Emerging Pathological Engagement of Ferroptosis in Gut Diseases

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Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn’s disease, is mainly characterized by chronic and progressive inflammation that damages the gastrointestinal mucosa. Increasing studies have enlightened that dysregulated cell death occurs in the inflamed sites, leading to the disruption of the intestinal barrier and aggravating immunological response. Ferroptosis, a newly characterized form of regulated cell death, is driven by the lethal accumulation of iron-catalyzing lipid peroxides, which damages the gastrointestinal mucosa. Increasing studies have enlightened that dysregulated cell death occurs in the inflamed sites, leading to the disruption of the intestinal barrier and aggravating immunological response. Ferroptosis, a newly characterized form of regulated cell death, is driven by the lethal accumulation of iron-catalyzing lipid peroxides, which damages the gastrointestinal mucosa. Increasing studies have enlightened that dysregulated cell death occurs in the inflamed sites, leading to the disruption of the intestinal barrier and aggravating immunological response. Ferroptosis, a newly characterized form of regulated cell death, is driven by the lethal accumulation of iron-catalyzing lipid peroxides, which damages the gastrointestinal mucosa. Increasing studies have enlightened that dysregulated cell death occurs in the inflamed sites, leading to the disruption of the intestinal barrier and aggravating immunological response. Ferroptosis, a newly characterized form of regulated cell death, is driven by the lethal accumulation of iron-catalyzing lipid peroxides, which damages the gastrointestinal mucosa. Increasing studies have enlightened that dysregulated cell death occurs in the inflamed sites, leading to the disruption of the intestinal barrier and aggravating immunological response. Ferroptosis, a newly characterized form of regulated cell death, is driven by the lethal accumulation of iron-catalyzing lipid peroxides, which damages the gastrointestinal mucosa. Increasing studies have enlightened that dysregulated cell death occurs in the inflamed sites, leading to the disruption of the intestinal barrier and aggravating immunological response. Ferroptosis, a newly characterized form of regulated cell death, is driven by the lethal accumulation of iron-catalyzing lipid peroxides, which damages the gastrointestinal mucosa. Increasing studies have enlightened that dysregulated cell death occurs in the inflamed sites, leading to the disruption of the intestinal barrier and aggravating immunological response. Ferroptosis, a newly characterized form of regulated cell death, is driven by the lethal accumulation of iron-catalyzing lipid peroxides, which damages the gastrointestinal mucosa. Increasing studies have enlightened that dysregulated cell death occurs in the inflamed sites, leading to the disruption of the intestinal barrier and aggravating immunological response. Ferroptosis, a newly characterized form of regulated cell death, is driven by the lethal accumulation of iron-catalyzing lipid peroxides, which damages the gastrointestinal mucosa. Increasing studies have enlightened that dysregulated cell death occurs in the inflamed sites, leading to the disruption of the intestinal barrier and aggravating immunological response. Ferroptosis, a newly characterized form of regulated cell death, is driven by the lethal accumulation of iron-catalyzing lipid peroxides, which damages the gastrointestinal mucosa. Increasing studies have enlightened that dysregulated cell death occurs in the inflamed sites, leading to the disruption of the intestinal barrier and aggravating immunological response. Ferroptosis, a newly characterized form of regulated cell death, is driven by the lethal accumulation of iron-catalyzing lipid peroxides, which damages the gastrointestinal mucosa. Increasing studies have enlight...
the characterization of core regulatory components (e.g., SLC7A11, GPX4, FSP1, P53, and NRF2) support the fundamental understanding of the ferroptotic cell death (Figure 1). Moreover, emerging pieces of evidence suggest the pathological implication of dysregulated ferroptosis in the occurrence or progression of various human diseases. Herein, we summarize the recent advances of ferroptosis and dissect the potential engagement of ferroptosis in the pathogenesis of gastrointestinal diseases, attempting to elaborate the possibility of targeting ferroptosis in the therapeutic designs for the clinical intervention of gastrointestinal diseases.

2. Ferroptosis

Numerous pioneering studies have enlightened the fundamental characteristics of ferroptosis prior to the concept termed. In 1955, Eagle found that cystine deprivation triggers cell death with a distinct microscopic morphology compared to the deprivation of other amino acids [6, 7]. In the following decades, increasing pieces of evidence emerged that cystine deprivation leads to oxidative cell death in fibroblasts [8], embryonic cortical neurons [9, 10], and hepatocytes [11]. Besides, this cell death could be mitigated by the lipophilic antioxidant vitamin E [8] and the iron chelator deferoxamine (DFO) [12].

In 2003, Dolma and colleagues performed a lethal compound screen of genotype-selective antitumor agents and found that Erastin performs specific lethal cytotoxicity of engineered cells expressing oncogenic RAS. However, this cell death sharply differs from apoptosis. Specifically, neither caspase activation nor nuclear fragmentation was observed [4]. In 2008, two RAS-selective lethal compounds, RSL3 and RSL5, were identified in another compound screen [13]. RSL3 and RSL5 induce similar nonapoptotic cell death. Importantly, RSL3- and Erastin-mediated cell death could be alleviated by DFO and vitamin E but not by the apoptosis inhibitor z-VAD or necroptosis inhibitor necrostatin-1. Therefore, ferroptosis was coined to describe this iron- and lipid peroxidation-dependent cell death [1].

