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Review Article

Ferroptosis and Ferroptosis-related autophagy: new therapeutic targets for gastric cancer

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Abstract: Gastric cancer (GC) is still the biggest factor in cancer-related death worldwide, and existing therapies have low therapeutic effectiveness. A possible cancer treatment target is ferroptosis, an iron-dependent kind of lipid peroxidation-induced regulated cell death. Recent studies further reveal that autophagy associated with ferroptosis modulates ferroptosis by regulating iron homeostasis, lipid metabolism, and redox balance. This review systematically describes the role of ferroptosis-related autophagy and ferroptosis in the pathogenesis and development of GC. We highlight key molecular mechanisms and propose ferroptosis-related biomarkers as potential diagnostic and therapeutic targets. Our findings underscore the translational potential of targeting ferroptosis-autophagy networks for GC treatment.

Keywords: Gastric cancer, ferroptosis, ferritinophagy, lipophagy, clockophagy

Introduction

GC is one of the majority of prevalent tumors that are malignant in the world, with an average survival rate that is fewer than 12 months in late stages [1, 2]. GC is still the cancer with the fifth highest prevalence and the fourth greatest cause of cancer-related deaths worldwide, despite the fact that its incidence and mortality have greatly dropped in all nations over the last few decades [3]. According to the pertinent research from 2023, GC accounts for around 50% of the global rate and has the third-highest incidence and fatality rate of any kind of cancer in China [3]. Many important factors now are linked to GC, including Helicobacter pylori infection, aging, a high-salt diet, cigarette use, and drinking liquor [4, 5]. Conventional treatment for GC mainly includes endoscopic resection and chemotherapy, and despite recent advances in GC treatment due to immune-related therapies in recent years [6], the current clinical efficacy is limited, and we need to further explore the underlying mechanisms to provide guidance for clinical treatment. In recent years, ferroptosis has drawn more interest as cell death methods have been studied. Numerous malignant tumors are intimately associated with ferroptosis, a common non-apoptotic form of cell death. It is described as a kind of cell death caused by lipid peroxidation that ruptures the plasma membrane and an imbalance in iron homeostasis [7]. Numerous studies show that targeting ferroptosis is effective against cancer [8-10]. In addition, some studies suggest that partially selective autophagy can effectively regulate ferroptosis to influence cancer development and progression. Therefore, this time, we will take ferroptosis and its selective autophagy as an entry point and analyze its possible mechanism in inhibiting GC, which will provide a direction for the treatment of GC.

Ferroptosis

As a ubiquitous occurrence, cell death is essential to an organism's growth and development. These days, autophagy, necroptosis, pyropto-

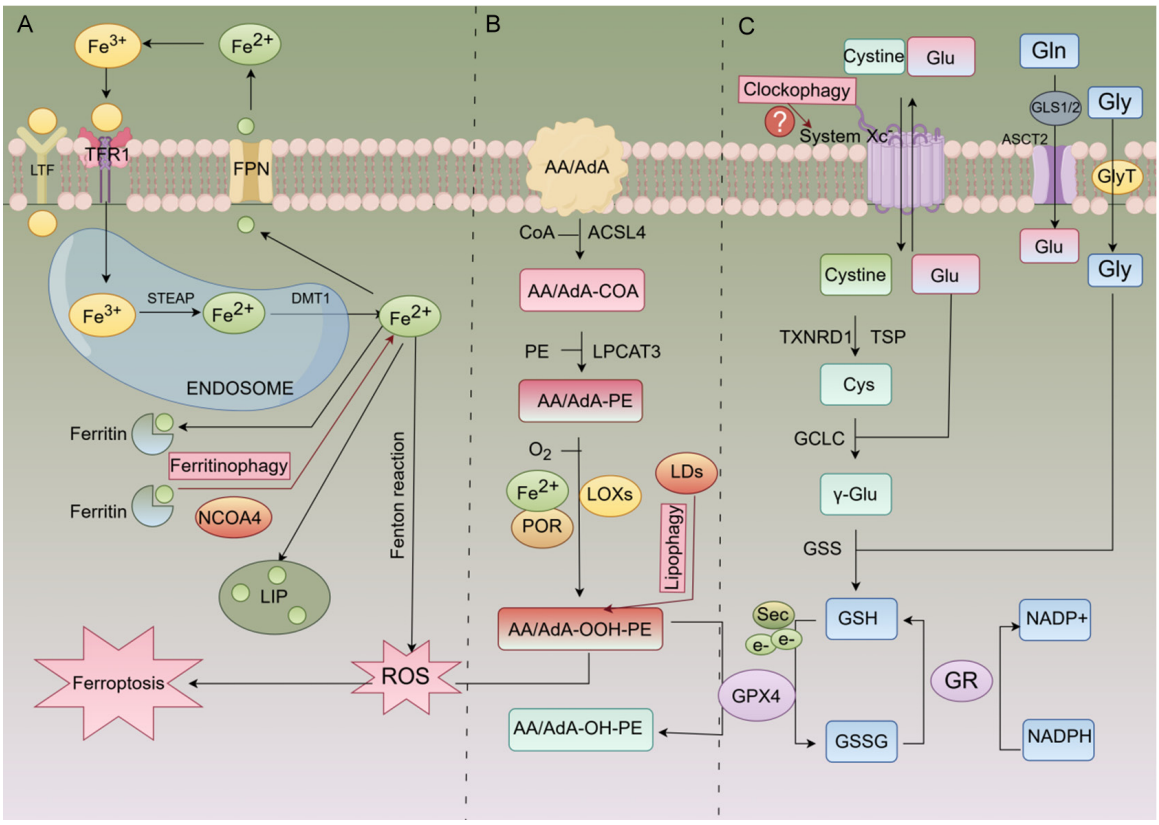

Figure 1. A. Abnormal intracellular iron ion metabolism leads to iron ion overload, causing a Fenton reaction to produce ROS. B. Polyunsaturated fatty acids form lipid peroxides in the presence of various enzymes and ROS. C. Glutamic acid (GLU), cysteine, and glycine (Gly) form GSH in the presence of various enzymes and transporter proteins. GSH provides sun-substituted cysteine residues and two electrons for the reduction of lipid peroxides by GPX4.

sis, and apoptosis are the main mechanisms of cell death. According to Dixon, eruptosis refers to the iron-dependent growth of lipid peroxides that results in programmed cell death [7]. The primary mechanism is cell rupture triggered by an increase of lipid peroxides in the cytosol as a result of an imbalance between iron-ion-dependent production and elimination of intracellular reactive oxygen species (ROS). **Figure 1** illustrates the specific mechanism of this process.

