hedeskov CJ and Esmann V: Respiration and glycolysis of normal human lymphocytes. Blood 28: 163-174, 1966.
36. Fox CJ, Hammerman PS and Thompson CB: Fuel feeds function: Energy metabolism and the T-cell response. Nat Rev Immunol 5: 844-852, 2005.

37. O'Sullivan D: The metabolic spectrum of memory T cells. Immunol Cell Biol 97: 636-646, 2019.
38. Lian W, Yang P, Li L, Chen D and Wang C: A ceRNA network-mediated over-expression of cuproptosis-related gene SLC31A1 correlates with poor prognosis and positive immune infiltration in breast cancer. Front Med (Lausanne) 10: 1194046, 2023.
39. Yi WJ, Yuan Y, Bao Q, Zhao Z, Ding HS and Song J: Analyzing immune cell infiltration and copper metabolism in diabetic foot ulcers. J Inflamm Res 17: 3143-3157, 2024.
40. Zhou L, Mao H, Wen Y, Chen Z and Zhang L: Cuproptosis promotes inflammatory osteolysis via GYS1-mediated glycogen metabolism. Int J Oral Sci 18: 13, 2026.
41. Linz R and Lutsenko S: Copper-transporting ATPases ATP7A and ATP7B: Cousins, not twins. J Bioenerg Biomembr 39: 403-407, 2007.
42. Tadini-Buoninsegni F and Smeazzetto S: Mechanisms of charge transfer in human copper ATPases ATP7A and ATP7B. IUBMB Life 69: 218-225, 2017.
43. White C, Lee J, Kambe T, Fritsche K and Petris MJ: A role for the ATP7A copper-transporting ATPase in macrophage bactericidal activity. J Biol Chem 284: 33949-33956, 2009.
44. Ladomersky E, Khan A, Shanbhag V, Cavet JS, Chan J, Weisman GA and Petris MJ: Host and pathogen copper-transporting P-type atpases function antagonistically during salmonella infection. Infect Immun 85: e00351-17, 2017.
45. Liu J, Tang H, Chen F, Li C, Xie Y, Kang R and Tang D: NFE2L2 and SLC25A39 drive cuproptosis resistance through GSH metabolism. Sci Rep 14: 29579, 2024.
46. Liu S, Yan W, Zhang W, Zhang J, Li Z, Guo Y, Chen HY and Xu JJ: Nanoenhanced-cuproptosis results from the synergy of calcium overload and GSH depletion with the increasing of intracellular Ca/Mn/Cu ions. Adv Sci (Weinh) 12: e2412067, 2025.
47. Zhang L, Tsai IC, Ni Z, Chen B, Zhang S, Cai L and Xu Q: Copper chelation therapy attenuates periodontitis inflammation through the cuproptosis/autophagy/lysosome axis. Int J Mol Sci 25: 5890, 2024.
48. Mak TW, Grusdat M, Duncan GS, Dostert C, Nonnenmacher Y, Cox M, Binsfeld C, Hao Z, Brüstle A, Itsumi M, *et al*: Glutathione primes T cell metabolism for inflammation. Immunity 46: 675-689, 2017.
49. Li L, Cheng H, Gong L, Huang Y, Yang J, Yan Q, Dai S and Wang J: Cuproptosis/OXPHOS tendency prediction of prognosis and immune microenvironment of esophageal squamous cell carcinoma: Bioinformatics analysis and experimental validation. Gene 902: 148156, 2024.
50. Yang L, Li X, Jiang Y, Zhang M, Wu T, Pi P, Han Z, Zhang Z, Kong F, Lu X, *et al*: ASPP2 inhibits hepatocellular carcinoma growth by regulating cuproptosis via mitochondrial protein lipoylation. Cell Death Dis: Apr 24, 2026 (Epub ahead of print).
51. Xiong C, Ling H, Hao Q and Zhou X: Cuproptosis: p53-regulated metabolic cell death? Cell Death Differ 30: 876-884, 2023.
52. El Kasmi KC and Stenmark KR: Contribution of metabolic reprogramming to macrophage plasticity and function. Semin Immunol 27: 267-275, 2015.
53. Galván-Peña S and O'Neill LAJ: Metabolic reprograming in macrophage polarization. Front Immunol 5: 420, 2014.
54. Li S, Jiang K, Wang T, Zhang W, Shi M, Chen B and Hua Z: Nanobody against PDL1. Biotechnol Lett 42: 727-736, 2020.
55. Hegde PS, Karanikas V and Evers S: The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition. Clin Cancer Res 22: 1865-1874, 2016.
56. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, *et al*: Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 515: 563-567, 2014.
57. Galon J and Bruni D: Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov 18: 197-218, 2019.
58. Yang W and Cong Y: Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases. Cell Mol Immunol 18: 866-877, 2021.
59. Halfvarson J, Brislawn CJ, Lamendella R, Vázquez-Baeza Y, Walters WA, Bramer LM, D'Amato M, Bonfiglio F, McDonald D, Gonzalez A, *et al*: Dynamics of the human gut microbiome in inflammatory bowel disease. Nat Microbiol 2: 17004, 2017.
60. Xu B, Zhang L, Wu D, Qi Z, Cao J, Li W, Fan L, Shi Y, Wu Y and Li G: CuO nanoparticles elicit intestinal immunotoxicity in zebrafish based on intestinal microbiota dysbiosis. Food Funct 15: 7619-7630, 2024.
61. Zhang L, Zhang D, Li S, Xu B, Jiang F, Nie Y, Li G Xu B, Jiang F, Nie Y and Li G: CuO nanoparticles trigger cuproptosis-linked mitochondrial damage and gut microbiota-metabolome disruption in zebrafish. Environ Pollut 396: 127834, 2026.
62. Balasubramanian S, Haneen MA, Sharma G and Perumal E: Acute copper oxide nanoparticles exposure alters zebrafish larval microbiome. Life Sci 336: 122313, 2024.
63. Yang M, Zheng H, Xu K, Yuan Q, Aihaiti Y, Cai Y and Xu P: A novel signature to guide osteosarcoma prognosis and immune microenvironment: Cuproptosis-related lncRNA. Front Immunol 13: 919231, 2022.
64. Liu H: Pan-cancer profiles of the cuproptosis gene set. Am J Cancer Res 12: 4074-4081, 2022.
65. Baba Y, Higa JK, Shimada BK, Horiuchi KM, Suhara T, Kobayashi M, Woo JD, Aoyagi H, Marh KS, Kitaoka H and Matsui T: Protective effects of the mechanistic target of rapamycin against excess iron and ferroptosis in cardiomyocytes. Am J Physiol Heart Circ Physiol 314: H659-H668, 2018.
66. Cao JY and Dixon SJ: Mechanisms of ferroptosis. Cell Mol Life Sci 73: 2195-2209, 2016.
67. Wang S, Liu W, Wang J and Bai X: Curculigoside inhibits ferroptosis in ulcerative colitis through the induction of GPX4. Life Sci 259: 118356, 2020.
68. Huang J, Zhang J, Wang F, Zhang B and Tang X: Comprehensive analysis of cuproptosis-related genes in immune infiltration and diagnosis in ulcerative colitis. Front Immunol 13: 1008146, 2022.
69. Long X, Zhu N, Qiu J, Yu X, Ruan X, Wang X and Tian L: Necroptosis in inflammatory bowel disease: A potential effective target. Zhong Nan Da Xue Xue Bao Yi Xue Ban 47: 1289-1298, 2022 (In Chinese).