2.1. Ferroptosis Inducers and Inhibitors. Potent ferroptosis inducers and specific ferroptosis inhibitors have been identified during the last decade. According to the respective mechanisms of action, ferroptosis inducers are currently classified into four groups:

(1) Glutathione (GSH) Scavengers. Erastin depletes GSH by suppressing cystine uptake via restraining the cystine/glutamine antiporter system XC− [13]. Additionally, two metabolically stable derivatives, Piperazine Erastin [14] and
Imidazole Ketone Erastin [15], equip better water solubility and perform better antitumor activity in the xenograft tumor model. Likewise, sulflazaline [16], sorafenib [17], and artesunate [18] also drive ferroptosis through exhausting GSH.

(2) Glutathione Peroxidase 4 (GPX4) Inhibitors. GPX4 is the sole peroxidase for catalyzing lipid peroxides into the corresponding lipid alcohols with the assistance of its cofactor GSH [19]. This class of inducers, including RSL3, Altretamine [20], and DPI17 [14], could directly inhibit GPX4.

(3) FIN56. FIN56 initiates ferroptosis via two distinct mechanisms. FIN56 induces GPX4 degradation in an elusive manner. Alternatively, FIN56 activates squalene synthase to deplete coenzyme Q10 (CoQ10) in the mevalonate pathway and thus impair the cellular antioxidant capacity [21].

(4) FINO2. FINO2 represents a unique type of organic lipophilic peroxide, which oxidizes cellular labile iron preferentially, leading to extensive oxidation of PUFAs. In addition, indirect inactivation of GPX4 also contributes to the lethal potency of FINO2 [22].

Similarly, the specific ferroptosis inhibitors could antagonize ferroptosis via different mechanisms. Firstly, iron chelators could confine labile free iron, leading to the deceleration of lipid peroxidation. Secondly, β-mercaptoethanol subverts Erastin-induced ferroptosis through forming disulfide with cystine and facilitating cystine uptake bypass system Xc⁻ [23]. Thirdly, radical-trapping antioxidants, including vitamin E and aromatic amine-based ferrostatin-1 (Fer-1) and liproxstatin-1 (Lip-1), could halt the cascade of propagating lipid radicals and protect lipids from autoxidation [3, 24]. Fourthly, lipoxigenase (LOX) inhibitors, such as Zileuton (5-LOX inhibitor), Baicaline (12-LOX inhibitor), and NDGA (general LOX inhibitor), could counteract lipid peroxidation catalyzed by LOXs [25, 26]. Moreover, thiazolidinedione, the inhibitor of acyl-CoA synthetase long-chain family member 4 (ACSL4), represses the activation of PUFAs esterification and consequently reduces the oxidizable substrates addicted by ferroptosis [27]. The identification of these inducers and inhibitors supported the primary understanding of the principal program of ferroptosis.

2.2. Iron and Ferroptosis. The trace element iron is critically important for tremendous biochemical processes, including oxygen transport, DNA synthesis, transcription, damage repair, redox reactions, and mitochondrial electron transport [28]. Iron also acts as a redox-active toxicant when excessive labile iron is available, which catalyzes reactive oxygen species (ROS) generation via the Fenton reaction. In general, most circulating iron is bound to the transferrin (TF) in the form of ferric iron (Fe³⁺). TF-Fe is captured by transferrin receptor 1 (TFR1) on the cell membrane and absorbed through endocytosis. Fe³⁺ then escaped from the TF, reduced to ferrous iron (Fe²⁺) mediated by the endosome reductase (e.g., six-transmembrane epithelial antigen of the prostate 3), and subsequently released to the cytosol by divalent metal transporter 1 (DMT1/SLC11A2). Cytosolic iron is persistently sequestered by ferritin or transported into mitochondria for the biosynthesis of the iron-sulfur cluster or heme, two vital iron-containing cofactors for hundreds of proteins. The excessive cellular iron could be exported by ferroportin (FPN) [28].

Iron-dependent lipid peroxidation is one of the most fundamental characteristics of ferroptosis. It is thus expectable that manipulation of cellular iron metabolism or availability could change the ferroptotic sensitivity. Importantly, knockdown of iron regulatory proteins 1 and 2 (IRP1/2), the master cellular iron sensors and regulators, sharply decreases the labile iron pool (LIP) and antagonizes ferroptosis [1, 29]. Similarly, knockdown of TFR1 or ectopic overexpression of FPN impairs effective intracellular iron accumulation and abrogates ferroptosis [30, 31]. In addition, phosphorylation of heat shock protein beta-1 was reported to combat Erastin-induced ferroptosis by hindering TFR1 traffic through sustaining actin filaments and thus antagonizing iron uptake [32]. Recent studies revealed that ferroptinophagy, a selective autophagy to degrade ferritin for iron motivation, plays a crucial role in ferroptosis initiation. Nuclear receptor coactivator 4 (NCOA4) acts as the selective cargo receptor responsible for recruiting and delivering ferritin to lysosomes for degradation [33]. Knockdown of autophagy-related genes (e.g., Atg5 and Atg7) or ferritinophagy-specific Ncoa4 impairs ferroptinophagy and reduces the cellular labile iron, leading to ferroptotic insensitivity in various cell lines [34, 35]. Burgeoning pieces of evidence have put forward an indispensable involvement of iron in ferroptosis. At least two potential mechanisms including the Fenton reaction and activation of the enzymatic activity of iron-containing LOXs are implicated in iron facilitating the ferroptotic program [36].