Abnormal iron metabolism

Iron, as one of the essential trace elements for living organisms, is involved in various cellular life activities. Tf-iron is formed when extracellular iron ions tie to transferrin and are transported intracellularly into endosomes via mutual recognition and binding to the cell membrane's transferrin receptor 1 (TFR1/TFRC) [11]. In addition, lactotransferrin (LTF) and solute carrier family 39 member 14 (SLC39A14) are additional pathways via which iron ions can enter cells [12]. STEAP reductase in the endosome transforms iron ions that enter it into 2-valent iron ions, which are next passed on to the cytoplasm by divalent metal transfer protein 1 (DMT1) [13]. Iron ions in the cytoplasm are mainly stored in an inactive form in ferritin, with a small portion forming an unstable iron pool (LIP) and another portion being transported to the outside of the cell via membrane iron transport proteins (FPN). In general, intracellular iron ions form a dynamic balance between uptake, efflux, and utilization to maintain normal cellular activity. However, when the cytosol is overloaded with iron ions, through the Fenton reaction, the extra iron ions generate a significant quantity of ROS [14]. Iron ions are cofactors for lipid-oxidizing lipoxygenase (LOX), a direct participant in lipid peroxidation. At the same time, iron can also react with phospholipid hydroperoxides (PLOOH) and produce ROS [15]. A significant buildup of intracellular ROS

eventually leads to overoxidation of the lipids in the cell membrane, which produces a buildup of lipid peroxides and ultimately results in cell rupture and death.

Lipid peroxidation

The peroxidation of polyunsaturated fatty acids (PUFA) in the plasma membrane is another significant aspect of ferroptosis. Arachidonic acid (AA) and adrenaline (AdA) serve as crucial mediators that push cells to ferroptosis, according to lipidomics research [16]. Because PUFA contains very active hydrogen ions, it is susceptible to oxidation by ROS at its diallyl position, forming peroxides [17]. In the presence of acyl-CoA synthetase long-chain family 4 (ACSL4), AA and AdA bind to the acetyl coenzyme A (CoA) to generate AA-CoA or AdA-CoA contracts for difference for each when the lipid peroxidation process begins [18]. With the help of LPCAT3, AA-CoA and AdA-CoA were subsequently esterified with phosphatidylethanolamine (PE) to create AA-PE and AdA-PE [19]. Finally, lipid peroxides such as PE-AA-OOH and PE-AdA-OOH can be produced via non-enzymatic Fenton reactions involving AA-PE and AdA-PE or by enzymatic catalysis by LOX and/or cytochrome P450 oxidoreductase (POR) [20]. Cell rupture eventually results in the formation of several secondary products, including malondialdehyde and 4-hydroxynonenal, which finally cause cellular ferroptosis [21]. In this process, glutathione peroxidase 4 (GPX4) serves as a key target to inhibit ferroptosis by targeting lipid peroxidation.

GPX4

Glutathione peroxidase (GPx) is an important intracellular protective mechanism. The GPx family includes glutathione peroxidase 1-8 [22]. We now know that ferroptosis is significantly influenced by GPX4 because of its ability to reduce lipid peroxides to their corresponding alcohols. GPX4, a selenoprotein, contains selenocysteine in its active site. The process requires a selenocysteine residue provided by glutathione by two electrons. During the reduction of GPX4, GSH supplies the two electrons and selenocysteine residues (Sec) needed for the simultaneous transformation of oxidized glutathione (GSSG). Glutathione reductase (GR) and NADPH convert GSSG back into GSH after recycling.

GSH

GSH is an important tripeptide synthesized from three substances, glutamate (GLU), cysteine, and glycine (Gly), and is able to provide essential selenocysteine residues and two electrons to GPX4 during ferroptosis. GSH biosynthesis involves a two-step enzymatic cascade process. Glutaminase 1/2 (GLS1/2) degrades outside glutamine (GLN) to glutamate, which is then absorbed by the alanine-serine-cysteine transporter 2 (ASCT2) and transported inside the cell. Methionine can be converted to cysteine by the sulfur-transfer route, while cystine is converted to cysteine in response to glutathione as well as thioredoxin reductase 1 (TXNRD1) [23]. Cysteine enters the cell via the System Xc-, whereas glycine enters directly through the glycine transporter protein (GlyT). During the process of producing glutathione, the catalytic component of glutamate cysteine ligase (GCLC) first converts cysteine and glutamic acid into the dipeptide γ-glutamylcysteine. When glutathione synthetase (GSS) is present, glycine and the former combine to create GSH. Notably, cysteine is a limiting substrate for GSH production, indicating that System Xc^-, which transports cysteine in this process, is a crucial ferroptotic target.

System Xc^-

System Xc^- (cystine/glutamate countertransport system), a chloride-dependent and sodium-independent retrotranslocator protein of cysteine and glutamate. System Xc^- consists of the subunits SLC3A2 and SLC7A11. These two subunits have distinct functions and are joined by an extracellular covalent disulfide link. These two subunits have distinct functions and are joined by an extracellular covalent disulfide link. Among them, SLC7A11 is the core component, as it has system specificity and assumes the major transport function. SLC3A2, on the other hand, mainly plays a role in maintaining structural stability. Immobilized on the cell membrane, System Xc^- forms GSH by converting intracellular glutamate to extracellular cysteine in a 1:1 ratio.