70. Pierdomenico M, Negroni A, Stronati L, Vitali R, Prete E, Bertin J, Gough PJ, Aloi M and Cucchiara S: Necroptosis is active in children with inflammatory bowel disease and contributes to heighten intestinal inflammation. Am J Gastroenterol 109: 279-287, 2014.
71. Rodriguez DA, Quarato G, Liedmann S, Tummers B, Zhang T, Guy C, Crawford JC, Palacios G, Pelletier S, Kalkavan H, *et al*: Caspase-8 and FADD prevent spontaneous ZBP1 expression and necroptosis. Proc Natl Acad Sci USA 119: e2207240119, 2022.
72. D'Argenio G, Farrace MG, Cosenza V, De Ritis F, Della Valle N, Manguso F and Piacentini M: Expression of apoptosis-related proteins in rat with induced colitis. Int J Colorectal Dis 19: 451-460, 2004.
73. Geng Z, Zuo L, Li J, Yin L, Yang J, Duan T, Wang L, Zhang X, Song X, Wang Y and Hu J: Ginkgetin improved experimental colitis by inhibiting intestinal epithelial cell apoptosis through EGFR/PI3K/AKT signaling. FASEB J 38: e23817, 2024.
74. Fang Y, Tian S, Pan Y, Li W, Wang Q, Tang Y, Yu T, Wu X, Shi Y, Ma P and Shu Y: Pyroptosis: A new frontier in cancer. Biomed Pharmacother 121: 109595, 2020.
75. Cai H, Zhang J, Xu H, Sun W, Wu W, Dong C, Zhou P, Xue C, Nan Y, Ni Y, *et al*: ALOX5 drives the pyroptosis of $CD4^+$ T cells and tissue inflammation in rheumatoid arthritis. Sci Signal 17: eadh1178, 2024.
76. Lei Q and Yi T: Research progresses of the effective mechanism of pyroptosis and its related diseases. J Med Postgrad 2017: 648-652, 2017.
77. Liu X, Zhou M, Dai Z, Luo S, Shi Y, He Z and Chen Y: Salidroside alleviates ulcerative colitis via inhibiting macrophage pyroptosis and repairing the dysbacteriosis-associated Th17/Treg imbalance. Phytother Res 37: 367-382, 2023.
78. Li H, Sun Y, Yao Y, Ke S, Zhang N, Xiong W, Shi J, He C, Xiao X, Yu H, *et al*: USP8-governed GPX4 homeostasis orchestrates ferroptosis and cancer immunotherapy. Proc Natl Acad Sci USA 121: e2315541121, 2024.
79. Shui S, Zhao Z, Wang H, Conrad M and Liu G: Non-enzymatic lipid peroxidation initiated by photodynamic therapy drives a distinct ferroptosis-like cell death pathway. Redox Biol 45: 102056, 2021.
80. Kiraz Y, Adan A, Kartal Yandim M and Baran Y: Major apoptotic mechanisms and genes involved in apoptosis. Tumour Biol 37: 8471-8486, 2016.
81. Zhang C, Akanyibah FA, Wang X, Mao F and Shang A: The role of apoptosis and its potential as a therapeutic target in inflammatory bowel disease associated with colorectal cancer. Am J Transl Res 17: 5718-5745, 2025.
82. Burdette BE, Esparza AN, Zhu H and Wang S: Gasdermin D in pyroptosis. Acta Pharm Sin B 11: 2768-2782, 2021.

83. Solon M, Ge N, Hambro S, Haller S, Jiang J, Baca M, Preston J, Maltzman A, Wickliffe KE, Liang Y, *et al*: ZBP1 and TRIF trigger lethal necroptosis in mice lacking caspase-8 and TNFR1. Cell Death Differ 31: 672-682, 2024.
84. Grootjans S, Vanden Berghe T and Vandenabeele P: Initiation and execution mechanisms of necroptosis: An overview. Cell Death Differ 24: 1184-1195, 2017.
85. Kuribayashi K, Mayes PA and El-Deiry WS: What are caspases 3 and 7 doing upstream of the mitochondria? Cancer Biol Ther 5: 763-765, 2006.
86. Forcina GC and Dixon SJ: GPX4 at the crossroads of lipid homeostasis and ferroptosis. Proteomics 19: e1800311, 2019.
87. Lossi L: The concept of intrinsic versus extrinsic apoptosis. Biochem J 479: 357-384, 2022.
88. Xie Y, Hou W, Song X, Yu Y, Huang J, Sun X, Kang R and Tang D: Ferroptosis: Process and function. Cell Death Differ 23: 369-379, 2016.
89. Tang D, Chen X and Kroemer G: Cuproptosis: A copper-triggered modality of mitochondrial cell death. Cell Res 32: 417-418, 2022.
90. Kerr JF, Wyllie AH and Currie AR: Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26: 239-257, 1972.
91. Bai Y, Pan Y and Liu X: Mechanistic insights into gasdermin-mediated pyroptosis. Nat Rev Mol Cell Biol 26: 501-521, 2025.
92. Wang Q, Chen H, Lv Z, Zhang P, Li Y, Zhao C and Li S: The molecular mechanism of cuproptosis and research progress in pancreatic diseases. Ann Med 58: 2608490, 2026.
93. Akanyibah FA, Zhu Y, Jin T, Ocansey DKW, Mao F and Qiu W: The function of necroptosis and its treatment target in IBD. Mediators Inflamm 2024: 7275309, 2024.
94. Xiang Z, Mei H, Wang H, Yao X, Rao J, Zhang W, Xu A and Lu L: Cuproptosis and its potential role in musculoskeletal disease. Front Cell Dev Biol 13: 1570131, 2025.
95. Wang Y, Zhu Y, Wang Y, Liu Y, Wang P and Yu M: Cuproptosis at the crossroads of tumor microenvironment inflammation and metabolic rewiring mechanisms and therapeutic opportunities. Mediators Inflamm 2026: 2952331, 2026.
96. Li JY, Yao YM and Tian YP: Ferroptosis: A trigger of proinflammatory state progression to immunogenicity in necroinflammatory disease. Front Immunol 12: 701163, 2021.
97. Ciftci YC, Vatansever İE and Akgül B: Unraveling the intriguing interplay: Exploring the role of lncRNAs in caspase-independent cell death. Wiley Interdiscip Rev RNA 15: e1862, 2024.
98. Zhang P, Zhou C, Ren X, Jing Q, Gao Y, Yang C, Shen Y, Zhou Y, Hu W, Jin F, *et al*: Inhibiting the compensatory elevation of xCT collaborates with disulfiram/copper-induced GSH consumption for cascade ferroptosis and cuproptosis. Redox Biol 69: 103007, 2024.
99. Arnér ES and Schmidt EE: Unresolved questions regarding cellular cysteine sources and their possible relationships to ferroptosis. Adv Cancer Res 162: 1-44, 2024.
100. Ma Z, Ye W, Wang J, Huang X, Huang J, Li X, Hu C, Li C, Zhou Y, Lin X, *et al*: Glutamate dehydrogenase 1: A novel metabolic target in inhibiting acute myeloid leukaemia progression. Br J Haematol 202: 566-577, 2023.
101. Tu B, Song K, Zhou ZY, Lin LC, Liu ZY, Sun H, Zhou Y, Sha JM, Shi Y, Yang JJ, *et al*: SLC31A1 loss depletes mitochondrial copper and promotes cardiac fibrosis. Eur Heart J 46: 2458-2474, 2025.
