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The Tumor Suppressor Protein p53 and the Ferroptosis Network

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Abstract

Ferroptosis is a form of lipid peroxidation-induced cell death that can be regulated in many ways, from altering the activity of antioxidant enzymes to the level of transcription factors. The p53 tumor suppressor is ‘the guardian of the genome’ that participates in the control of cell survival and division under various stresses. Beyond its effects on apoptosis, autophagy, and cell cycle, p53 also regulates ferroptosis either through a transcriptional or posttranslational mechanism. On one hand, p53 can enhance ferroptosis by inhibiting the expression of SLC7A11 (solute carrier family 7 member 11) or by enhancing that of SAT1 (spermidine/spermine N1-acetyltransferase 1) and GLS2 (glutaminase 2). On the other hand, p53 suppresses ferroptosis through the direct inhibition of DPP4 (dipeptidyl peptidase 4) activity or by the induction of CDKN1A/p21 (cyclin dependent kinase inhibitor 1A) expression. Here, we review recent discoveries and emerging trends in the study of the ferroptosis network and highlight the context-dependent impact of p53 on ferroptosis and oxidative stress.

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Introduction

Discovered in the 1970s, the tumor suppressor protein p53 (TP53) plays a critical role in the cellular response to various stresses, including DNA damage, hypoxia, nutrition starvation, and oncogene activation [1]. Activation of p53 can lead to survival or death, depending on the levels of stress [2]. Low levels of stress or damage trigger p53 activation to induce cell cycle arrest, DNA repair, and survival. p53 can protect against oxidative stress-induced DNA damage and death via downregulation of the production of reactive oxygen species (ROS) in cells. In contrast, high levels of stress or injury result in the activation of p53 to induce apoptosis and death. Unfortunately, p53 is usually mutated or depleted in many cancers, which limits the antitumor function of p53. Many studies have been focusing on the identification of p53 target genes that mediate tumor suppressor function. In addition to acting as a transcriptional factor in the nucleus, transcription-independent functions of cytosolic p53 are documented in the processes controlling cell death and metabolism, including apoptosis and autophagy [3]. For example, cytosolic p53 can directly bind to pro-apoptotic members of the BCL-2 family (BAX [BCL2 associated X, apoptosis regulator] and BBC3/PUMA [BCL2 binding component 3]) to increase mitochondrial membrane permeabilization and the release of pro-apoptotic factors from the mitochondria [4, 5]. Unlike nuclear p53, which acts as an autophagy-promoting transcription factor [6, 7], cytosolic p53 can block autophagy in response to nutrient starvation or mTOR inhibition [8]. These context-dependent roles of p53 in survival and death are regulated in a fine-tuned manner by its ubiquitination, phosphorylation, acetylation, and other modifications [9, 10]. Over the last three years, studies in both cell cultures and animal models have established that p53 represents a novel regulator of ferroptosis [11-14] (Fig. 1), a form of regulated cell death characterized by the accumulation of lethal iron or lipid hydroperoxides (e.g., PUFA-OOH) [15]. In this review, we will summarize the molecular mechanism of ferroptosis and focus on the current understanding of connections between p53 and ferroptosis and its potential as a target in cancer therapy.

Ferroptosis basics

Since its discovery in 2012 [15], the study of ferroptosis has been a fast-growing field in cell death research [16]. The process and function of ferroptosis, as well as its impact in disease susceptibility, has been recently well-reviewed [17, 18]. We first briefly introduce the major inducers and regulators of ferroptosis.