Bypass of ferroptosis

The NADH-FSP1-CoQ10 signaling pathway is a signaling axis independent of GPX4. Apoptosis-inducing factor-associated mitochondria-asso-

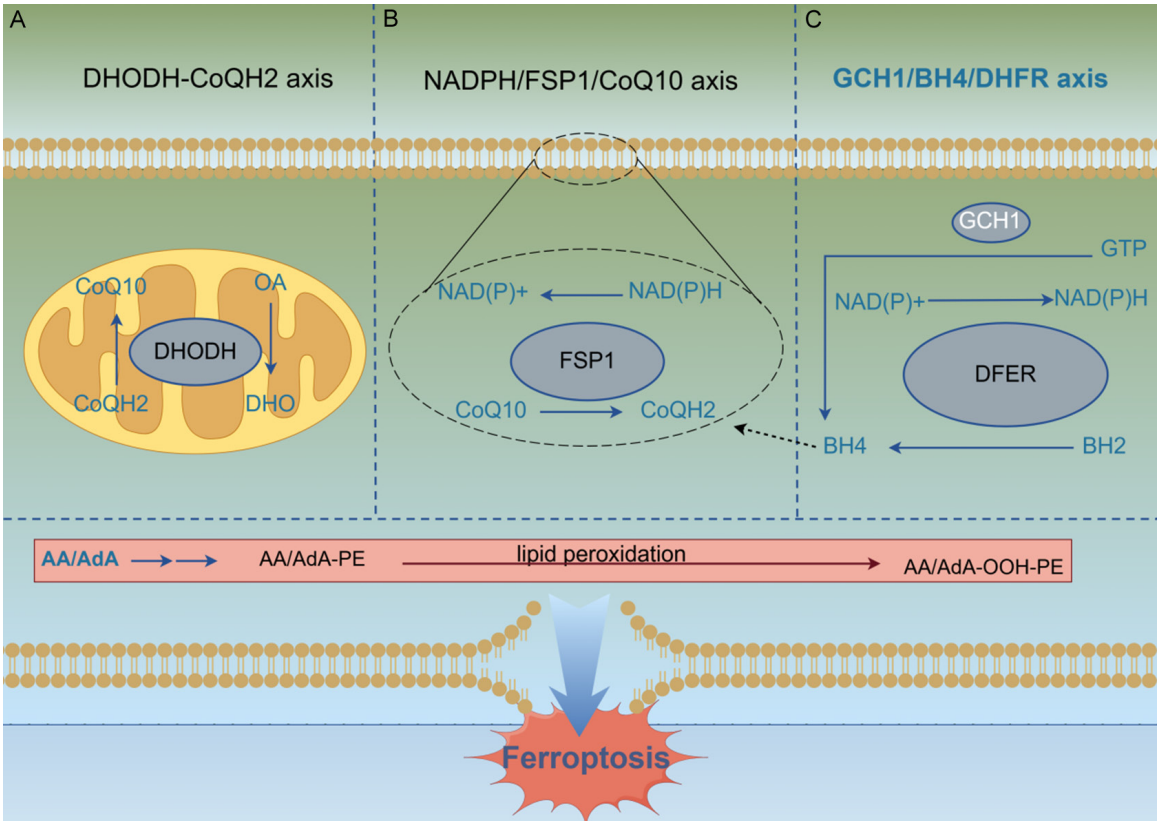

Figure 2. Three bypass pathways for ferroptosis. A. DHODH-CoQH2 axis. B. NADPH/FSP1/CoQ10 axis. C. GCH1/BH4/DHFR axis.

ciated FSP1 was found to contribute to apoptosis independently of caspase 1 [24]. According to recent research, FSP1 can facilitate the transformation of ubiquinone (CoQ10) into ubiquinol [25]. Furthermore, it is evident from similar research that $CoQH_2$ can prevent ferroptosis by ensnaring lipophilic free radicals. Furthermore, ubiquinone can be converted to dihydrobiquinone ($CoQH_2$) by the flavin-dependent enzyme hydroorotate dehydrogenase (DHODH), which is found in the mitochondrial membrane.

GCH1-BH4-DFER is another anti-ferroptosis pathway that is not dependent on GPX4. GTP cyclic hydrolase-1 (GCH1) can be generated to produce the lipophilic radical-trapping antioxidant (RTA) tetrahydrobiopterin (BH4). BH4 promotes $CoQH_2$ regeneration to counteract lipid peroxidation and iron metabolism [26-28]. Dihydrofolate reductase (DHFR) regenerates BH4 from its oxidized state, boronic anhydride (BH2). It seems clear that $CoQH_2$ is the last mechanism by which all of the aforementioned paracrine mechanisms prevent ferroptosis; see **Figure 2**.

Autophagy associated with ferroptosis

Ferritinophagy

As mentioned above, most of the iron ions in the cell are stored in ferritin, which maintains the dynamic balance of iron ions in the cell. The hollow iron storage proteins ferritin heavy chain (FTH1) and ferritin light chain (FTL), which have 24 subunits each, have the capacity to oxidize up to 4,500 Fe^{2+} ions to Fe^{3+} [29, 30]. Ferritin has a major impact on the control of iron ion homeostasis. When a cell lacks iron ions, ferritin is carried to the cell's lysosomes, where it is broken down and iron ions are released. Also, the transport of ferritin to the lysosome is affected when iron is abundant [31]. Ferritin is known to be transported to the lysosome by two different pathways: The first is macroautophagy. And the transport-mediated route is dependent on the endosomal sorting complexes (ESCRT) [32-35].