102. Yu P, Li K, Luo S, Yan R, Yi X, Fang C, Ma S, Wang G, Luo F, Chen X, *et al*: Cuproptosis facilitates chronic skin inflammation by regulating the α-ketoglutarate/H3K4me3/ferritin heavy chain 1 signaling pathway-mediated ferroptosis. MedComm (2020) 6: e70425, 2025.
103. Vladimirov YA, Proskurnina EV and Alekseev AV: Molecular mechanisms of apoptosis. Structure of cytochrome c-cardiolipin complex. Biochemistry (Mosc) 78: 1086-1097, 2013.
104. Pan M, Cheng ZW, Huang CG, Ye ZQ, Sun LJ, Chen H, Fu BB, Zhou K, Fang ZR, Wang ZJ, *et al*: Long-term exposure to copper induces mitochondria-mediated apoptosis in mouse hearts. Ecotoxicol Environ Saf 234: 113329, 2022.
105. Chen Y, Nan Y, Xu L, Dai A, Orteg RMM, Ma M, Zeng Y and Li J: Polystyrene nanoplastics exposure induces cognitive impairment in mice via induction of oxidative stress and ERK/MAPK-mediated neuronal cuproptosis. Part Fibre Toxicol 22: 13, 2025.
106. Schieber M and Chandel NS: ROS function in redox signaling and oxidative stress. Curr Biol 24: R453-R462, 2014.
107. Wei H, Xiong M and Min L: ROS-mediated cell death and phase separation in gynecological malignancies. Eur J Med Res 30: 578, 2025.
108. Formigari A, Gregianin E and Irato P: The effect of zinc and the role of p53 in copper-induced cellular stress responses. J Appl Toxicol 33: 527-536, 2013.
109. Hainaut P, Rolley N, Davies M and Milner J: Modulation by copper of p53 conformation and sequence-specific DNA binding: role for Cu(II)/Cu(I) redox mechanism. Oncogene 10: 27-32, 1995.
110. Narayanan VS, Fitch CA and Levenson CW: Tumor suppressor protein p53 mRNA and subcellular localization are altered by changes in cellular copper in human Hep G2 cells. J Nutr 131: 1427-1432, 2001.
111. Liu J, Zhang C, Hu W and Feng Z: Tumor suppressor p53 and metabolism. J Mol Cell Biol 11: 284-292, 2019.
112. Du W, Amarachintha S, Wilson AF and Pang Q: SCO2 mediates oxidative stress-induced glycolysis to oxidative phosphorylation switch in hematopoietic stem cells. Stem Cells 34: 960-971, 2016.
113. Nirmala JG and Lopus M: Cell death mechanisms in eukaryotes. Cell Biol Toxicol 36: 145-164, 2020.
114. Deigendesch N, Zychlinsky A and Meissner F: Copper regulates the canonical NLRP3 inflammasome. J Immunol 200: 1607-1617, 2018.
115. Tao X, Wan X, Wu D, Song E and Song Y: A tandem activation of NLRP3 inflammasome induced by copper oxide nanoparticles and dissolved copper ion in J774A.1 macrophage. J Hazard Mater 411: 125134, 2021.
116. Dong J, Wang X, Xu C, Gao M, Wang S, Zhang J, Tong H, Wang L, Han Y, Cheng N and Han Y: Inhibiting NLRP3 inflammasome activation prevents copper-induced neuropathology in a murine model of Wilson's disease. Cell Death Dis 12: 87, 2021.
117. Wu H, Guo H, Liu H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X and Zhao L: Copper sulfate-induced endoplasmic reticulum stress promotes hepatic apoptosis by activating CHOP, JNK and caspase-12 signaling pathways. Ecotoxicol Environ Saf 191: 110236, 2020.
118. Tsui KH, Hsiao JH, Lin LT, Tsang YL, Shao AN, Kuo CH, Chang R, Wen ZH and Li CJ: The cross-communication of cuproptosis and regulated cell death in human pathophysiology. Int J Biol Sci 20: 218-230, 2024.
119. Tang D, Kang R, Berghe TV, Vandenabeele P and Kroemer G: The molecular machinery of regulated cell death. Cell Res 29: 347-364, 2019.
120. Weinlich R, Oberst A, Beere HM and Green DR: Necroptosis in development, inflammation and disease. Nat Rev Mol Cell Biol 18: 127-136, 2017.
121. Carneiro BA and El-Deiry WS: Targeting apoptosis in cancer therapy. Nat Rev Clin Oncol 17: 395-417, 2020.
122. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, *et al*: Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell 149: 1060-1072, 2012.
123. Capelletti MM, Manceau H, Puy H and Peoc'h K: Ferroptosis in liver diseases: An overview. Int J Mol Sci 21: 4908, 2020.
124. Tan Y, Chen Q, Li X, Zeng Z, Xiong W, Li G, Li X, Yang J, Xiang B and Yi M: Pyroptosis: A new paradigm of cell death for fighting against cancer. J Exp Clin Cancer Res 40: 153, 2021.
125. Bergsbaken T, Fink SL and Cookson BT: Pyroptosis: Host cell death and inflammation. Nat Rev Microbiol 7: 99-109, 2009.
126. Hasinoff BB, Yadav AA, Patel D and Wu X: The cytotoxicity of the anticancer drug elesclomol is due to oxidative stress indirectly mediated through its complex with Cu(II). J Inorg Biochem 137: 22-30, 2014.
127. Kirshner JR, He S, Balasubramanyam V, Kepros J, Yang CY, Zhang M, Du Z, Barsoum J and Bertin J: Elesclomol induces cancer cell apoptosis through oxidative stress. Mol Cancer Ther 7: 2319-2327, 2008.
128. Feng Y, Wu JJ, Sun ZL, Liu SY, Zou ML, Yuan ZD, Yu S, Lv GZ and Yuan FL: Targeted apoptosis of myofibroblasts by elesclomol inhibits hypertrophic scar formation. EBioMedicine 54: 102715, 2020.
129. Qi G, Sun D, Tian Y, Xu C, Zhang Y, Wang D, Ma K, Xu S and Jin Y: Fast activation and tracing of caspase-3 involved cell apoptosis by combined electrostimulation and smart signal-amplified SERS nanoprobes. Anal Chem 92: 7861-7868, 2020.
130. Matsuoka K and Kanai T: The gut microbiota and inflammatory bowel disease. Semin Immunopathol 37: 47-55, 2015.

131. Ito T and Kayama H: Roles of fibroblasts in the pathogenesis of inflammatory bowel diseases and IBD-associated fibrosis. Int Immunol 37: 377-392, 2025.
132. Steinwurz F, Machado MB, Veitia G, De Paula JA, Bautista Martinez S, Vergara BI, Capdevielle B, Martinez Silva FA and Ramirez AL: Latin America consensus statement inflammatory bowel disease: Importance of timely access to diagnosis and treatment. Ther Adv Gastroenterol 16: 17562848231207312, 2023.
133. Krause JL, Engelmann B, Schaepe SS, Rolle-Kampczyk U, Jehmlich N, Chang HD, Slanina U, Hoffman M, Lehmann J, Zenclussen AC, *et al*: DSS treatment does not affect murine colonic microbiota in absence of the host. Gut Microbes 16: 2297831, 2024.