Inducers

Erastin

Oncogenic RAS mutations, including K-RAS, H-RAS, and N-RAS, have been shown to drive the development of various cancers across different cells of origin and etiologies. These oncogenes therefore are highly attractive targets for anticancer drug discovery, colliding with the fact that thus far no direct RAS inhibitors have been introduced into clinical practice [19]. Erastin, the first inducer of ferroptosis, was identified through a high-throughput small molecule screening searching for agents that selectively killed RAS mutated cancer cells, including H-Ras-mutant engineered human foreskin fibroblasts

(BJeLR), N-Ras-mutant HT-1080 cells (a fibrosarcoma cell line), and K-Ras-mutant Calu-1 cells (a lung cancer cell line) [20, 21]. The prosurvival RAS-RAF-MEK-ERK pathway in cancer cells is required for erastin-induced ferroptosis [20]. However, the previous conclusion that erastin fails to induce cell death in RAS wild type cells has been challenged by recent studies. This evidence includes: 1) Erastin can trigger leukemia cell death in a RAS-independent manner [22]; 2) Normal cells without RAS mutation such as kidney tubule cells and fibroblasts are sensitive to erastin [12, 23-26]; 3) Forced expression of mutant RAS limits the anticancer activity of erastin in RMS13 cells (a rhabdomyosarcoma cell line) [27]. In addition, an early report described that the direct target of erastin is the mitochondrial VDAC (voltage-dependent anion channel)-2 and -3, which cause mitochondrial injury with increased mitochondrial membrane permeabilization [20]. Indeed, knockdown of VDAC2 or VADC3 by RNAi limits erastin-induced ferroptosis [20]. However, increasing evidence indicates that the major target of erastin is the antiporter system X_c^- , which localizes in the cell membrane [15]. Although the half-life of erastin is relatively short in vivo, it exhibits anticancer activity in multiple mouse models, indicating that yet-to-be-discovered metabolites produced from erastin may mediate antineoplastic effects [28, 29].

RSL3

RSL3 was also identified through a high-throughput small molecule screening campaign designed to identify agents that selectively killed H-Ras-mutant engineered BJeLR cells in a non-apoptotic manner [30]. Similar to erastin, the original study indicated that iron accumulation, ROS production, and RAS-RAF-MEK-ERK activation are required for RSL3-induced ferroptosis [30]. Unlike erastin, signaling through mitochondrial VDAC2 or VADC3 and membrane system X_c^- do not seem to be required for RSL3-induced ferroptosis [30]. In contrast, GPX4 (glutathione peroxidase 4) is inhibited by RSL3 [31]. The early study suggests that RSL3 binds GPX4 to inhibit its enzymatic activity and hence to interfere with its capacity to prevent lipid peroxidation [31]. However, recent studies indicate that RSL3 as well as erastin can induce GPX4 protein degradation [32-34]. HSPA5 (heat shock protein family A [Hsp70] member 5), a molecular chaperone that contributes to endoplasmic reticulum (ER) homeostasis, can inhibit GPX4 degradation through a protein-protein interaction [34]. Moreover, the transcription factor ATF4 (activating transcription factor 4), which is involved in the ER stress response, is required for HSPA5 and SLC7A11 (solute carrier family 7 member 11) upregulation to inhibit ferroptosis [34, 35]. In contrast, ATF4-mediated expression of DDIT3/CHOP (DNA damage inducible transcript 3) contributes to the sensitization of cells to TNFSF10/TRAIL (TNF superfamily member 10)-induced apoptosis that is mediated by ferroptotic agents such as erastin and artesunate [36]. These findings build evidence supporting a complex interplay between ER stress, ferroptosis, and apoptosis.

Regulators

System X_c^-

The cystine-glutamate antiporter system X_c^- is composed of a substrate-specific subunit SLC7A11 and a regulatory subunit SLC3A2 (solute carrier family 3 member 2). System X_c^-

X_c^- -mediated cystine uptake is required for the production of cysteine and subsequent synthesis of glutathione (GSH) [37]. In addition to erastin and glutamate, other drugs, including sulfasalazine and sorafenib, can block system X_c^- activity and subsequently lead to GSH depletion and ferroptosis [38]. These system X_c^- inhibitors are termed type I ferroptosis inducers. In contrast, β -mercaptoethanol-induced cystine uptake inhibits erastin-induced ferroptosis in HT-1080 cells [15]. Indeed, erastin can elicit negative feedback loop that limits ferroptosis. This feedback regulation is based on the capacity of erastin to induce SLC7A11 expression in an iron- and ROS-independent manner [15]. Mechanistically, ATF4 and p53 have been reported to promote or inhibit SLC7A11 gene transcription in ferroptosis, respectively [12, 35]. Of note, knockdown of SLC7A11 increases erastin-induced death, which indicates that another non-system X_c^- pathway may contribute to its cytotoxicity. The molecular targets of erastin in the regulation of oxidative injury during ferroptosis remain to be further explored.