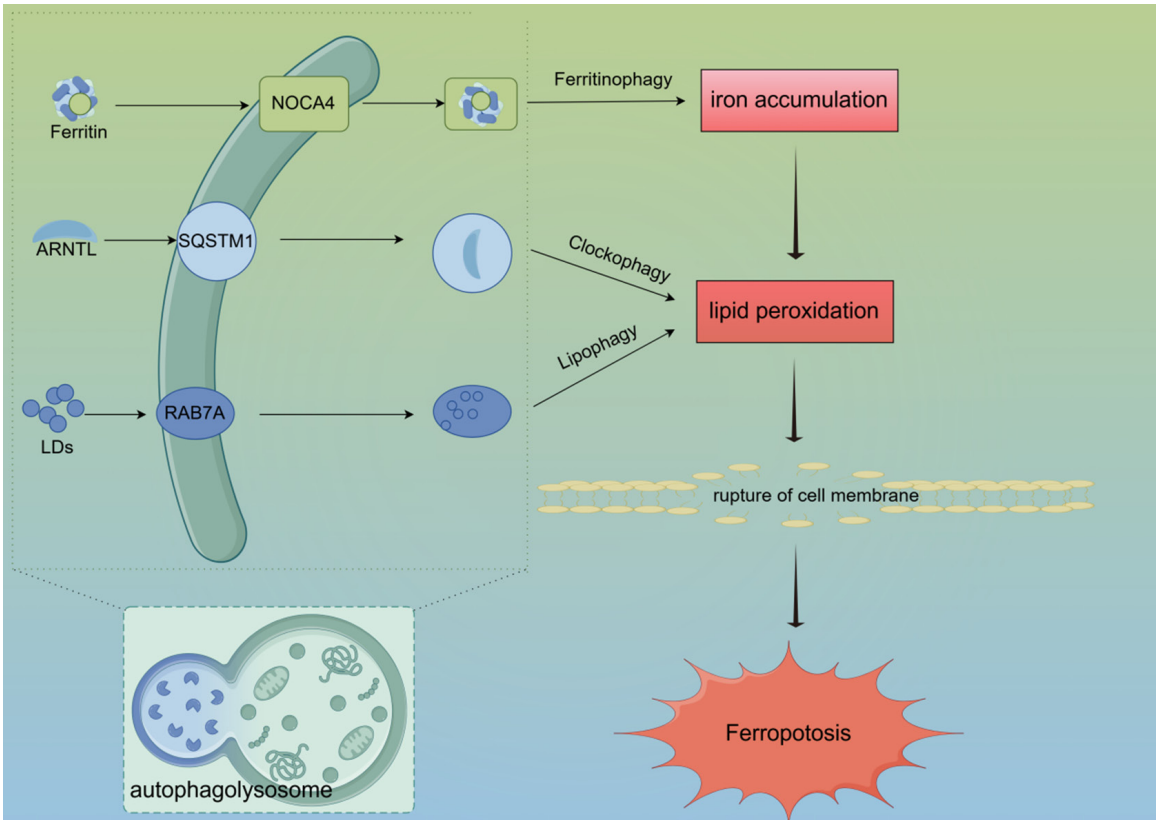

Figure 3. Selective autophagy for three types of ferroptosis. Ferritin binds to NOCA4, and after ferritinophagy occurs, ferrous ions are released, leading to intracellular iron accumulation and ultimately to the onset of ferroposis. ARNTL binds to SQSTM and undergoes clockophagy, leading to lipid peroxidation and ferroptosis. LDs bind to RABA7 and undergo lipophagy, leading to lipid peroxidation and ferroptosis. The above autophagy process occurs in the autophagolysosome.

Ferritin is drawn to the lysosome by nuclear receptor coactivator 4 (NCOA4) through the previously mentioned pathway when the iron autophagy process is triggered. This process, known as ferritinophagy, causes ferritin to degrade and release free iron [36]. Specifically, ferritinophagy, as an autophagy mechanism for removing the major iron storage protein ferritin, and the abnormal iron accumulation it causes can trigger and exacerbate ferroptosis. Notably, NCOA4 is now recognized as an essential factor in the ferritinophagy process, and cells lacking NCOA4 are unable to degrade ferritin [33, 35, 37]. It is easy to see that NCOA4 is a key factor in ferritinophagy.

Ferritinophagy is mainly mediated by NCOA4 and regulated by intracellular iron ion levels [38]. Poly(C)-binding protein 1 (PCBP1) takes up ferric ions in iron shortage and moves them to ferritin, which has both heavy and light chains [39]. Subsequently, NCOA4 was transferred to nascent autophagosomes after binding to a conserved surface of FTH1 of the above ferritin [40, 41]. Finally, autophagosomes and lysosomes fuse, where ferritin is degraded and iron ions are randomly released into the cytoplasm. Understandably, as ferritinophagy and iron ions are released into the cytoplasm, this will cause a Fenton reaction and elevated ROS, inevitably promoting ferroptosis. Furthermore, in an atmosphere of iron ions, the C-terminus in NCOA4 is bound by the HECT and RLD domains, which comprise E3 ubiquitin protein ligase 2 (HERC2), resulting in proteasome-dependent degradation of NCOA4 [31, 42]. Subsequently, NCOA4 levels will decrease, ferritinophagy will be inhibited, and ferritin's iron ion storage will relatively increase [43]. It should come as no surprise that ferritinophagy can control ferroptosis by affecting ROS generation and intracellular iron homeostasis; see **Figure 3**.

Lipophagy

Lipophagy is a selective autophagy that primarily involves autophagic lysosomes breaking down lipid droplets (LDs) and producing free fatty acids (FAs) to promote lipid metabolism. At present, lipophagy can be divided into macrophagocytosis and microphagocytosis. Using autophagosomes to target and engulf LDs for breakdown upon fusion with lysosomes, macrolipophagy is a kind of selective autophagy. Microadipophagy is a unique form of adipophagy in which the LDs interact directly with lysosomes or lysosome-like organelles and does not require autophagosomes to target the LDs. During LDs degradation, protein kinase A triggers the phosphorylation of perilipins, followed by the recognition of the LDs surface proteins perilipin 2 and perilipin 3 by heat shock cognate 70 and their binding to the lysosomal-associated membrane protein 2 [44]. Immediately afterward, LDs are directly degraded to fatty acids by lipases and other enzymes, and this pathway is known as lipolysis. Rab7 and Rab10 recruit lysosomal and LC3-positive autophagic membranes, respectively, to the LD for degradation, and the process is then lipophagy. Through LC3-interacting regions (LIRs), a variety of selective autophagy receptors (SARs) identify and locate certain targets and attract autophagosomes [45, 46]. After autophagy is initiated, the autophagosome extends in order to fully engulf its specific target, eventually closing the autophagosome pore. A related study clarifies that adipose autophagy promotes RSL3-induced ferroptosis in hepatocytes [47]. Meanwhile, di(2-ethylhexyl) phthalate induces ferroptosis by inducing lipophagy, leading to lipid peroxidation [48]. Timosaponin AIII increases Rab7-mediated lipophagy in colorectal cancer cells, which results in lipid peroxidation and ferroptosis [49]. Notably, related studies have clarified that increased adipophagy produces PUFA, promoting lipid peroxidation and subsequent ferroptosis. Meanwhile, related studies clarified that RAB7A is a central regulator of adipophagy, and knockdown of RAB7A in vitro inhibited adipose autophagy-mediated ferroptosis [47, 50]. The end result of adipose autophagy is the onset and exacerbation of free fatty acid release, lipid peroxidation, and ferroptosis. See **Figure 3**.