134. Cai M, Mao Y, Gao W, Wang Z, Mao J and Sha R: Insights into diosgenin against inflammatory bowel disease as functional food based on network pharmacology and molecular docking. Heliyon 10: e37937, 2024.
135. Shah SC and Itzkowitz SH: Colorectal cancer in inflammatory bowel disease: Mechanisms and management. Gastroenterology 162: 715-730 e3, 2022.
136. Desai J, Elnaggar M, Hanfy AA and Doshi R: Toxic megacolon: Background, pathophysiology, management challenges and solutions. Clin Exp Gastroenterol 13: 203-210, 2020.
137. Rieder F, Zimmermann EM, Remzi FH and Sandborn WJ: Crohn's disease complicated by strictures: A systematic review. Gut 62: 1072-1084, 2013.
138. D'Alessio S, Ungaro F, Noviello D, Lovisa S, Peyrin-Biroulet L and Danese S: Revisiting fibrosis in inflammatory bowel disease: The gut thickens. Nat Rev Gastroenterol Hepatol 19: 169-184, 2022.
139. Shen B: Endoscopic management of inflammatory bowel disease-associated complications. Curr Opin Gastroenterol 36: 33-40, 2020.
140. Sange AH, Srinivas N, Sarnaik MK, Modi S, Pisipati Y, Vaidya S, Syed Gaggatur N and Sange I: Extra-intestinal manifestations of inflammatory bowel disease. Cureus 13: e17187, 2021.
141. Murray A, Nguyen TM, Parker CE, Feagan BG and MacDonald JK: Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 8: CD000543, 2020.
142. Ford AC, Khan KJ, Sandborn WJ, Hanauer SB and Moayyedi P: Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent ulcerative colitis: A meta-analysis. Clin Gastroenterol Hepatol 10: 513-519, 2012.
143. Ford AC, Bernstein CN, Khan KJ, Abreu MT, Marshall JK, Talley NJ and Moayyedi P: Glucocorticosteroid therapy in inflammatory bowel disease: Systematic review and meta-analysis. Am J Gastroenterol 106: 590-600, 2011.
144. Sandborn WJ, Danese S, D'Haens G, Moro L, Jones R, Bagin R, Huang M, David Ballard E, Masure J and Travis S: Induction of clinical and colonoscopic remission of mild-to-moderate ulcerative colitis with budesonide MMX 9 mg: Pooled analysis of two phase 3 studies. Aliment Pharmacol Ther 41: 409-418, 2015.
145. Masuda M, Fukata N, Sano Y, Nishimon S, Aoi M, Tomiyama T, Fukui T, Omiya M, Okazaki K and Naganuma M: Analysis of the initial dose and reduction rate of corticosteroid for ulcerative colitis in clinical practice. JGH Open 6: 612-620, 2022.
146. Gisbert JP, Niño P, Cara C and Rodrigo L: Comparative effectiveness of azathioprine in Crohn's disease and ulcerative colitis: Prospective, long-term, follow-up study of 394 patients. Aliment Pharmacol Ther 28: 228-238, 2008.
147. Pugliese D, Aratari A, Festa S, Ferraro PM, Monterubbianesi R, Guidi L, Scribano ML, Papi C and Armuzzi A: Sustained clinical efficacy and mucosal healing of thiopurine maintenance treatment in ulcerative colitis: A real-life study. Gastroenterol Res Pract 2018: 4195968, 2018.
148. Sequier L, Caron B, Loeuille D, Honap S, Jairath V, Netter P, Danese S, Sibilia J and Peyrin-Biroulet L: Systematic review: Methotrexate-A poorly understood and underused medication in inflammatory bowel disease. Aliment Pharmacol Ther 60: 686-700, 2024.
149. Weisshof R, Aharoni Golan M, Sossenheimer PH, El Jurdi K, Ollech JE, Pekow J, Cohen RD, Sakuraba A, Dalal S and Rubin DT: Real-world experience with tofacitinib in IBD at a tertiary center. Dig Dis Sci 64: 1945-1951, 2019.
150. Sandborn WJ, Ghosh S, Panes J, Schreiber S, D'Haens G, Tanida S, Siffledeen J, Enejosa J, Zhou W, Othman AA, *et al*: Efficacy of upadacitinib in a randomized trial of patients with active ulcerative colitis. Gastroenterology 158: 2139-2149.e14, 2020.
151. Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, *et al*: Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 141: 1194-1201, 2011.
152. Kamal ME, Werida RH, Radwan MA, Askar SR, Omran GA, El-Mohamdy MA and Hagag RS: Efficacy and safety of infliximab and adalimumab in inflammatory bowel disease patients. Inflammopharmacology 32: 3259-3269, 2024.
153. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, Adedokun OJ, Li K, Peyrin-Biroulet L, Van Assche G, *et al*: Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 381: 1201-1214, 2019.
154. Sands BE, D'Haens G, Clemow DB, Irving PM, Johns JT, Hunter Gibble T, Abreu MT, Lee S, Hisamatsu T, Kobayashi T, *et al*: Two-year efficacy and safety of mirikizumab following 104 weeks of continuous treatment for ulcerative colitis: Results from the LUCENT-3 open-label extension study. Inflamm Bowel Dis 30: 2245-2258, 2024.
155. Feagan BG, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, Louis E, Franchimont D, Dewit O, Seidler U, *et al*: Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: A randomised, double-blind, placebo-controlled phase 2 study. Lancet 389: 1699-1709, 2017.
156. Xing R, Wang H, Zhang W, Ma X, Guan J and Chen X: Clinical significance of the ratio of serum copper to zinc in patients with inflammatory bowel disease. Chin J Dig 41: 665-670, 2021.
157. Ritland S, Elgjo K, Johansen O and Steinnes E: Liver copper content in patients with inflammatory bowel disease and associated liver disorders. Scand J Gastroenterol 14: 711-715, 1979.
158. Mohammadi E, Qujeq D, Taheri H and Hajian-Tilaki K: Evaluation of serum trace element levels and superoxide dismutase activity in patients with inflammatory bowel disease: Translating basic research into clinical application. Biol Trace Elem Res 177: 235-240, 2017.
159. Piątek-Guziewicz A, Paśko P, Wcisło K, Dąbek-Drobny A, Przybylska-Feluś M, Kaczmarczyk O, Zagrodzki P, Mach T and Zwolińska-Wcisło M: Serum levels of selected micronutrients in patients with inflammatory bowel disease in clinical remission. Pol Arch Intern Med 131: 701-708, 2021.
160. Kamel AY, Johnson ZD, Hernandez I, Nguyen C, Rolfe M, Joseph T, Dixit D, Shen S, Chaudhry N, Pham A, *et al*: Micronutrient deficiencies in inflammatory bowel disease: An incidence analysis. Eur J Gastroenterol Hepatol 36: 1186-1192, 2024.
161. Schneider T, Caviezel D, Ayata CK, Kiss C, Niess JH and Hruz P: The copper/zinc ratio correlates with markers of disease activity in patients with inflammatory bowel disease. Crohns Colitis 360 2: otaa001, 2020.
162. Makevic V, Milovanovich ID, Popovac N, Janković S, Janković V, Stefanović S, Bukumiric Z and de Luka SR: Oligoelements in serum and intestinal tissue of pediatric IBD patients. J Trace Elem Med Biol 79: 127239, 2023.