GPX4

Glutathione peroxidases (GPXs) including GPX1-8 play key roles in the regulation of oxidative stress. Among them, GPX4 seems to be special in protecting cells against membrane lipid peroxidation in ferroptosis [31]. GSH-dependent GPX4 activity catalyzes the reduction of lipid hydroperoxides to alcohols or free hydrogen peroxide to water [39]. Several GPX4 inhibitors such as RSL3 and FIN56 are categorized as type II ferroptosis inducers [31]. GPX4 degradation seems to be a universal event in the induction of ferroptosis [33, 34, 40]. GPX4 inhibitors induce ferroptosis even in conditions in which the GSH pool is intact, contrasting with the effects of type I ferroptosis inducers (system X_c^- inhibitors) that cause GSH depletion [31]. Genetic depletion of GPX4 can trigger ferroptosis in an iron-, MEK-, and ROS-dependent manner in vitro or in vivo [23, 24, 31]. However, induction of ferroptosis is not the only reason for the increased tissue injury in mice in which GPX4 expression is abolished in a conditional or inducible fashion. In some cases, increased apoptosis and necroptosis also contribute to GPX4 deficiency-induced tissue injury in vivo [41-44]. Further investigation is needed to understand the function of GPX4 in various types of regulated cell death. Other GPXs such as GPX7 and GPX8 may participate in the control of ferroptosis [31]. Finally, functional relationship between GPXs and other antioxidant systems remains to be further explored.

NFE2L2

NFE2L2/NRF2 (nuclear factor, erythroid 2 like 2) is a master transcription factor that controls the cellular response to oxidative or electrophilic stresses [45]. Embarking on the search for novel transcription factor in ferroptosis, we discovered that activation of NFE2L2 by type I ferroptosis inducers such as erastin and sorafenib can inhibit ferroptosis in liver cancer cells [46]. This process is generally divided into two phases: 1) Stabilization of NFE2L2 by SQSTM1/p62 (sequestosome 1) and 2) NFE2L2-mediated expression of antioxidant proteins and detoxifying enzymes. In normal, non-stressed conditions, NFE2L2 is constantly degraded by the ubiquitination-proteasome system. In response to erastin and sorafenib, SQSTM1 (a stress-inducible and multifunctional protein in autophagy) binds KEAP1 ([kelch-like ECH-associated protein 1], an adaptor protein of Cullin-3 ubiquitin ligase) and then arrests ubiquitination of NFE2L2 and increases its protein stability [46].

NFE2L2 then translocates to the nucleus and promotes the transcription of cytoprotective genes. We identified metallothionein-1G (a cysteine residue-rich protein) as a direct NFE2L2 target gene contributing to ferroptosis resistance [47]. NFE2L2 also promotes SLC7A11 and GPX4 expression in some cases [48, 49]. These findings suggest that NFE2L2 may be a central anti-ferroptosis transcription factor.

ACSL4

ACSL (Acyl-coenzyme A synthetase long-chain) family members, including ACSL1, ACSL3, ACSL4, ACSL5, and ACSL6, are expressed at the ER and mitochondrial outer membrane, where they can synthesize acyl-coenzyme A from fatty acids. Impaired ACSL pathways had previously been implicated in the regulation of apoptosis, depending on cell type [50-52]. We found that ACSL4 plays a key role in promoting erastin-induced ferroptosis through 5-HETE-mediated lipotoxicity by accumulation of lipid intermediates. ACSL4 (but not ACSL1, ACSL3, ACSL5, and ACSL6) expression correlates with cellular sensitivity to erastin-induced ferroptosis [53]. Suppression of ACSL4 expression by RNA interference increases ferroptosis resistance in HepG2 (human hepatoblastoma) and HL-60 (acute myeloid leukemia) cells, whereas overexpression of ACSL4 by gene transfection restores ferroptosis sensitization in LNCaP (a human prostate carcinoma cell line) and K562 cells (a chronic myeloid leukemia cell line) [53]. Two independent groups confirmed that ACSL4 is a critical driver of ferroptosis, and knockout of ACSL4 using CRISPR/Cas9 technology reverses ferroptosis induced by GPX4 deficiency [54, 55]. Collectively, these studies indicate that ACSL4 is not only a biomarker of, but also a contributor to, ferroptosis.