Clockophagy

Clockophagy is the mechanism by which autophagy preferentially breaks down ARNTL/BMAL1 using the cargo receptor SQSTM1/p62. Clockophagy autophagically breaks down ARNTL by using the cargo receptor SQSTM1 and the vital autophagic components ATG5 and ATG7. This mechanism is frequently started by GPX4 inhibitors. Hypoxia inducible factor 1 subunit alpha is destabilized by ARNTL degradation, which in turn stimulates the transcription of egl-9 family hypoxia inducible factor 2 [51]. And considerable studies have clarified that HIF1A can regulate ferroptosis through various pathways regulating SLC7A11 [52-55], but the exact mechanism is not clear. See **Figure 3**.

Ferroptosis and its associated autophagy

In the limited number of studies available, the majority view is that the regulation of ferritinophagy by NCOA4 is an important component of ferroptosis [56]. However, it is worth mentioning that ferritin, because of its iron storage function, has an apparent autophagic ability to activate and exacerbate ferroptosis by modulating the levels of intracellular ions. A considerable number of studies also regulate ferroptosis by inhibiting or activating ferritinophagy, which somehow is supposed to act as an upstream regulator of ferroptosis. Similarly, adipose autophagy and clockophagy regulate ferroptosis by modulating intracellular free fatty acids and SLC7A11, respectively, apparently acting upstream of ferroptosis.

The role of ferroptosis and its associated autophagy in GC

Helicobacter pylori is intimately linked to the development of stomach cancer. Ferritin, transferrin, and iron homeostasis have all been shown in several studies to have a direct impact on Helicobacter pylori pathogenicity and survival [57-59]. MiR-375, which inhibits Helicobacter pylori-induced GC, was found to trigger ferroptosis by targeting SLC7A11 to reduce GSH levels [60, 61]. According to a similar study, the development of GC was linked to reduced expression of Cytoplasmic Polyadenylation Element Binding Protein 1, which activates transcription factors that block GSH-specific transferase [62]. The ferroptosis inducer erastin significantly reduced the ability to

survive of four GC cell lines in this study: AGS, SNU-1, Hs-746T, and HGC-27 [62]. The ability of erastin to effectively suppress the activity of GC cells by acting on system Xc- has been more clearly confirmed by pertinent research [63]. Bupivacaine and other anesthetics prevent the growth of GC cells by inducing ferroptosis, which is mediated by the miR-489-3p/SLC7A11 axis [64]. Furthermore, similar pharmacological investigations have discovered that by blocking GPX4 activity, apatinib, an effective treatment for GC, can cause ferroptosis in GC cells [65, 66]. Cysteine dioxygenase 1 increases the production of GSH and GPX4 in cells, which reduces ferroptosis in cells of GC [67, 68]. Tanshinone IIA inhibits tumor proliferation and metastasis by increasing lipid peroxidation levels and decreasing glutathione levels in GC cells [68]. Actinidia chinensis (Planch) possesses antiproliferative and anti-migratory actions in GC cells and dramatically and dose-dependently down-regulates the expression of GPX4 [69]. Physcion 8-O-beta-glucopyranoside induces ferroptosis in GC through altering the miR103a-3p/GLS2 axis, whereas miR103a-3p regulates ferroptosis in cells of GC by altering intracellular GSH levels [70]. The above findings indicate that System Xc^-/gsh/gpx4, a classical signaling pathway for ferroptosis, is closely associated with GC, and it is reasonable to believe that GC can be effectively treated by targeting the above signaling pathway. In a related study investigating the GPX4 inhibitor polypeptide B (PB) for the treatment of GC [71], by promoting ferritinophagy and transporting Fe^{3+} into cells via TFRC, PB may increase Fe^{2+} levels, as demonstrated by in vitro experiments that suggest it can alter the synthesis of TFRC, NOCA4, and FTH1. In the meantime, in vivo experiments have shown that PB may also stop tumor growth in a GC in situ mice model by regulating the expression of GPX4, TFRC, NOCA4, and FTH1. According to research on GC, a significant portion of the tumor stroma causes NK cells to produce more unstable iron, which causes ferroptosis by exporting iron to the TME and stimulating FSTL1-ferritinophagy mediated by NCOA4 [72]. Another experiment investigating epithelial-mesenchymal transition (EMT) in GC clarified that the EMT process in GC cells is associated with NCOA4-mediated ferritinophagy, which suggests that the process of ferritinophagy in cells of GC has the capacity to regulate metastasis and drug resistance [73]. In an experiment, NOP2/Sun RNA Methyltransferase 5 (NSUN5) was observed to be elevated in GC tumor tissues, and it was found that NSUN5 unidirectionally regulated the level of FTH1 in GC cells and that silencing of NSUN5 or FTH1 would inhibit GC tumor growth [74]. Additional studies demonstrated that polyphyllin I induced GC cancer cells by regulating the NRF2/FTH1 pathway [75]. At the same time, the above study was able to show that ferritinophagy and ferroptosis usually occur together in GC. One study even clarified that ferritinophagy in GC works by promoting ferroptosis to inhibit EMT [76].

In GC studies, few articles have explicitly suggested a relationship between GC and lipophagy. However, some studies have clarified the relationship between proteins involved in the induction of lipophagy and GC, filling the gap in this area. GGT7, or γ-glutamyltransferase 7, is often downregulated in GC and induces autophagy by recruiting RAB7. And Gamma-Glutamyltransferase 7 (GGT7) inhibits intracellular ROS and mitogen-activated protein kinase (MAPK) signaling associated with its process to suppress GC [77]. Another study also found that targeting RAB7 modulates autophagy levels in GC [78]. The surface of LDs has been shown to contain early 30 Rab GTPases [79], and recent reports suggest that this family of GTPases adversely affects response to classical lipophagy and LD turnover [80]. Rab7 is one of the most prominent Rabs on the LD surface and is involved in autophagosome maturation [81, 82]. Similarly, Rab10 has been reported to affect GC by regulating autophagy [83, 84]. Additionally, Rab18 has been discovered to be substantially linked to medication resistance and the value-added of GC [85, 86]. A clinical study employing GC tissues suggests that LC3 expression might serve as a valuable new diagnostic for assessing the outlook for sufferers who advanced GC after neoadjuvant chemotherapy (NACT) [87]. Furthermore, LC3's function as an autophagy-related factor in GC has been elucidated by a significant number of research studies [88, 89]. However, a number of studies have demonstrated that phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR) signaling prevents stomach cancer via regulating autophagy [90, 91]. It has also been clarified that modulation of mTOR can thereby promote

lipid renewal in hypothalamic neurons and achieve coordination between autophagy and lipolysis [92, 93]. MTOR appears to regulate lipophagy in a manner similar to autophagy, although the mechanism by which it promotes lipophagy remains to be fully elucidated [80]. Another study clarified the high expression of RAB7A in GC tissues while speculating that RAB7A may affect patient prognosis via boosting ECM breakdown and triggering the PI3K/AKT signaling pathway to encourage tumor invasion [94]. From the above, it is easy to see that there is a close link between lipophagy and GC, but more research is needed to explore the mechanism.