163. Skalny AV, Mazaletskaya AL, Ajsuvakova OP, Bjørklund G, Skalnaya MG, Chao JC, Chernova LN, Shakieva RA, Kopylov PY, Skalny AA and Tinkov AA: Serum zinc, copper, zinc-to-copper ratio, and other essential elements and minerals in children with attention deficit/hyperactivity disorder (ADHD). J Trace Elem Med Biol 58: 126445, 2020.
164. Wazir SM and Ghobrial I: Copper deficiency, a new triad: Anemia, leucopenia, and myeloneuropathy. J Community Hosp Intern Med Perspect 7: 265-268, 2017.
165. Hall AC, Young BW and Bremner I: Intestinal metallothionein and the mutual antagonism between copper and zinc in the rat. J Inorg Biochem 11: 57-66, 1979.
166. Robinett NG, Peterson RL and Culotta VC: Eukaryotic copper-only superoxide dismutases (SODs): A new class of SOD enzymes and SOD-like protein domains. J Biol Chem 293: 4636-4643, 2018.
167. Rosa AC, Corsi D, Cavi N, Bruni N and Dosio F: Superoxide dismutase administration: A review of proposed human uses. Molecules 26: 1844, 2021.
168. Alzoghaibi MA, Al-Mofleh IA and Al-Jebreen AM: Antioxidant activities for superoxide dismutase in patients with Crohn's disease. J Basic Clin Physiol Pharmacol 25: 59-62, 2014.
169. Alsaffar RM, Ali A, Rashid SM, Ahmad SB, Alkholifi FK, Kawoosa MS, Ahmad SP and Rehman MU: Zerumbone protects rats from collagen-induced arthritis by inhibiting oxidative outbursts and inflammatory cytokine levels. ACS Omega 8: 2982-2991, 2023.

170. Zhang MS, Liang JH, Yang MJ, Ren YR, Cheng DH, Wu QH, He Y and Yin J: Low serum superoxide dismutase is associated with a high risk of cognitive impairment after mild acute ischemic stroke. Front Aging Neurosci 14: 834114, 2022.
171. Schanne G, Vincent A, Chain F, Ruffié P, Carbonne C, Quévrain E, Mathieu E, Balfourier A, Bermúdez-Humarán LG, Langella P, *et al*: SOD mimics delivered to the gut using lactic acid bacteria mitigate the colitis symptoms in a mouse model of inflammatory bowel diseases. Free Radic Res 59: 262-273, 2025.
172. Fu W, Huang Z, Li W, Xu L, Yang M, Ma Y, Liu H, Qian H and Wang W: Copper-luteolin nanocomplexes for Mediating multi-faceted regulation of oxidative stress, intestinal barrier, and gut microbiota in inflammatory bowel disease. Bioact Mater 46: 118-133, 2024.
173. Zhou YH, Liu XP, Gu XM, Lv HX, Yang Y, Cai ZX, Di B, Wang CK, Gao YY and Jin L: Effects of dietary nano-composite of copper and carbon on antioxidant capacity, immunity, and cecal microbiota of weaned ira white rabbits. Animals (Basel) 15: 184, 2025.
174. van De Sluis B, Rothuizen J, Pearson PL, van Oost BA and Wijmenga C: Identification of a new copper metabolism gene by positional cloning in a purebred dog population. Hum Mol Genet 11: 165-173, 2002.
175. Burstein E, Hoberg JE, Wilkinson AS, Rumble JM, Csomos RA, Komarck CM, Maine GN, Wilkinson JC, Mayo MW and Duckett CS: COMMD proteins, a novel family of structural and functional homologs of MURR1. J Biol Chem 280: 22222-22232, 2005.
176. de Bie P, van de Sluis B, Burstein E, Duran KJ, Berger R, Duckett CS, Wijmenga C and Klomp LW: Characterization of COMMD protein-protein interactions in NF-kappaB signalling. Biochem J 398: 63-71, 2006.
177. Pisani LF, Tontini G, Vecchi M, Croci GA and Pastorelli L: NF-kB pathway is involved in microscopic colitis pathogenesis. J Int Med Res 50: 03000605221080104, 2022.
178. Ibrahim S, Zhu X, Luo X, Feng Y and Wang J: PIK3R3 regulates ZO-1 expression through the NF-kB pathway in inflammatory bowel disease. Int Immunopharmacol 85: 106610, 2020.
179. Li H and Burstein E: COMMD1 regulates inflammation and colitis-associated cancer progression. Oncoimmunology 3: e947891, 2014.
180. Qiu W, Wu B, Wang X, Buchanan ME, Regueiro MD, Hartman DJ, Schoen RE, Yu J and Zhang L: PUMA-mediated intestinal epithelial apoptosis contributes to ulcerative colitis in humans and mice. J Clin Invest 121: 1722-1732, 2011.
181. Li H, Chan L, Bartuzi P, Melton SD, Weber A, Ben-Shlomo S, Varol C, Raetz M, Mao X, Starokadomskyy P, *et al*: Copper metabolism domain-containing 1 represses genes that promote inflammation and protects mice from colitis and colitis-associated cancer. Gastroenterology 147: 184-195.e3, 2014.
182. Martin F, Linden T, Katschinski DM, Oehme F, Flamme I, Mukhopadhyay CK, Eckhardt K, Tröger J, Barth S, Camenisch G and Wenger RH: Copper-dependent activation of hypoxia-inducible factor (HIF)-1: Implications for ceruloplasmin regulation. Blood 105: 4613-4619, 2005.
183. Sun L, Li T, Tang H, Yu K, Ma Y, Yu M, Qiu Y, Xu P, Xiao W and Yang H: Intestinal epithelial cells-derived hypoxia-inducible factor-1α is essential for the homeostasis of intestinal intraepithelial lymphocytes. Front Immunol 10: 806, 2019.
184. Valle-Noguera A, Sancho-Temiño L, Castillo-González R, Villa-Gómez C, Gomez-Sánchez MJ, Ochoa-Ramos A, Yagüe-Fernández P, Soler Palacios B, Zorita V, Raposo-Ponce B, *et al*: IL-18-induced HIF-1α in ILC3s ameliorates the inflammation of C. rodentium-induced colitis. Cell Rep 42: 113508, 2023.
185. Nelius E, Fan Z, Sobecki M, Krzywinska E, Nagarajan S, Ferapontova I, Gotthardt D, Takeda N, Sexl V and Stockmann C: The transcription factor HIF-1α in NKp46+ ILCs limits chronic intestinal inflammation and fibrosis. Life Sci Alliance 7: e202402593, 2024.
186. Lu H, Lin J, Xu C, Sun M, Zuo K, Zhang X, Li M, Huang H, Li Z, Wu W, *et al*: Cyclosporine modulates neutrophil functions via the SIRT6-HIF-1α-glycolysis axis to alleviate severe ulcerative colitis. Clin Transl Med 11: e334, 2021.
187. Zhou C, Li L, Li T, Sun L, Yin J, Guan H, Wang L, Zhu H, Xu P, Fan X, *et al*: SCFAs induce autophagy in intestinal epithelial cells and relieve colitis by stabilizing HIF-1α. J Mol Med (Berl) 98: 1189-1202, 2020.
188. Li X, Wen J, Jiao L, Wang C, Hong Q, Feng J and Hu C: Dietary copper/zinc-loaded montmorillonite improved growth performance and intestinal barrier and changed gut microbiota in weaned piglets. J Anim Physiol Anim Nutr (Berl) 105: 678-686, 2021.