2.3. Lipid Peroxides and Ferroptosis. As the cornerstone of cell membranes, lipid composition directly determines the biomembrane properties including fluidity, permeability, and integrity [37]. Increasing studies suggest that lipid peroxidation serves as the ultimate executor for ferroptotic cell death, although the exact mechanism is vague [38]. Lipid peroxidation leads to lipidomic alteration and compromise of the biomembrane properties (increased membrane curvature and permeability, formation of structured lipid pores, and micellization) [39, 40], which initiate exacerbating feedback to destruct biomembrane structure and dynamics. Furthermore, 4-hydroxy-2-nonenals (4-HNEs) and malondialdehydes (MDAs), two major secondary lipid peroxidation products generated by the decomposition of oxidized PUFAs, could bring out abnormal covalent modifications in proteins and nucleic acids, which could also initiate the death program [41, 42].

PUFAs, rather than saturated fatty acids or monounsaturated fatty acids (MUFAFs), are preferentially oxidized by reactive radicals [26, 43, 44]. By utilizing redox lipidomic assay, it was reported that only PLs containing PUFAs (especially arachidonoyl (AA) and adrenoyl (AdA)) are the lipid precursors to undergo peroxidation preceding ferroptosis
Exposure to exogenous PUFAs increases ferroptotic sensitivity. In striking contrast, supplementation of deuterated PUFAs, which are inactive to hydrogen abstraction, or administration of exogenous MUFAs (oleic acid (OA)), which competitively reduce PUFA incorporation into PLs, remodels the lipidomic composition, decreases the accumulation of lipid peroxides, and thus potently protects cells from ferroptosis [45–47]. Furthermore, pharmacological or genetic suppression of lysocephatidylcholine acyltransferase 3 (Lpcat3) and Acss1, which are responsible for PUFAs activation and subsequent esterification for membrane insertion, sharply prevents ferroptosis [1, 27, 45, 48, 49].

LOXs are nonheme, iron-containing dioxygenases with diverse isoforms, which oxidize AA at different carbon positions [43, 50]. Early studies had demonstrated that deficiency or silence of arachidonate-15-lipoxygenase (Alox15) (encoding 12/15-LOX) or arachidonate-15-lipoxygenase type B (Alox15b) and arachidonate lipoxygenase 3 (Alox3) leads to dramatic resistance to GSH depletion-induced cell death [47, 51, 52]. Moreover, supplementation of 5-, 12-, and 15-hydroperoxyeicosatetraenoic acid, the production of LOX catalysis, accelerates the ferroptotic program elicited by GPX4 depletion [5]. Furthermore, inactivation of Alox15 is not sufficient to rescue the embryonic lethality of Gpox1−/− mice [5, 50, 53]. One potential assumption is that LOX-mediated lipid peroxidation mainly contributes to the initial build-up of the cellular lipid peroxide pool, while lipid autooxidation dominates the subsequent ferroptotic execution [25]. The alternative assumption is that other enzymes exist to catalyze lipid peroxidation bypass LOXs. Specifically, it was recently reported that NADPH-cytochrome P450 reductase (POR) and NADH-cytochrome b5 reductase (CYB5R1) could mediate the peroxidation of PUFAs of membrane PLs. By transferring electrons from the donor NADPH, POR and CYB5R1 support the generation of hydrogen peroxides, which subsequently react with iron to generate reactive hydroxyl radicals for the PUFA peroxidation [54, 55].

2.4. Antioxidant Defense Systems and Ferroptosis. To date, three major antioxidant defense systems have been elaborated to protect cells from ferroptosis including the GPX4-GSH axis, FSP1-CoQ10-NADPH axis, and GCH1-BH4 axis.

The selenoprotein GPX4 is the sole peroxide scavenger that reduces the deleterious lipid peroxides to nontoxic lipid alcohols within biomembranes at the cost of oxidizing two GSH to GSSG [14, 56]. GSH, a thiol-containing tripeptide (γ-glutamate-cysteine-glycine) serving as an indispensable cofactor of GPX4, is recycled by NAD(P)H and glutathione reductase [57]. In this regard, disruption of GSH synthesis could initiate ferroptosis in diverse circumstances. Pharmacological inhibition of system Xc−, the antiporter composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2), essential for exchanging intracellular glutamate and extracellular cysteine, was reported to trigger ferroptosis in multiple types of cultured cells [1, 58, 59]. Notably, P53 facilitates ferroptosis by transcriptionally downregulating SLC7A11 [60]. CD8+ T cells enhance ferroptosis of tumor cells through releasing interferon gamma (IFNγ) and repressing the expression of SLC3A2 and SLC7A11 in tumor cells [61]. Moreover, nuclear factor erythroid 2-related factor 2 (NRF2) was reported to combat ferroptotic cell death via upregulating SLC7A11 and thus facilitating GSH synthesis [62]. Collaboratively, these studies illuminate the core role of the GPX4-GSH axis in scavenging lipid peroxides and counteracting ferroptosis.