NCOA4

Autophagy is an intracellular degradation pathway that is regulated by the autophagy-related (ATG) proteins and their posttranslational modification [56]. It has been thought that ferroptosis differs from autophagy [15], but recent experimental evidence has revealed that ferroptosis may constitute a form of autophagic cell death that can be specifically regulated by ferritinophagy [57, 58]. The role of nonselective and selective autophagy in cellular homeostasis is complex, with opposite effects on survival and death, depending on the type of stressors and context of cargos [59-61]. Ferritinophagy is the process of autophagic degradation of ferritin that requires classic ATG proteins such as ATG5 and ATG7 and the specific cargo receptor NCOA4 (nuclear receptor coactivator 4) to control cellular iron homeostasis [62]. We found that erastin stimulates the formation of autophagosomes, the double-membrane vesicles that are responsible for delivering cytoplasmic material to lysosomes [58]. More strikingly, the interaction between NCOA4 and ferritin occurs within the autophagosomes and may depend on specific autophagy [58]. Finally, selective autophagy of ferritin driven by NCOA4 increases toxic iron-induced ROS production to induce ferroptosis [58]. It remains unknown whether other forms of selective autophagy such as mitophagy (removal of mitochondria via autophagy) and lipophagy (degradation of lipids via autophagy) may similarly favor ferroptosis.

HSPs

HSPs (heat shock proteins) are highly conserved in eukaryotes and function as molecular chaperones to participate in the regulation of protein assembly, folding, export, and turn-over

[63]. HSPs can be rapidly induced under various stressful conditions such as heat shock, oxidative stress and oncogenic stress. Based on their molecular size, HSPs are divided into six distinct subfamilies: HSP100, HSP90, HSP70, HSP60, small HSP, and HSP10. Among them, HSPB1 (a member of the small HSPs) and HSPA5 (a member of HSP70 and the primary ER chaperone) are negative regulators of ferroptosis [28, 34]. Protein kinase C-mediated HSPB1 phosphorylation diminishes toxic iron-induced ROS production in ferroptosis [28], whereas HSPA5 confers protection against ferroptosis by increasing GPX4 protein stability [34]. HSF1 (heat shock transcription factor 1) plays a central role in the transcriptional activation of HSPs that also protect cells against ferroptosis [28]. Moreover, evidence is emerging that HSF1 and NFE2L2 engage in crosstalk by sharing overlapping transcriptional targets for cytoprotection in response to various stressors [64].