189. Jiao L, Wang CC, Wu H, Gong R, Lin FH, Feng J and Hu C: Copper/zinc-loaded montmorillonite influences intestinal integrity, the expression of genes associated with inflammation, TLR4-MyD88 and TGF-β1 signaling pathways in weaned pigs after LPS challenge. Innate Immun 23: 648-655, 2017.
190. Hu Y, Li T, Tang S, Lai A, Sun C, Chen B, Cai B, Zhang L and Yin H: Effects of dietary copper deficiency on colonic barrier integrity, inflammatory markers, and gut microbiota composition in mice. Nutrients 18: 1707, 2026.
191. Vasilyev VB: Looking for a partner: Ceruloplasmin in protein-protein interactions. Biometals 32: 195-210, 2019.
192. Niu L, Zhou Y, Lu L, Su A and Guo X: Ceruloplasmin deficiency impaired brain iron metabolism and behavior in mice. Cell Biochem Biophys 80: 385-393, 2022.
193. Das S and Sahoo PK: Ceruloplasmin, a moonlighting protein in fish. Fish Shellfish Immunol 82: 460-468, 2018.
194. Lang M, Braun CL, Kanost MR and Gorman MJ: Multicopper oxidase-1 is a ferroxidase essential for iron homeostasis in Drosophila melanogaster. Proc Natl Acad Sci USA 109: 13337-13342, 2012.
195. Stallhofer J, Veith L, Diegelmann J, Probst P, Brand S, Schnitzler F, Olszak T, Török H, Mayerle J, Stallmach A and Beigel F: Iron deficiency in inflammatory bowel disease is associated with low levels of vitamin D modulating serum hepcidin and intestinal ceruloplasmin expression. Clin Transl Gastroenterol 13: e00450, 2022.
196. Gul Baykalir B, Aksit D, Dogru MS, Hanım Yay A, Aksit H, Seyrek K and Attesahin A: Lycopene ameliorates experimental colitis in rats via reducing apoptosis and oxidative stress. Int J Vitam Nutr Res 86: 27-35, 2016.
197. Zoller H, Wolf M, Blumenstein I, Primas C, Lindgren S, Thomsen LL, Reinisch W and Iqbal T: Hypophosphataemia following ferric derisomaltose and ferric carboxymaltose in patients with iron deficiency anaemia due to inflammatory bowel disease (PHOSPHARE-IBD): A randomised clinical trial. Gut 72: 644-653, 2023.
198. Rucker RB, Kosonen T, Clegg MS, Mitchell AE, Rucker BR, Uriu-Hare JY and Keen CL: Copper, lysyl oxidase, and extracellular matrix protein cross-linking. Am J Clin Nutr 67 (Suppl 5): 996S-1002S, 1998.
199. Lu PY, Niu GJ, Hong PP and Wang JX: Lysyl oxidase-like protein recognizes viral envelope proteins and bacterial polysaccharides against pathogen infection via induction of expression of antimicrobial peptides. Viruses 14: 2072, 2022.
200. Jasmer-McDonald K, Petris M, Shanbhag V and Gudekar N: Abstract 5806: Exploring the role of copper-dependent lysyl oxidase (LOX) in metastatic growth. Cancer Res 77 (Suppl 13): S5806, 2017.
201. Hashmi AN, Ahmed Dharejo R, Zubair UB, Khan N, Kashif I, Ajmal M, Taj R, Qamar R and Azam M: Association of dopamine β-hydroxylase polymorphism rs1611115 and serum levels with psychiatric disorders in Pakistani population. Int J Neurosci 134: 551-559, 2024.
202. Rush RA and Geffen LB: Dopamine beta-hydroxylase in health and disease. Crit Rev Clin Lab Sci 12: 241-277, 1980.
203. Li M, Dong M, Wang W, Li H, Liu Z, Wang L, Wang K and Song L: A membrane-bound dopamine β-hydroxylase highly expressed in granulocyte of Pacific oyster Crassostrea gigas. Dev Comp Immunol 104: 103563, 2020.
204. Olivares C and Solano F: New insights into the active site structure and catalytic mechanism of tyrosinase and its related proteins. Pigment Cell Melanoma Res 22: 750-760, 2009.
205. Matoba Y, Bando N, Oda K, Noda M, Higashikawa F, Kumagai T and Sugiyama M: A molecular mechanism for copper transportation to tyrosinase that is assisted by a metallochaperone, caddie protein. J Biol Chem 286: 30219-30231, 2011.
206. Dudzińska E, Gryzinska M, Ognik K, Gil-Kulik P and Kocki J: Oxidative stress and effect of treatment on the oxidation product decomposition processes in IBD. Oxid Med Cell Longev 2018: 7918261, 2018.
207. Jian Z, Guo H, Liu H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X and Zhao L: Oxidative stress, apoptosis and inflammatory responses involved in copper-induced pulmonary toxicity in mice. Aging (Albany NY) 12: 16867-16886, 2020.

208. Liu H, Guo H, Jian Z, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X and Zhao L: Copper induces oxidative stress and apoptosis in the mouse liver. Oxid Med Cell Longev 2020: 1359164, 2020.
209. Guo H, Ouyang Y, Wang J, Cui H, Deng H, Zhong X, Jian Z, Liu H, Fang J, Zuo Z, *et al*: Cu-induced spermatogenesis disease is related to oxidative stress-mediated germ cell apoptosis and DNA damage. J Hazard Mater 416: 125903, 2021.
210. Yip NC, Fombon IS, Liu P, Brown S, Kannappan V, Armesilla AL, Xu B, Cassidy J, Darling JL and Wang W: Disulfiram modulated ROS-MAPK and NFκB pathways and targeted breast cancer cells with cancer stem cell-like properties. Br J Cancer 104: 1564-1574, 2011.
211. Turski ML, Brady DC, Kim HJ, Kim BE, Nose Y, Counter CM, Winge DR and Thiele DJ: A novel role for copper in Ras/mitogen-activated protein kinase signaling. Mol Cell Biol 32: 1284-1295, 2012.
212. Hu F, Huang J, Bing T, Mou W, Li D, Zhang H, Chen Y, Jin Q, Yu Y and Yang Z: Stimulus-responsive copper complex nanoparticles induce cuproptosis for augmented cancer immunotherapy. Adv Sci (Weinh) 11: e2309388, 2024.
213. Rath E, Moschetta A and Haller D: Mitochondrial function-gatekeeper of intestinal epithelial cell homeostasis. Nat Rev Gastroenterol Hepatol 15: 497-516, 2018.
214. Ho GT, Aird RE, Liu B, Boyapati RK, Kennedy NA, Dorward DA, Noble CL, Shimizu T, Carter RN, Chew ETS, *et al*: MDR1 deficiency impairs mitochondrial homeostasis and promotes intestinal inflammation. Mucosal Immunol 11: 120-130, 2018.
215. Sünderhauf A, Hicken M, Schlichting H, Skibbe K, Ragab M, Raschdorf A, Hirose M, Schäffler H, Bokemeyer A, Bettenworth D, *et al*: Loss of mucosal p32/gC1qR/HABP1 triggers energy deficiency and impairs goblet cell differentiation in ulcerative colitis. Cell Mol Gastroenterol Hepatol 12: 229-250, 2021.
216. Jackson DN, Panopoulos M, Neumann WL, Turner K, Cantarel BL, Thompson-Snipes L, Dassopoulos T, Feagins LA, Souza RF, Mills JC, *et al*: Mitochondrial dysfunction during loss of prohibitin 1 triggers Paneth cell defects and ileitis. Gut 69: 1928-1938, 2020.