The FSP1-CoQ10-NADPH pathway was recently characterized to compensate and synergize with the canonical GPX4-GSH pathway to detoxify lipid peroxides and defend against ferroptosis. Two independent studies based on genome-wide CRISPR-Cas9 screening for genes against ferroptosis in the absence of GPX4 coincidently identified that the flavoprotein ferroptosis suppressor protein 1 (FSP1, previously known as AIFM2) restrains ferroptosis by catalyzing the reduction of ubiquinone (namely, CoQ10) to ubiquinol in an NADPH-dependent manner [63, 64]. Intriguingly, CoQ10 is mainly generated from the mevalonate pathway, which has been demonstrated to dominate ferroptotic sensitivity. Specifically, the mevalonate-derived isopentenyl pyrophosphate can modulate the translation of selenocysteine-containing GPX4 by stabilizing the Sec-specific tRNA expression [65].

More recently, a novel mechanistic scheme accounting for cell endogenous protection from ferroptosis converges on the GCH1-BH4 axis. By utilizing whole-genome CRISPR-Cas9 screening, GTP cyclohydrolase-1 (GCH1) was nominated as a key factor to antagonize ferroptosis [66, 67]. The natural antioxidant tetrahydrobiopterin (BH4) generated by GCH1 was found to suppress ferroptosis through selectively protecting membrane PLs with two PUFA tails from oxidative degradation or alternatively promoting CoQ10 biosynthesis, which is crucial for the elimination of lipid peroxides. The proposal of the GCH1-BH4 axis provides further insights into ferroptosis resistance.

3. Ferroptosis and Inflammatory Bowel Disease

IBD, including ulcerative colitis (UC) [68] and Crohn’s disease (CD) [69], is mainly characterized by severe gastrointestinal tract inflammation and mucosal destruction. UC is primarily disordered in the large intestine, featuring continuous mucosal inflammation beginning in the rectum and then generally extending proximally in gut tracts. Rectal bleeding, diarrhea, and abdominal pain, accompanied with ulcerations and erythema formation, are widely manifested in UC. CD principally occurs in the ileum and colon, and the typical clinical manifestations include abdominal pain, chronic diarrhea, weight loss, and fatigue. Although the exact etiology of IBD is not well understood, a combination of genetic susceptibility, harmful environmental factors, deregulated host immune system, and gut microbiota dysbiosis has been proved to be associated with the pathogenesis of IBD [70]. With the rapidly rising incidence and prevalence, IBD has emerged as a global health challenge, which will bring a considerable rise in healthcare costs [71].

The monolayer intestinal epithelial cells (IECs) covering the intestinal wall play a critical role in nutrient absorption
and physical separation of the hosts from the harmful gut bacteria in the intestinal lumen. IECs are composed of multiple types of epithelial cells that differentiate from intestinal stem cells residing in the crypts, including nutrient-absorptive enterocytes, mucin glycoprotein-producing goblet cells, antimicrobial peptide-secreting Paneth cells, and hormone-secreting enteroendocrine cells [72]. It is well documented that apoptotic cell death has been observed in these different types of epithelial cells at the inflamed sites in patients with UC and CD [73, 74]. Furthermore, induction of epithelial cell apoptosis has also been evident in independent animal colitis models [75–77]. In the meantime, the expression of apoptosis-associated proteins such as the Fas cell surface death receptor, Fas ligand, BCL2 associated X, and tumor protein p53 (P53) is dramatically increased at cell surface death receptor, Fas ligand, BCL2 associated X, and tumor protein p53 (P53) is dramatically increased at the inflamed sites [78]. Excessive endoplasmic reticulum (ER) stress, accompanied with the overproduction of proinflammatory cytokines [82], has been observed in these different types of epithelial cells at the inflamed sites in patients with UC and CD [73, 74]. Furthermore, induction of epithelial cell apoptosis has also been evident in independent animal colitis models [75–77]. In the meantime, the expression of apoptosis-associated proteins such as the Fas cell surface death receptor, Fas ligand, BCL2 associated X, and tumor protein p53 (P53) is dramatically increased at the inflamed sites [78]. Excessive endoplasmic reticulum (ER) stress, accompanied with the overproduction of proinflammatory cytokines [82], has been observed in these different types of epithelial cells at the inflamed sites in patients with UC and CD [73, 74]. Furthermore, induction of epithelial cell apoptosis has also been evident in independent animal colitis models [75–77].

3.2. GSH and IBD. GSH depletion is a critical signature of ferroptosis. It is now well understood that GSH exhaustion and GPX4 inactivation are widely observed in the inflamed mucosa from patients with IBD and in experimental animal models of colitis [102, 103]. The elevated oxidative insult in inflamed sites exhausts the endogenous GSH, while the reduced plasma cysteine and decreased enzymatic activity of mucosal γ-glutamylcysteine synthetase and γ-glutamyltransferase essential for GSH biosynthesis decelerate the de novo synthesis of GSH in patients with CD and UC [104]. Administration of the specific inhibitor of γ-glutamylcysteine synthetase, the rate-limiting enzyme for GSH synthesis, leads to a rapid decline of GSH and a substantial loss of the epithelial cells in the jejunal and colonic mucosa [105]. On the contrary, replenishment of GSH through administration of GSH [106], GSH ester [106], N-acetylcysteine [107], or L-cysteine [108] could restore the intestinal GSH abundance and significantly improve colonic health. GSH could confer the cellular antioxidative capacity by directly scavenging ROS and supporting the enzymatic activity of glutathione S-transferases to defend against oxidative stress, which are protective for the gastrointestinal tract from chronic inflammation [109].