Clockophagy has often been overlooked in recent years of research. Some papers have discussed and studied the relationship between clockophagy and cancer, but almost no articles have discussed the relationship between clockophagy and GC. However, in a 2014 study, it was determined that circadian disruption may be linked to the development of GC by looking at the expression profiles of eight biological clock genes in the cancerous and noncancerous tissues of 29 patients with GC. These genes include BMAL1, Casein Kinase I ε, Clock Circadian Regulator, Cryptochrome Circadian Regulator 1, Cryptochrome Circadian Regulator 2, Period Circadian Regulator 1, Period Circadian Regulator 2, and Period Circadian Regulator 3 [95]. Single nucleotide polymorphisms (SNPs) may affect the clinical outcome of GC by changing gene expression, per a 2019 study on gastric carcinogenesis and progression and the circadian positive feedback loop genes (CLOCK, BAML1, and neuronal PAS domain protein 2 (NPAS2)) [96]. It is well known that Helicobacter pylori is the main pathogenic factor of GC. A study clarifies that Helicobacter pylori infection-induced disturbances in BMAL1 expression and rhythm exacerbate gastritis [97]. Thus, the clockophagy phase's potential involvement in stomach cancer cannot be disregarded.

Diagnosis and treatment of ferroptosis and GC

Ferroptosis and proliferation, invasion, and metastasis of GC cells

The proliferation, invasion, and metastasis of tumor cells are the key events in the development of malignant tumors. Studies have shown that ROS, as a normal product of cell metabolism, can promote cell proliferation [98], and the intracellular ROS production will increase significantly due to the accelerated metabolism and excessive proliferation of cancer cells [99]. Studies have found that low concentrations of ROS can promote cell adaptation to stress conditions by regulating autophagy and helping cell survival [99] and migration of GC cells [100]. It is worth noting that high concentrations of ROS and the consumption of antioxidant enzymes will lead to cell death [101], during which ROS will attack mitochondria or cause mitochondrial damage-dependent apoptosis [102]. In addition, it has been found that in cells of GC, the accumulation of ROS can increase the level of ferroptosis in cells of GC, thus significantly inhibiting the proliferation of tumor cells [103, 104]. By directly regulating GPX4, SLC7A11, and FTH1, STAT3 inhibition has been shown in previous studies to regulate ferroptosis in GC. It is also proven that STAT3 has been identified as a successful therapeutic target for GC because of its critical involvement in the evolution of GC [105]. In several drug studies, tanshinone IIA, Actinidia chinensis (Planch), physcion 8-O-β-glucopyranoside, and other substances showed anti-tumor growth, invasion, and metastasis through ferroptosis [68-70].

Ferroptosis and drug resistance in GC

The biggest barrier to clinical efficacy is drug resistance in cells of GC. The formation of GC and chemotherapy resistance are closely related to the destruction of the Wnt/β-catenin signaling system [106]. Because of genetic changes and aberrant growth, cancer cells are more susceptible to ROS oxidative stress than healthy cells, so preserving the antioxidant GSH is crucial to their survival and growth [107]. Chemotherapy is still one of the primary treatments for the treatment of GC. Inhibition of STAT3 can inhibit the negative regulatory axis of ferroptosis, inhibit the growth of GC, and reduce chemotherapy resistance [105]. Activating transcription factor 3 (ATF3) can reduce cisplatin resistance of GC [105]. ADP ribosylation factor 6 (ARF6) can regulate erastin-induced lipid peroxidation, and inhibition of ARF6 can reduce the resistance of GC cells to capecitabine [108]. In cells of GC, Wnt/β-catenin signal transduction is activated to