217. Ni J, Wu GD, Albenberg L and Tomov VT: Gut microbiota and IBD: Causation or correlation? Nat Rev Gastroenterol Hepatol 14: 573-584, 2017.
218. Liao J, Li Q, Lei C, Yu W, Deng J, Guo J, Han Q, Hu L, Li Y, Pan J, *et al*: Toxic effects of copper on the jejunum and colon of pigs: Mechanisms related to gut barrier dysfunction and inflammation influenced by the gut microbiota. Food Funct 12: 9642-9657, 2021.
219. Ma Z, Gao X, Yang X, Lin L, Wei X, Wang S, Li Y, Peng X, Zhao C, Chen J, *et al*: Low-dose florfenicol and copper combined exposure during early life induced health risks by affecting gut microbiota and metabolome in SD rats. Ecotoxicol Environ Saf 245: 114120, 2022.
220. Dai J, Yang X, Yuan Y, Jia Y, Liu G, Lin N, Xiao H, Zhang L and Chen J: Toxicity, gut microbiota and metabolome effects after copper exposure during early life in SD rats. Toxicology 433-434: 152395, 2020.
221. Chen Y, Li X, Sun R, Ji J, Yang F, Tian W, Ji W and Huang Q: A broad cuproptosis landscape in inflammatory bowel disease. Front Immunol 13: 1031539, 2022.
222. Ai L, Ren Y, Zhu M, Lu S, Qian Y, Chen Z and Xu A: Synbindin restrains proinflammatory macrophage activation against microbiota and mucosal inflammation during colitis. Gut 70: 2261-2272, 2021.
223. Leonardi I, Li X and Iliev ID: Macrophage interactions with fungi and bacteria in inflammatory bowel disease. Curr Opin Gastroenterol 34: 392-397, 2018.
224. Geng Z, Yuan Y, He D, Lee H, Wang H, Niu N, Ni Z, Abdullah S, Tang Z and Qu P: RNA-Seq analysis of obese Pdha1$^{fl/fl}$Lyz2-Cre mice induced by a high-fat diet. Exp Anim 72: 112-122, 2023.
225. Sun J, Li J, Guo Z, Sun L, Juan C, Zhou Y, Gu H, Yu Y, Hu Q, Kan Q and Yu Z: Overexpression of pyruvate dehydrogenase e1α subunit inhibits warburg effect and induces cell apoptosis through mitochondria-mediated pathway in hepatocellular carcinoma. Oncol Res 27: 407-414, 2019.
226. Tsukamoto T and Nigam SK: Role of tyrosine phosphorylation in the reassembly of occludin and other tight junction proteins. Am J Physiol 276: F737-F750, 1999.
227. Zou M, Zhang W, Zhu Y and Xu Y: Identification of 6 cuproptosis-related genes for active ulcerative colitis with both diagnostic and therapeutic values. Medicine (Baltimore) 102: e35503, 2023.
228. Yuan Y, Fu M, Li N and Ye M: Identification of immune infiltration and cuproptosis-related subgroups in Crohn's disease. Front Immunol 13: 1074271, 2022.
229. Wu W, Dong J, Lv Y and Chang D: Cuproptosis-Related genes in the prognosis of colorectal cancer and their correlation with the tumor microenvironment. Front Genet 13: 984158, 2022.
230. Du Y, Lin Y, Wang B, Li Y, Xu D, Gan L, Xiong X, Hou S, Chen S, Shen Z and Ye Y: Cuproptosis patterns and tumor immune infiltration characterization in colorectal cancer. Front Genet 13: 976007, 2022.
231. Shi X, Yan Z, Ding R, Xia F, Du Y, Wang X and Peng Q: Integrated bioinformatics and experiment validation reveal cuproptosis-related biomarkers and therapeutic targets in sepsis-induced myocardial dysfunction. BMC Infect Dis 25: 445, 2025.
232. Chen Y, Liao L, Wang B and Wu Z: Identification and validation of immune and cuproptosis-related genes for diabetic nephropathy by WGCNA and machine learning. Front Immunol 15: 1332279, 2024.
233. Chen YT, Xu XH, Lin L, Tian S and Wu GF: Identification of three cuproptosis-specific expressed genes as diagnostic biomarkers and therapeutic targets for atherosclerosis. Int J Med Sci 20: 836-848, 2023.
234. Li Y and Kan X: Cuproptosis-related genes MTF1 and LIPT1 as novel prognostic biomarker in acute myeloid leukemia. Biochem Genet 62: 1136-1159, 2024.
235. Zhu Y, Chen X, Geng S, Li Q, Li Y, Yuan H and Jiang H: Identification of the cuproptosis-related hub genes and therapeutic agents for sarcopenia. Front Genet 14: 1136763, 2023.
236. Xiao F, Huang G, Yuan G, Li S, Wang Y, Tan Z, Liu Z, Tomlinson S, He S, Ouyang G and Zeng Y: Identification and validation of potential diagnostic signature and immune cell infiltration for HIRI based on cuproptosis-related genes through bioinformatics analysis and machine learning. Front Immunol 15: 1372441, 2024.
237. Chen S, Zhou Z, Wang Y, Chen S and Jiang J: Machine learning-based identification of cuproptosis-related markers and immune infiltration in severe community-acquired pneumonia. Clin Respir J 17: 618-628, 2023.
238. Tegoni M, Valensin D, Toso L and Remelli M: Copper chelators: Chemical properties and bio-medical applications. Curr Med Chem 21: 3785-3818, 2014.
239. Ding X, Xie H and Kang YJ: The significance of copper chelators in clinical and experimental application. J Nutr Biochem 22: 301-310, 2011.
240. Baldari S, Di Rocco G and Toietta G: Current biomedical use of copper chelation therapy. Int J Mol Sci 21: 1069, 2020.
241. Pan Q, Kleer CG, van Golen KL, Irani J, Bottema KM, Bias C, De Carvalho M, Mesri EA, Robins DM, Dick RD, *et al*: Copper deficiency induced by tetrathiomolybdate suppresses tumor growth and angiogenesis. Cancer Res 62: 4854-4859, 2002.
242. Morisawa A, Okui T, Shimo T, Ibaragi S, Okusha Y, Ono M, Nguyen TTH, Hassan NMM and Sasaki A: Ammonium tetrathiomolybdate enhances the antitumor effects of cetuximab via the suppression of osteoclastogenesis in head and neck squamous carcinoma. Int J Oncol 52: 989-999, 2018.
243. Calderon-Aparicio A, Cornejo A, Orue A and Rieber M: Anticancer response to disulfiram may be enhanced by co-treatment with MEK inhibitor or oxaliplatin: Modulation by tetrathiomolybdate, KRAS/BRAF mutations and c-MYC/p53 status. Ecancermedicalscience 13: 890, 2019.
244. Huang YF, Kuo MT, Liu YS, Cheng YM, Wu PY and Chou CY: A dose escalation study of trientine plus carboplatin and pegylated liposomal doxorubicin in women with a first relapse of epithelial ovarian, tubal, and peritoneal cancer within 12 months after platinum-based chemotherapy. Front Oncol 9: 437, 2019.
245. Kirk FT, Munk DE, Swenson ES, Quicquaro AM, Vendelbo MH, Larsen A, Schilsky ML, Ott P and Sandahl TD: Effects of tetrathiomolybdate on copper metabolism in healthy volunteers and in patients with Wilson disease. J Hepatol 80: 586-595, 2024.