3.3. GPX4 and IBD. Antioxidant enzyme GPX4 is responsible for scavenging lipid hydroperoxides and antagonizing ferroptosis [5]. Early studies indicated a genetic association between GPX4 and CD by using a meta-analysis of GWAS [110, 111]. Reduced GPX4 activity accompanied with elevated lipid peroxidation was characterized in the intestinal epithelium in patients with CD. A diet enriched in PUFAs, but not saturated fatty acids, induces focal enteritis in IEC-specific Gpx4−/− mice. More strikingly, IEC Gpx4−/− mice are more susceptible to colonic inflammation induced by DSS, as compared to the wild-type littermates, highlighting the notion that GPX4 is crucial for maintaining gut homeostasis by protecting from lipid peroxidation [112]. Furthermore, an increasing number of studies have suggested a tight association between IBD and the secondary metabolites of lipid peroxidation such as MDA and 4-HNE [112, 113]. The content of AA, one of the most oxidizable PUFAs
preferentially for lipid peroxidation, is markedly elevated in PLs of the colonic mucosa in patients with UC [114, 115]. Therefore, the inactivation of GPX4 and the elevation of lipid peroxides indicate the possibility that GPX4 determines gut homeostasis by antagonizing lipid peroxidation. Moreover, a reduced level of serum selenium was evidenced to be associated with the pathogenesis of UC and CD [116, 117]. Selenium deficiency exacerbates intestinal injury [118], while selenium supplementation has been reported to be protective in IBD patients [119–122]. It is still elusive whether selenium supplementation ameliorating intestinal injury depends on the transcriptional activation of GPX4 or not [65, 123]. In addition, selenium supplementation in cultured Caco-2 cells could significantly prevent the transport of lipid hydroperoxides and thus decline cellular lipid peroxidation [124].

3.4. LOXs and IBD. LOXs catalyze the production of lipid hydroperoxides and drive ferroptotic cell death [45, 50]. Several LOX isoforms have been identified to be involved in the pathogenesis of IBD. More specifically, the levels of Alox5 and Alox15 are upregulated in the colonic mucosa in patients with IBD and in the experimental colitis mouse model, respectively [125, 126]. Systemic deletion of Alox15 suppresses the production of lipid peroxidation metabolite 12-hydroxyeicosatetraenoic acid, stabilizes the tight junction protein ZO-1 and maintains the intestinal barrier integrity, decreases macrophage infiltration, and reduces the expression of proinflammatory genes, thus alleviating colonic damage in DSS-induced experimental colitis in mice. Conversely, transgenic overexpression of human Alox15 renders mice more susceptible to DSS-induced colitis [127]. Similarly, deficiency of Alox15 was reported to protect mice from DNBS-induced mucosal injury. Phosphatidylethanolamine-binding protein 1 (PEBP1) is a master regulatory molecule for 15-LOX by dominating the substrate specificity of 15-LOX to PUFA-phosphatidylethanolamines (PUFA-PE), facilitating the generation of lipid peroxides [128]. It suggested a positive correlation between the PEBP1 expression and the severity of IBD. More importantly, PEBP1 deficiency protects mice from DSS- or TNBS-induced colitis and accelerates mucosal recovery from injury [129]. Similarly, the supplementation of Zileuton, the potent 5-LOX inhibitor, maintains the tight junction proteins to prevent the decrease in the tight junctional permeability induced by TNBS [130]. Other 5-LOX-selective inhibitors, including A-64077 and MK-0591, could alleviate the inflammatory status in the colon of UC patients [131–134]. Collectively, these studies suggest a critical role of LOXs and their metabolites in determining gut inflammation and intestinal homeostasis.

3.5. GCH1/BH4 and IBD. Folate, also known as folic acid and vitamin B9, is regarded as a major endogenous antioxidant to defend against oxidative insults [135]. It is well recognized that folate is commonly deficient in patients with UC due to malabsorption [136, 137]. Administration of folate or its metabolic precursor BH4 was evidenced to relieve colitis-related tissue damage, detrimental inflammation, and malignant tumorigenesis [138, 139]. GCH1-mediated BH4 biosynthesis is crucial for ferroptosis resistance by remodeling lipidomic composition and suppressing lipid peroxidation [67, 140]. Ionizing radiation decreases BH4 levels and increases superoxide anion accumulation in patients and rats after radiotherapy due to the downregulation of GCH1. BH4 supplementation could prevent intestinal ischemia, improve vascular endothelial function, relieve intestinal villus injury, and thus alleviate radiation enteritis [141]. Collectively, these studies thus indicate an essential role of GCH1-mediated BH4 and folate biosynthesis in maintaining intestinal homeostasis.