Pro-death function of p53 in ferroptosis

Inhibition of SLC7A11 expression

The first report of p53 induction in response to ferroptosis was published in 2015 [12]. In this study, the authors found that p53 promotes ferroptosis in fibroblasts and certain cancer cells (human breast cancer MCF7 and human osteosarcoma U2OS) due to the transrepression of SLC7A11 expression (Fig. 1). In particular, p53^{3KR}, an acetylation-defective mutant in which 3 lysine residues (in positions 117, 161 and 162) have been replaced by arginine residues, is highly effective in repressing SLC7A11A, yet does not affect the expression of other known p53 target genes involved in the regulation of cell cycle (e.g., CDKN1A/p21) or apoptosis (e.g., BAX) [12]. In contrast, p53^{4KR98} (an acetylation-defective mutant in which an additional lysine in position 98 has been replaced) is unable to reduce SLC7A11A expression [65]. Moreover, induction of ferroptosis, but not cell-cycle arrest, apoptosis, or senescence, was found to be required for the tumor suppression function of p53^{3KR} in vitro and in vivo [12]. In human cancers, wild-type p53 is degraded by high levels of the oncogenic E3 ubiquitin protein ligase MDM2. Thus, the inhibition of MDM2-dependent proteasomal degradation of p53 presents an appealing therapeutic strategy for the treatment of cancer [66]. As expected, the level of p53 is increased in MDM2^{-/-} cells. Ferroptosis also contributes to the embryonic lethality observed in MDM2^{-/-} mouse embryos, which can be reversed by administration of ferroptosis inhibitors such as ferrostatin-1 [12]. However, the other study showed that ferrostatin-1 alone cannot prevent cell death induced by MDM2 deficiency [67], indicating different mechanisms in the regulation of the MDM2-p53 network in the determination of cell death. Of note, the anti-ferroptosis activation of ferrostatin-1 and liproxstatin-1 (another widely-used ferroptosis inhibitor) are mediated through their reactivity as radical-trapping antioxidants rather than their potency as inhibitors of lipoxygenases [68]. The site of levels of p53 acetylation is determined by six different histone acetyltransferases: CREBBP/CBP (CREB binding protein), EP300/p300 (E1A binding protein P300), KAT2B/PCAF (lysine acetyltransferase 2B), KAT5/Tip60 (lysine acetyltransferase 5), KAT8/MOF (lysine acetyltransferase 8), and KAT6A/MOZ (lysine acetyltransferase 6A) [69]. The ability of these acetyltransferases to regulate ferroptosis remains unclear.

Promotion of SAT1 expression

The low-molecular-weight polyamines, including putrescine, spermidine and spermine, are implicated in the regulation of cellular growth, proliferation, and differentiation. At the molecular level, SAT1 (spermidine/Spermine N1-acetyltransferase 1) is an important regulator in polyamine metabolism through acetylating spermidine and spermine using acetyl-coenzyme A [70]. Impaired polyamine metabolism and abnormal SAT1 expression is associated with various pathological conditions, including cancer [70]. The activity of SAT1 is increased in response to various stresses, including oxidative stress, heat shock, and inflammatory stimuli. Previous studies have observed that overexpression of SAT1 results in rapid depletion of cellular spermidine and spermine, which cause significant growth inhibition and mitochondrial apoptosis [71]. Recent research studies have found that SAT1 is a transcriptional target of p53 in MCF7, U2OS, A375 (a human melanoma cell line), and H1299 cells (a human lung cancer cell line) (Fig. 1) [13]. However, only ferrostatin-1, but not other cell death inhibitors (Z-VAD-FMK, necrostatin-1, and 3-methyladenine), can inhibit ROS-induced cell death in SAT1 Tet-on cells [13]. SAT1 depletion also inhibits p53- and p53^{3KR}-induced ferroptosis [13]. Mechanistically, SAT1 has no effects on the expression and activity of SLC7A11 and GPX4 [13]. In contrast, SAT1 induction correlates with the expression levels of ALOX15 (arachidonate 15-lipoxygenase), but not ALOX5 and ALOX12 [13]. Pharmacologic inhibition of ALOX15 by PD146176 attenuates SAT1-mediated ferroptosis, indicating that ALOX15 is a downstream effector of p53-induced SAT1 expression in ferroptosis [13]. However, how cancer cells activate this p53-SAT1-ALOX15 metabolic pathway and the molecular cues behind the ferroptosis have largely remained obscure.

Promotion of GLS2 expression

Glutamine metabolism is another target for alteration in ferroptosis. Glutamine is required for the induction of ferroptosis during serum-induced injury after amino acid starvation [72]. The first step of glutamine catabolism is its conversion to glutamate, which is catalyzed by cytosolic glutamine amidotransferases or by mitochondrial glutaminases [73]. Glutamate can be further converted into α -ketoglutarate, which is an important substrate for the citric acid cycle to produce ATP in the mitochondria [73]. As a core member of the mitochondrial glutaminases, GLS2 (glutaminase 2) has been recently identified as a transcriptional target of p53 and its expression is responsible for p53-mediated oxygen consumption, mitochondrial respiration, and ATP generation in cancer cells [74]. Moreover, GLS2 expression increases cellular antioxidant function through increased GSH production in HepG2, HCT116 (a human colorectal cancer cell line), and LN-2024 (a human glioblastoma cell line) cells [74]. Based on these findings [74], GLS2 should be a negative regulator of ferroptosis. However, a recent study observed that knockdown of GLS2 inhibits (but not promotes) serum-dependent ferroptosis in fibroblasts (Fig. 1) through control of glutaminolysis [72]. Whether the specific requirement of GLS2 in erastin- or RSL3-induced ferroptosis and whether GLS2 is responsible for p53-induced ferroptosis requires further investigation.