246. Schilsky ML, Czlonkowska A, Zuin M, Cassiman D, Twardowschy C, Poujois A, Gondim FAA, Denk G, Cury RG, Ott P, *et al*: Trientine tetrahydrochloride versus penicillamine for maintenance therapy in Wilson disease (CHELATE): A randomised, open-label, non-inferiority, phase 3 trial. Lancet Gastroenterol Hepatol 7: 1092-1102, 2022.
247. Kim H, Jo S, Kim IG, Kim RK, Kahm YJ, Jung SH and Lee JH: Effect of copper chelators via the TGF-β signaling pathway on glioblastoma cell invasion. Molecules 27: 8851, 2022.

248. Gartner EM, Griffith KA, Pan Q, Brewer GJ, Henja GF, Merajver SD and Zalupski MM: A pilot trial of the anti-angiogenic copper lowering agent tetrathiomolybdate in combination with irinotecan, 5-flurouracil, and leucovorin for metastatic colorectal cancer. Invest New Drugs 27: 159-165, 2009.
249. Shen S, O'Brien T, Yap LM, Prince HM and McCormack CJ: The use of methotrexate in dermatology: A review. Australas J Dermatol 53: 1-18, 2012.
250. Yang Z, Mo J, Li W, Zhao Z and Mei S: Methotrexate polyglutamates. Expert Rev Clin Pharmacol 17: 1025-1037, 2024.
251. Pannu AK: Methotrexate overdose in clinical practice. Curr Drug Metab 20: 714-719, 2019.
252. Kantarjian HM, Sekeres MA, Ribrag V, Rousselot P, Garcia-Manero G, Jabbour EJ, Owen K, Stockman PK and Oliver SD: Phase I study assessing the safety and tolerability of barasertib (AZD1152) with low-dose cytosine arabinoside in elderly patients with AML. Clin Lymphoma Myeloma Leuk 13: 559-567, 2013.
253. Larsen SL, Yde CW, Laenkholm AV, Rasmussen BB, Duun-Henriksen AK, Bak M, Lykkesfeldt AE and Kirkegaard T: Aurora kinase B is important for antiestrogen resistant cell growth and a potential biomarker for tamoxifen resistant breast cancer. BMC Cancer 15: 239, 2015.
254. Zhang Z, Mou L, Pu Z and Zhuang X: Construction of a hepatocytes-related and protein kinase-related gene signature in HCC based on ScRNA-Seq analysis and machine learning algorithm. J Physiol Biochem 79: 771-785, 2023.
255. Flamant M, Paul S and Roblin X: Golimumab for the treatment of ulcerative colitis. Expert Opin Biol Ther 17: 879-886, 2017.
256. Melo AT, Campanilho-Marques R and Fonseca JE: Golimumab (anti-TNF monoclonal antibody): Where we stand today. Hum Vaccin Immunother 17: 1586-1598, 2021.
257. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, *et al*: Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology 146: 96-109.e1, 2014.
258. Hibi T, Imai Y, Senoo A, Ohta K and Ukyo Y: Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: A phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study). J Gastroenterol 52: 1101-1111, 2017.
259. Jiang CZ, Yu WL and Hua ZC: Clinical efficacy of infliximab in patients with crohn disease in different locations of disease pathology: A meta-analysis. Clin Invest Med 44: E27-E35, 2021.
260. Halpin SJ, Hamlin PJ, Greer DP, Warren L and Ford AC: Efficacy of infliximab in acute severe ulcerative colitis: A single-centre experience. World J Gastroenterol 19: 1091-1097, 2013.
261. Engel T, Ungar B, Yung DE, Ben-Horin S, Eliakim R and Kopylov U: Vedolizumab in IBD-lessons from real-world experience; a systematic review and pooled analysis. J Crohns Colitis 12: 245-257, 2018.
262. Kopylov U, Ron Y, Avni-Biron I, Koslowsky B, Waterman M, Daher S, Ungar B, Yanai H, Maharshak N, Ben-Bassat O, *et al*: Efficacy and safety of vedolizumab for induction of remission in inflammatory bowel disease-the israeli real-world experience. Inflamm Bowel Dis 23: 404-408, 2017.
263. Ibraheim H, Samaan MA, Srinivasan A, Brain O, Digby-Bell J, Irving PM, Norman I, Jawad I, Biedermann J, Ibarra A, *et al*: Effectiveness and safety of vedolizumab in inflammatory bowel disease patients aged 60 and over: An observational multicenter UK experience. Ann Gastroenterol 33: 170-177, 2020.
264. Albshesh A, Taylor J, Savarino EV, Truyens M, Armuzzi A, Ribaldone DG, Shitrit AB, Fibelman M, Molander P, Liefferinckx C, *et al*: Effectiveness of third-class biologic treatment in Crohn's disease: A multi-center retrospective cohort study. J Clin Med 10: 2914, 2021.
265. Danese S, Sandborn WJ, Colombel JF, Vermeire S, Glover SC, Rimola J, Siegelman J, Jones S, Bornstein JD and Feagan BG: Endoscopic, radiologic, and histologic healing with vedolizumab in patients with active Crohn's disease. Gastroenterology 157: 1007-1018.e7, 2019.
266. Van der Auwera P, Van Laethem Y, Defresne N, Husson M and Klastersky J: Comparative serum bactericidal activity against test anaerobes in volunteers receiving imipenem, clindamycin, latamoxef and metronidazole. J Antimicrob Chemother 19: 205-210, 1987.
267. Budziński ML, Sokn C, Gobbini R, Ugo B, Antunica-Noguerol M, Senin S, Bajaj T, Gassen NC, Rein T, Schmidt MV, *et al*: Tricyclic antidepressants target FKBP51 SUMOylation to restore glucocorticoid receptor activity. Mol Psychiatry 27: 2533-2545, 2022.
268. Al-Rubeaan K, Banah F, Alruwaily FG, Sheshah E, Alnaqeb D, AlQahtani AM, Ewais D, Al Juhani N, Hassan AH and Youssef AM: Longitudinal assessment of the quality of life and patterns of antidiabetic medication use in patients with type 2 diabetes, Saudi Arabia perspective, DISCOVER study. Curr Med Res Opin 39: 27-35, 2023.
269. Li Y, Chen J and Lun SY: Biotechnological production of pyruvic acid. Appl Microbiol Biotechnol 57: 451-459, 2001.
270. Silva Oliveira Junior M, Schira-Heinen J, Reiche L, Han S, de Amorim VCM, Lewen I, Gruchot J, Göttle P, Akkermann R, Azim K and Küry P: Myelin repair is fostered by the corticosteroid medrysone specifically acting on astroglial subpopulations. EBioMedicine 83: 104204, 2022.
271. Zhong X, Ma Z, Su Y, Li Z, Liao Y, Pan X, Zang L and Zhou S: Flavin adenine dinucleotide ameliorates hypertensive vascular remodeling via activating short chain acyl-CoA dehydrogenase. Life Sci 258: 118156, 2020.
272. Pang G, Hu K, Ji J, Xiong B, Han L, Pang J and Xiang S: Investigating hub genes in the relationship between septic cardiomyopathy and cuproptosis and potential Chinese herbal drug candidates with bioinformatic tools. Minerva Cardiol Angiol 72: 453-464, 2024.