3.6. The Emergence of Ferroptosis in Intestinal Diseases. As summarized above, the fundamental features of ferroptosis, including iron deposition, accumulation of lipid peroxidation, GSH exhaustion, GPX4 inactivation, and LOX upregulation, have been elucidated to be implicated in the pathogenesis of IBD. Additionally, recent studies have enlightened a direct engagement of ferroptosis in the pathogenesis of IBD. The ER stress signaling is involved in the IEC ferroptosis during chemical colitis, as evidenced by the elevated expression of ER stress-associated G protein-coupled receptor 78, phosphorylated eukaryotic initiation factor 2, activating transcription factor 4, and C/EBP homologous protein. Specifically, selective inhibition of protein kinase RNA-like endoplasmic reticulum kinase, the critical stress sensor of ER stress signaling, sharply reduces IEC ferroptosis and significantly ameliorates experimental colitis. NF-xB activation could protect against IEC cell death during acute intestinal inflammation. Importantly, specific deletion of the nuclear factor kappa B p65 subunit (NF-xBp65) in IECs leads to upregulated ER stress-mediated ferroptosis and aggravates DSS-induced colitis in mice [142]. More importantly, Fer-1, the specific inhibitor for ferroptosis, could ameliorate DSS-induced colitis [142]. Other well-characterized ferroptosis inhibitors, including Lip-1, iron chelator DFP, and antioxidant butylated hydroxyanisole, could all decelerate ferroptotic hallmarks and alleviate colonic damage [143]. Similarly, curculigoside, a natural ingredient from Curculigo orchioides Gaertn with multiple biological activities, was recently identified to attenuate DSS-induced UC in mice. Mechanistically, curculigoside supports GPX4 expression and thus protects against ferroptotic cell death in a selenium-dependent manner [144]. These research studies collaboratively put forward the notion of the pathological engagement of ferroptosis in colitis.

ACSL4 is responsible for the esterification of AA and AδA into PLs to facilitate the subsequent peroxidation. Genetic and pharmacological inhibition of ACSL4 protects cells from lipid peroxidation and ferroptosis [27, 45, 49]. It was previously reported that ACSL4 is upregulated in the ileum and colon of patients with CD and UC [145] and in DSS-induced experimental colitis in mice [143]. Intestinal ischemia/reperfusion injury is a life-threatening condition associated with a high mortality rate, which commonly occurs in numerous clinical pathologies such as small intestinal volvulus, acute mesenteric ischemia, shock, trauma, and small bowel transplantation [146]. Recently, Li and colleagues reported that ACSL4 is sharply induced in ischemic intestines compared with normal intestines, possibly via the
transcription factor special protein 1. More importantly, the core hallmarks of ferroptosis, including iron deposition, reduction of the GPX4 activity and GSH level, rupture of the outer mitochondrial membrane, and accumulation of lipid peroxidation, are manifested in the intestine after reperfusion. The typical ferroptosis inhibitor Lip-1 could strongly block lipid peroxidation and suppress cell death both in vitro and in vivo. Similarly, oral administration of rosiglitazone could inhibit ACSL4, suppress lipid peroxidation, and thus alleviate ischemia/reperfusion-related mucosal injury. Moreover, siRNA-mediated ACSL4 silence also protects Caco-2 cells from hypoxia/reoxygenation-induced lipid peroxidation and cell death [147]. Therefore, this study thus shed new light on the pathological engagement of ACSL4-mediated ferroptosis in intestinal ischemia/reperfusion injury.

3.7. Other Ferroptosis Regulators in Intestinal Diseases. Iron overload, lipid peroxidation, GSH depletion, and GPX4 inactivation constitute the fundamental features of ferroptosis. Besides, there are other ferroptosis regulators that have been evidenced to be associated with the pathogenesis or progression of intestinal diseases. P53, one of the most famous tumor suppressors, is mutated in many types of human cancers. Specifically, P53 is mutated in about 55%-60% of human colorectal cancers, and its mutations are associated with a poor prognosis in colorectal cancers [148]. Besides colorectal cancer, a high frequency of P53 mutations was also reported in patients with chronic UC [149]. In response to diverse stimuli, P53 is stabilized to mediate metabolic reprogramming, cell cycle arrest, cellular senescence, and even cell death [150]. Genetic depletion of P53 leads to a significantly reduced cell death of IECs, but the colonic inflammation is not altered in a murine colitis model [83]. Other studies indicated that the knockout of P53 leads to comparable histopathologic changes of chronic colitis. However, a significantly greater incidence

| Effect | Drug | Target | Mechanisms | Model | References |
|--------|------|--------|------------|-------|------------|
| Inhibitors | Rosuvastatin | ROS | Decreases the TNF-α level and reduces oxidative stress | UC mice, UC rats | [180, 181] |
| | Vitamin E | ROS | Protects against lipid peroxidation and scavenges free radicals | UC rats | [98, 99, 182, 183] |
| | TMG | ROS | Protects against lipid peroxidation and scavenges free radicals | UC rats | [184, 185] |
| | AA | ROS | Increases the activities of GPX and reduces oxidative stress | UC mice | [186, 187] |
| | 5-ASA | ROS | Scavenges oxygen-derived free radicals | IBD patients | [188, 189] |
| | CoQ10 | ROS | Antioxidant and anti-inflammatory properties | UC rats | [190, 191] |
| | Melatonin | ROS | Antioxidant and anti-inflammatory properties | UC rats, UC mice | [192, 193] |
| | LS | ROS | Reduces lipid peroxidation and restores the levels of innate antioxidants | UC mice | [113] |
| | BH4 | ROS | Reduces oxidative stress and rebalances lipid signaling via alkylglycerol monoxygenase | Uc mice | [139] |
| Inducers | Zileuton | 5-LOX | Functions as a 5-LOX inhibitor to increase PGE2 levels and reduces myeloperoxidase activity | IBD patients, UC rats | [134, 194] |