Pro-survival function of p53 in ferroptosis

Inhibition of DPP4 activity

Colorectal cancer (CRC) develops through a series of genetic modifications, including K-RAS mutation, p53 mutation, or p53 depletion, that transform the normal colonic epithelium to an adenoma and then ultimately adenocarcinoma. The status of K-RAS mutation did not affect ferroptosis sensitivity in CRC cells [14]. In contrast, we uncovered a pro-survival function of p53 in the inhibition of ferroptosis through the regulation of DPP4 (dipeptidyl peptidase-4) localization and activity, but not DPP4 expression (Fig. 1) [14]. Knockout, knockdown, or pharmacologic inhibition of p53 increases the anticancer activity of type I ferroptosis inducer (erastin and SAS), but not type II ferroptosis inducer (RSL3 and FIN56) [14]. Remarkably, DPP4 inhibitors (vildagliptin, alogliptin, and linagliptin), but not other protease inhibitors (doxycycline, ritonavir, atazanavir, VX-222, semagacestat, Z-FA-FMK, odanacatib, ZVAD-FMK, and DAPT), completely block erastin-induced cell death in p53-deficient CRC cells [14]. DPP4 has peptidase activity and its inhibitors are a relatively new class of oral diabetes drugs. Mechanistically, p53 depletion prevents nuclear accumulation of DPP4 and then triggers membrane-associated DPP4-mediated lipid peroxidation through binding to NOX1 (NADPH oxidase 1), which finally results in ferroptosis in CRC cells [14]. These results provide evidence of a unique metabolic role for p53, linking DPP4 activity and ROS homeostasis, which may contribute to an emerging anticancer strategy for improved antitumor efficacy in precision medicine.

Promotion of CDKN1A/p21 expression

The tumor suppressor CDKN1A/p21 (cyclin dependent kinase inhibitor 1A, also known as p21^{WAF1/Cip1}) is a key mediator of p53-dependent cell cycle arrest after DNA damage [75]. CDKN1A also has pro-survival functions in response to oxidative stress by inhibiting apoptosis. A recent study reports that p53-mediated CDKN1A expression delays the onset of ferroptosis in response to subsequent cystine deprivation in cancer cells (Fig. 1) [11]. Increased p53 expression by using the MDM2 inhibitor nutlin-3 blocks system x_c^- inhibitor-induced ferroptosis in HT-1080 cells [11]. In contrast, CRISPR/Cas9 technology-mediated p53 depletion cells are sensitive to ferroptosis [11], supporting a pro-survival function of p53 in ferroptosis. This reduced sensitivity to ferroptosis in wild type p53 cells requires p53-dependent expression of CDKN1A and subsequently, the production of intracellular GSH [11]. CDKN1A mediates its activities in cell cycle arrest, primarily by binding to and inhibiting the kinase activity of the cyclin-dependent kinases (CDKs) [75]. Interestingly, CDKN1A-mediated cell cycle arrest is not enough to inhibit ferroptosis since CDK4/6 inhibitors cannot block ferroptosis [11]. Understanding the mechanism of action of CDKN1A in ferroptosis may shed new light on the role of CDKN1A in the development and treatment of cancer.