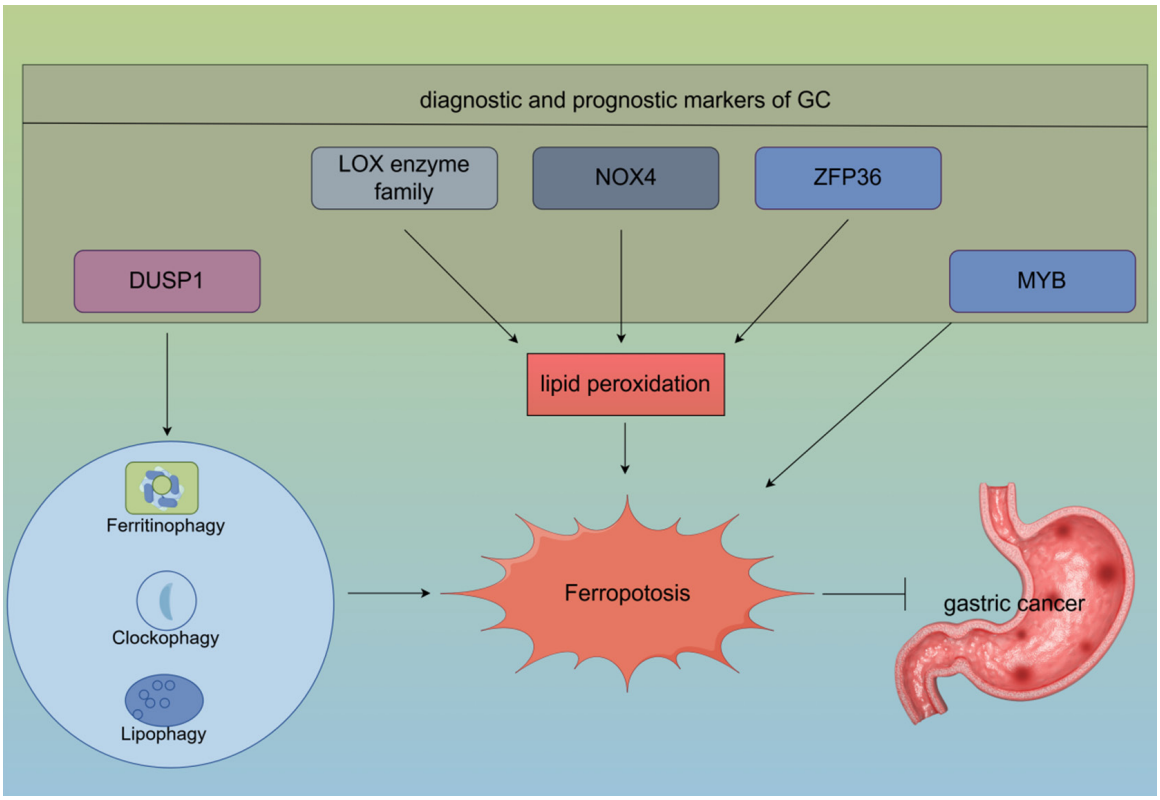

Figure 4. A schematic figure outlining the interactions among ferroptosis, ferroptosis-related autophagy, and diagnostic and prognostic markers of GC. Ferroptosis can inhibit the occurrence of gastric cancer. Ferroptosis-related autophagy, as an upstream of ferroptosis, inhibits the occurrence of gastric cancer by regulating ferroptosis. DUSP1 acts on ferroptosis-related autophagy as a potential target for gastric cancer, MYB can act as a potential target for gastric cancer by regulating ferroptosis, and the LOX enzyme family NOX4 and ZFP36 have been clearly identified as potential targets for gastric cancer by participating in the regulation of lipid peroxidation to regulate ferroptosis.

reduce the production of cellular lipid ROS, thereby preventing ferroptosis in GC cells, and direct binding of the β-catenin/TCF4 transcription complex to the GPX4 promoter region enables its expression. Thus preventing ferroptosis of cells [109]. These studies indicate that the regulation of ferroptosis in cells of GC is a useful strategy for treating drug-resistant GC cells.

Diagnosis and prognosis of ferroptosis and GC

Due to the low early diagnosis rate and limited treatment of GC, less than 10% of patients with advanced GC survive after five years [110]. On the contrary, up to 95% of patients who receive good therapy through early diagnosis will survive for five years [111]. Therefore, early diagnosis and treatment are extremely important for patients with GC. In current studies, targeting the metabolism of GC has become a target for cancer diagnosis and treatment [112]. The metabolism of GC cells is significantly different from that of normal cells, and ROS accumulated during metabolism becomes a breakthrough for early diagnosis [113]. Notably, NOX4 also promotes ferroptosis by increasing the production of ROS by increasing NADPH activity [114]. In addition, gene transcription regulator MYB can promote GC cell invasion, migration, and proliferation and is also considered to be an important risk factor for GC [115, 116]. Next, we will further explore the relevant targets of ferroptosis in GC.

Ferroptosis-related targets in GC

The majority of patients are in advanced stages of the disease when they receive their initial diagnosis, despite the fact that the 5-year survival rate for early GC is above 90% [117]. Early detection of GC is very critical for improving the prognosis of the 5-year survival rate [118]. Finding targets for early detection and research-

ing the associated pathophysiology of stomach cancer are therefore very crucial.

Currently, numerous ferroptosis-related genes have been shown to be diagnostic and prognostic markers of GC using machine learning and other techniques in a significant number of research studies. These mainly include the following genes: LOX [119, 120], NADPH oxidase 4 (NOX4) [121-125], zinc finger protein 36 (ZFP36) [126-130], dual-specificity phosphatase 1 (DUSP1) [119, 127, 131], and MYB [127, 128, 132, 133]. Furthermore, we have drawn a schematic figure outlining the interactions among ferroptosis, ferroptosis-related autophagy, and diagnostic and prognostic markers of GC; see **Figure 4**.

The LOX enzyme family is iron-dependent and promotes the accumulation of lipid peroxides [19]. In GC cells, 12-lipoxygenase facilitates the epithelial-mesenchymal transition for cancer metastasis via the Wnt/β-catenin signaling pathway [134, 135]. In GC, lipoxygenase stimulates EMT via the ERK signaling pathway. Increased NOX4 has been linked to lipid peroxidation, ferroptosis, and impaired mitochondrial activity in Alzheimer's disease studies [114]. In recent GC-related studies, NOX4 was able to regulate cell invasion and proliferation via regulating ROS and increasing iron apoptotic sensitivity in GC. Additional drug studies have clarified that both populin and XN4 (a novobiocin derivative) are able to target NOX4 and are effective in inducing ferroptosis to inhibit GC progression [136, 137].

ZFP36 is an RNA-binding protein that prevents ferroptosis and controls the body's reaction to lipid peroxidation [138]. A related study found that overexpression of ZFP36 alleviated the malignancy of associated GC cells by targeting the [139].

DUSP1 is an oncogene associated with tumorigenesis, progression, and drug resistance [140, 141]. DUSP1 expression in GC has been reported to be strongly related to survival [138], prognosis [126, 142], drug resistance [141], and treatment strategies [143]. In ferroptosis, DUSP1 as an autophagy regulator can regulate ferroptosis by regulating autophagy. In addition, tumor-related studies suggest that DUSP1 may be a potential target for overcoming drug resistance [144].

MYB is a well-characterized proto-oncogene protein that participates in multiple signaling pathways and is closely associated with a variety of cancers. Already in 2018, related articles revealed MYB as an attractive target for tumor therapy [145]. In recent articles, the MYB family has been reviewed, and it has been elaborated that the human family of MYB transcription factors is overproduced in a number of cancers and is associated with cancer progression and anticancer drug resistance [146, 147]. Targeting MYB can control the development and spread of cancer cells in GC, according to studies that have demonstrated a close relationship between MYB and the disease [116]. MYB has been discovered as a putative target of RSL3 in ferroptosis-related research. The target MYB controls cellular value-added, SLC7A11, GPX4, and epithelial junctional proteins, all of which RSL3 inhibits [148, 149]. Unfortunately, however, most of the current articles on MYB in GC are limited to predicting prognosis, etc., and do not explore the underlying mechanisms, despite the fact that this target has been defined as a key target in cancer in earlier years. We have summarized the key molecules, functions, and references of ferroptosis, ferroion-related autophagy, and ferroptosis inducers/inhibitors into a table for easy reading (**Table 1**).