**Table 1: Promising molecules targeting ferroptosis in IBD.**

**Abbreviations:** AA: acetic acid; AA: ascorbic acid; BH4: tetrahydrobiopterin; CoQ10: coenzyme Q10; DFP: deferiprone; DFO: deferoxamine; DSS: dextran sodium sulfate; Fer-1: ferrostatin-1; Lip-1: liproxstatin-1; LS: Lagerstroemia speciosa leaves; NAC: N-acetylcysteine; PTCA: 2(R,S)-n-propylthiazolidine-4(R)-carboxylic acid; SAM: S-adenosylmethionine; TMG: vitamin E derivative, 2-(alpha-D-glucopyranosyl)methyl-2,5,7,8-tetra-methylchroman-6-ol; TNBS: trinitrobenzene sulfonic acid; 5-ASA: 5-aminosalicylic acid.
and multiplicity of cancers are observed during P53 deficiency [151–153]. Recently, it was reported that P53 suppresses cystine uptake, disturbs GSH biosynthesis, and thus sensitizes cells to ferroptosis. Mechanistically, P53 transcriptionally restrains the expression of cystine/glutamate antiporter subunit SLC7A11 [60, 154, 155]. Alternatively, P53 could facilitate the ferroptotic program by directly activating its target gene spermidine/spermine N1-acetyltransferase 1 and the downstream Alox15 [156] or through transcriptionally upregulating the mitochondrial glutaminase 2 [30]. However, other studies suggest an opposite notion that P53 may inhibit ferroptotic cell death through dipeptidyl peptidase-4 [157] or cyclin-dependent kinase inhibitor 1A [158]. Whether P53-modulated ferroptotic sensitivity accounts for the pathogenesis or malignancy of colitis or not is still ambiguous.

The transcription factor NRF2, encoded by the Nfe2l2 gene, plays a central role in the cytoprotective antioxidant system in response to a variety of oxidative, inflammatory, and metabolic stresses. NRF2 dominates the basal and induced expression of a series of antioxidant response element-dependent genes [159]. The increased severity of DSS-induced colitis and the elevated susceptibility of colitis-associated colorectal cancer in Nrf2-ablated mice were found to be associated with the decreased expression of antioxidant genes and detoxifying enzymes, as well as the increased expression of proinflammatory cytokines [160, 161]. Among them, heme oxygenase-1 (HO-1) presents pronounced anti-inflammatory and antioxidative properties in protecting mice from colitis-associated inflammatory injury and oxidative stress [162, 163]. As the main antioxidant axis, NRF2/HO-1 also dominates ferroptotic sensitivity. Ectopic expression or activation of NRF2 counteracts ferroptosis, whereas knockdown of NRF2 elevates the ferroptotic sensitivity in response to diverse ferroptosis inducers [164–166]. It is thus expectable that a variety of compounds that activate NRF2 could alleviate colitis-associated mucosal damage and colonic inflammation [167].

In addition, other ferroptosis regulators, including NADPH oxidases [168–171] and CD44 [172–175], are evidenced to be associated with the pathogenesis of IBD in patients or in colitis models. These proteins, including P53, NRF2, NADPH oxidases, and CD44, are all multifaceted. Thus, the exact involvement of these molecules in mediating ferroptotic regulation in colitis needs further investigation.

4. Conclusive Remarks and Perspective

IBD is increasing worldwide and has become a global disease in both developed regions and developing countries. The increasing medicinal cost and substantial elevation in the risk of colorectal cancer are greatly affecting the life quality of patients and families. Although the exact pathogenesis of IBD is poorly defined, multiple lines of evidence indicate that genetic susceptibility, deleterious environmental factors, and an imbalanced gut microbial ecosystem could impinge on the gut homeostasis and thus facilitate inflammatory
response [195]. Uncontrolled cell death has been widely observed in the diseased mucosa in patients and animal models, which could disturb the tight junction of the intestinal barrier and then aggravate the inflammation by releasing the gut microorganisms.

Ferroptosis is a newly identified form of regulated cell death. Iron overload, GSH exhaustion, GPX4 inactivation, and lipid peroxidation are the major features of ferroptosis. Dysregulated ferroptosis has been evidenced to be implicated in the pathogenesis and progression of many human diseases [196]. Furthermore, targeting induction of ferroptosis provides a potential therapeutic strategy for the clinical intervention of cancers, especially the other traditional therapy-resistant cancers [197, 198]. As mentioned above, the major features of ferroptosis have been extensively observed in the diseased mucosa in patients and animal models. Importantly, genetic or pharmacological manipulation of ferroptosis-related genes could alter the incidence, severity, or progression of the experimental colitis by using the corresponding murine models. More directly, some potent ferroptosis inhibitors, including iron chelators, GSH or GSH derivate GSH ester, selenium, LOX inhibitors, folate, or BH4, could decline lipid peroxidation and alleviate colitis-associated intestinal injury (Table 1). Moreover, Fer-1 and Lip-1, two specific inhibitors of ferroptosis, could relieve colitis in murine models. On the contrary, the ferroptosis sensitizers, including iron, γ-glutamylcysteine synthetase inhibitor BSO, and dietary PUFAs, could accelerate lipid peroxidation and aggravate colitis. Collaboratively, these studies thus highlight the critical importance of dysregulated ferroptosis in the pathogenesis of IBD.