Conclusions and perspectives

It is clear that systemic or local iron overload can cause various pathological conditions and disease such as hemochromatosis [76-78]. Excess iron can be a risk for carcinogenesis and neurodegenerative diseases [79, 80]. However, the mechanism responsible for cell death in response to iron overload is not fully understood. Ferroptosis seems to be a unique form of

the cell death pathway linked to iron overload, in accordance with its name. The original study indicated that ferroptosis is different from other types of regulated cell death including apoptosis, necroptosis, and autophagy [15]. However, this notion has been challenged by recent studies. For example, erastin can induce CASP9/Caspase 9-dependent mitochondrial apoptosis in cancer cells [29]. Necroptosis-deficient cells seem more sensitive to ferroptosis [81]. In addition, the activation of autophagy appears to be a universal event among the induction of ferroptosis [57, 58]. The molecular mechanism in ferroptosis is more complex than previously thought [17, 18]. Indeed, these so-called core regulators of ferroptosis such as SLC7A11, GPX4, ACSL4, NFE2L2, and p53 have been engaged in the control of other types of regulated cell death. Unfortunately, the unique effector in the network of ferroptosis remains unknown and needs to be identified. The bidirectional control of ferroptosis by p53 through transcription-dependent and -independent mechanisms is context-dependent [11-14]. Furthermore, p53 is a multifunctional protein with multiple potential modifications and biochemical properties from the regulation by single-nucleotide polymorphism, long non-coding RNAs, and SOCS1 (suppressor of cytokine signaling 1) in ferroptosis [82-86]. Although the molecular switch between apoptosis and ferroptosis in p53-mediated cell death are poorly understood, certain Bcl-2 family members such as BID (BH3 interacting domain death agonist) and BBC3/PUMA may play a role in the regulation of the crosstalk between these two types of cell death through induction of mitochondrial metabolism or ER stress [36, 87]. A better understanding of the mechanisms by which p53 controls ferroptosis in cancer and non-cancer cells could allow us to develop new treatments for human diseases.

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Highlights

- Ferroptosis is a form of regulated cell death
- p53 plays a dual role in ferroptosis
- p53 enhances ferroptosis through targeting SLC7A11, SAT1 or GLS2
- p53 suppresses ferroptosis through targeting DPP4 or CDKN1A
- Activation of autophagy promotes ferroptosis

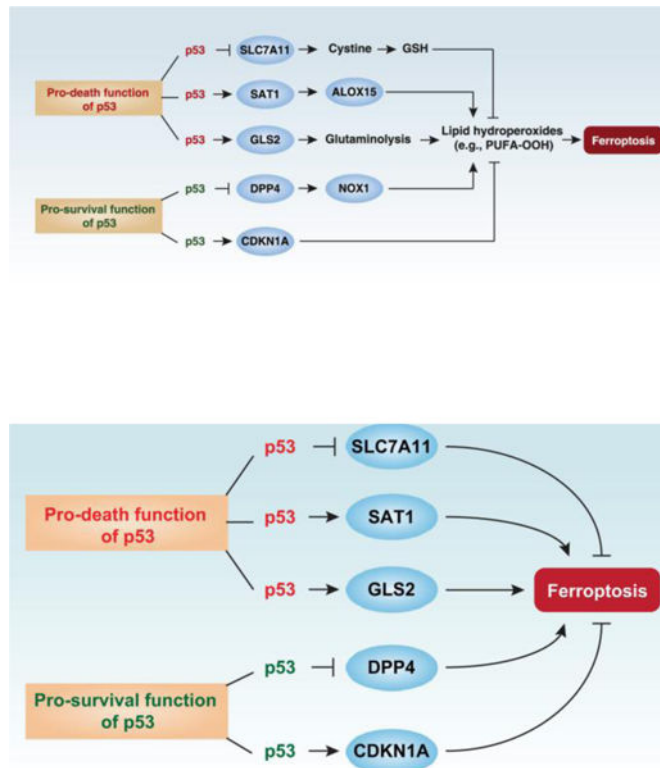


Figure 1.

The dual role of p53 in the control of ferroptosis. Ferroptosis is characterized by lipid peroxidation. p53 plays a context-dependent role in the regulation of lipid peroxidation in ferroptosis. On one hand, p53 can enhance ferroptosis through the inhibition of SLC7A11 expression or promotion of SAT1 and GLS2 expression. On the other hand, p53 could suppress ferroptosis through the inhibition of DPP4 activity or induction of CDKN1A/p21 expression.