Conclusions and outlook

As more and more research is being done on ferroptosis and the correlation with cancer, it is clear that ferroptosis is believed to be the key to treating cancer. Also, selective autophagy for ferroptosis was found to regulate ferroptosis in different ways. Although ferroptosis and its selective autophagy influence gastric carcinogenesis and progression to some extent. Unfortunately, their specific mechanisms of action in GC remain underappreciated. This article briefly discusses the concept and related mechanisms of cellular ferroptosis and its selective autophagy and highlights its importance in GC. Finally, we propose some relevant targets for ferroptosis in GC at the end of the paper, hoping to serve as a guideline for GC-related research. However, due to the insufficient research on ferroptosis and its selective autophagy in GC, there are still some limitations and challenges at present: 1. Potential ferroptosis biomarkers (such as LOX and MYB) lack large-

Table 1. Key molecules, their functions, and references for ferroptosis, ferroptosis-related autophagy, and ferroptosis inducers/inhibitors under investigation in GC

Category	Key Molecule	Function	Reference
Ferroptosis Core Molecules	TFR1/TFRC	Mediates extracellular iron ion uptake (binds transferrin-iron complex and transports to endosomes), maintaining intracellular iron pool.	[12]
	SLC39A14	Alternative pathway for iron ion entry into cells, supplementing iron uptake.	[12]
	DMT1	Transports Fe^{2+} (reduced by STEAP reductase in endosomes) from endosomes to cytoplasm.	[13]
	FPN	Exports intracellular iron ions to the outside, regulating iron efflux and maintaining iron homeostasis.	[14]
	ACSL4	Catalyzes binding of arachidonic acid (AA)/adrenic acid (AdA) to CoA, generating AA-CoA/AdA-CoA (initial step of lipid peroxidation in ferroptosis).	[18]
	LPCAT3	Esterifies AA-CoA/AdA-CoA with phosphatidylethanolamine (PE) to form AA-PE/AdA-PE (substrate for lipid peroxide production).	[19]
	LOX	Iron-dependent lipoxygenase; catalyzes AA-PE/AdA-PE to produce lipid peroxides, promoting ferroptosis.	[19]
	GPX4	Selenoprotein; reduces lipid peroxides to alcohols using GSH, the key inhibitor of ferroptosis.	[22]
	GSH	Tripeptide (GLU, cysteine, Gly); provides electrons and selenocysteine residues for GPX4, inhibiting lipid peroxidation.	[23]
	System Xc^- (SLC3A2/SLC7A11)	Cystine/glutamate antiporter (core subunit); imports cystine (precursor of GSH), regulating GSH synthesis and ferroptosis sensitivity.	[23]
	FSP1	Mediates NADH-CoQ10-CoQH2 axis; converts CoQ10 to CoQH2 (traps lipophilic free radicals), inhibiting ferroptosis independently of GPX4.	[25]
	GCH1	Produces tetrahydrobiopterin (BH4, a radical-trapping antioxidant); promotes CoQH2 regeneration, counteracting lipid peroxidation.	[27]
Ferroptosis-Related Autophagy Molecules	NCOA4	Cargo receptor for ferritinophagy; binds ferritin and delivers it to lysosomes for degradation, releasing free iron to promote ferroptosis.	[35]
	FTH1/FTL	Subunits of ferritin (iron storage protein); degraded via ferritinophagy to release Fe^{2+}, enhancing ferroptosis.	[31]
	RAB7A	Key regulator of lipophagy; recruits lysosomes to lipid droplets (LDs) for degradation, releasing free fatty acids (e.g., PUFA) to promote lipid peroxidation and ferroptosis.	[50]
	LC3	Marker of autophagosomes; interacts with lipophagy receptors (via LIRs) to engulf LDs, mediating lipophagy-dependent ferroptosis.	[87]
	SQSTM1/p62	Cargo receptor for clockophagy; binds ARNTL/BMAL1 and delivers it to autophagosomes for degradation, regulating HIF1A and ferroptosis.	[51]
	ARNTL/BMAL1	Circadian clock protein; degraded via clockophagy; its loss destabilizes HIF1A, indirectly regulating ferroptosis.	[51]

Ferroptosis Inducers in GC	Erastin	Inhibits System Xc^-, reduces GSH levels, and induces ferroptosis; suppresses survival of GC cell lines (AGS, SNU-1, Hs-746T, HGC-27).	[63]
	RSL3	Inhibits GPX4 activity, triggers lipid peroxidation; targets MYB to downregulate SLC7A11/GPX4, promoting ferroptosis in GC.	[148]
	Apatinib	GC therapeutic; inhibits GPX4 to induce lipid peroxidation and ferroptosis, suppressing GC cell growth.	[66]
	Bupivacaine	Anesthetic; regulates miR-489-3p/SLC7A11 axis to induce ferroptosis, inhibiting GC cell proliferation.	[64]
	Tanshinone IIA	Increases lipid peroxidation and decreases GSH levels; induces ferroptosis to inhibit GC cell stemness and metastasis.	[68]
	Actinidia chinensis (Planch)	Downregulates GPX4 expression; induces ferroptosis to suppress GC cell proliferation and migration.	[69]
	Physcion 8-O-β-glucopyranoside	Regulates miR-103a-3p/GLS2 axis; induces ferroptosis in GC cells.	[70]
	Polyphyllin B (PB)	Modulates iron metabolism (TFRC, NCOA4, FTH1) and induces ferroptosis; inhibits GC tumor growth in situ mouse models.	[71]
Ferroptosis Inhibitors/ Regulators in GC	STAT3	Regulates ferroptosis negative axis; upregulates SLC7A11/GPX4 in GC, promoting cell survival and chemotherapy resistance.	[105]
	DUSP1	Oncogene in GC; regulates autophagy to inhibit ferroptosis, enhancing drug resistance (e.g., apatinib).	[141]
	MYB	Proto-oncogene; upregulates SLC7A11/GPX4 in GC; its inhibition (e.g., by RSL3) promotes ferroptosis.	[148]

scale studies to verify the underlying mechanisms of treating GC. 2. Targeted ferroptosis for GC treatment requires further research to avoid excessive killing of normal cells by the drug. 3. Selective autophagy related to ferroptosis is relatively rare in GC studies. In view of the above key points, the content of this review urgently needs to be supplemented by new research advances.

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Disclosure of conflict of interest

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