It should not be ignored that abnormalities of both the innate and adaptive immune responses against harmful intestinal microorganisms, antigens, or extrinsic pathogens play important roles in the pathogenesis of IBD. The healthy mucosa contains a delicate balance of innate lymphoid cells, macrophages, neutrophils, and dendritic cells, as well as the adaptive immune response associated with T and B cells. The hyperactivation of the intestinal immune system due to the epithelial cell death and intestinal barrier disruption leads to the subsequently excessive secretion of proinflammatory cytokines and chemokines, which could result in secondary damage to the intestinal mucosa and a vicious cycle [199, 200]. Furthermore, previous studies indicated resistance to cell death of lamina propria lymphocytes in inflamed tissues in UC patients due to the altered expression of cell death-associated proteins [201–203]. Therefore, it is supposed that the IEC ferroptosis leads to intestinal barrier disruption, gut microorganism release, and hyperactivation of intestinal immune response, resulting in aggravation of colitis-associated mucosal injury. Furthermore, the ferroptotic IECs would release some immunogenic molecules, which may further facilitate local inflammation (Figure 2) [204]. However, besides IECs, whether intestinal immune cells undergo ferroptosis in the pathogenesis of intestinal injury or not is elusive. If so, whether this ferroptosis in certain types of intestinal immune cells contributes to the pathogenesis or progression of intestinal diseases or not needs more investigations.

Regarding the beneficial effect of diverse ferroptosis inhibitors in relieving colitis-associated tissue injury (Table 1), it is of great therapeutic potential for selective manipulation of ferroptosis in the prevention and intervention of colitis. Therefore, more extensive investigations are needed to further dissect the exact implication of ferroptosis in the pathogenesis of IBD and other related intestinal diseases. Specifically, to dissect the detailed underlying molecular mechanism for which ferroptosis mediates mucosal damage in inflamed tissues, to explore the specific types of epithelial cells in which dysregulated ferroptosis occurs leading to the hyperactivation of intestinal inflammation, and to identify the more selective and potent ferroptosis inhibitors with lower side effects for pharmacological intervention of IBD will help to obtain the full aerial view of ferroptosis and provide some future translational applications.

**Abbreviations**

- 4-HNEs: 4-Hydroxy-2-nonenals
- 5-ASA: 5-Aminosalicylic acid
- AA: Arachidonoyl
- ACSL4: Acyl-CoA synthetase long-chain family member 4
- AdA: Adrenoyl
- ALOX: Arachidonate lipoxygenase
- BH4: Tetrahydrobiopterin
- CD: Crohn’s disease
- CoQ10: Coenzyme Q10
- CYB5R1: NADH-cytochrome b5 reductase
- DAMPs: Damage-associated molecular patterns
- DFO: Deferoxamine
- DFP: Deferiprone
- DMT1: Divalent metal transporter 1
- DSS: Dextran sodium sulfate
- ER: Endoplasmic reticulum
- Fe2+: Ferrous iron
- Fe3+: Ferric iron
- Fer-1: Ferrostatin-1
- FPN: Ferroportin
- FSP1: Ferroptosis suppressor protein 1
- GCH1: GTP cyclohydrolase-1
- GPX4: Glutathione peroxidase 4
- GSH: Glutathione
- HFE: Hemochromatosis gene
- HFO: Heme oxygenase-1
- IBD: Inflammatory bowel disease
- IECs: Intestinal epithelial cells
- IFNγ: Interferon gamma
- IRP1/2: Iron regulatory proteins 1 and 2
- LIP: Labile iron pool
- Lip-1: Liproxstatin-1
- FO: Deferiprone
- Lipoxigenases
- LPCAT3: Lyso phosphatidylcholine acyltransferase 3
- MDA: Malondialdehydes
- MUFA: Monounsaturated fatty acids
- NCOA4: Nuclear receptor coactivator 4
- NF-κB: Nuclear factor kappa B
- NRF2: Nuclear factor erythroid 2-related factor 2
P53: Tumor protein p53
PE: Phospholipid
PEBP1: PE-binding protein 1
PLs: Phospholipids
POR: P450 reductase
PUFAs: Polyunsaturated fatty acids
ROS: Reactive oxygen species
SLC3A2: Solute carrier family 3 member 2
SLC7A11: Solute carrier family 7 member 11
TF: Transferrin
TFR1: Transferrin receptor 1
TNBS: 2,4,6-Trinitrobenzene sulfonic acid
TNF-α: Tumor necrosis factor alpha
UC: Ulcerative colitis.

Conflicts of Interest
The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors’ Contributions
Weihua Gao and Ting Zhang contributed equally to this work.

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