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Review article

Inaugurating a novel adjuvant therapy in urological cancers: Ferroptosis

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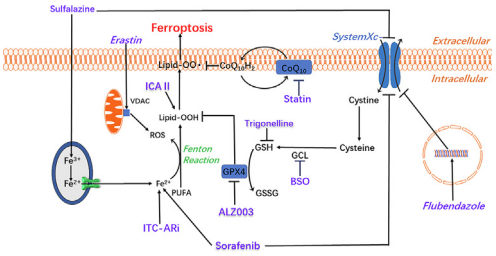
HIGHLIGHTS

- It is a detailed timeline that discovery and development of the main mechanism and participators on ferroptosis.
- The summary, nanoparticles in ferroptosis applications, was a highlight in the review. It is a significant assist to create various nanoparticles that could induce ferroptosis.
- There are plenty of logical graphics to summarize the current drugs and small-molecule inhibitors which could induce ferroptosis.

GRAPHICAL ABSTRACT



Classic and important pathways to induce ferroptosis and a number of drugs that could be used to treat cancers

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ABSTRACT

Ferroptosis, a distinctive form of programmed cell death, is involved in numerous diseases with specific characteristics, including certain cell morphology, functions, biochemistry, and genetics, that differ from other forms of programmed cell death, such as apoptosis. Many studies have explored ferroptosis and its associated mechanisms, drugs, and clinical applications in diseases such as kidney injury, stroke, ischemia-reperfusion injury, and prostate cancer. In this review, we summarize the regulatory mechanisms of some ferroptosis inducers, such as enzalutamide and erastin. These are current research focuses and have already been studied extensively. In summary, this review focuses on the use of ferroptosis induction as a therapeutic strategy for treating tumors of the urinary system.

Introduction

Urological cancers, including prostate cancer (PCa), renal cell carcinoma (RCC), and bladder cancer (BCa), have been persistent global public health issues.[1] Among men, PCa is the second most common malignancy worldwide, accounting for 15% of all cancer diagnoses. Furthermore, PCa is the fifth most common cause of cancer-related death.[2–4] Androgen deprivation therapy (ADT) is initially effective for most patients, but many patients relapse and develop castration-resistant prostate cancer (CRPC), which remains incurable.

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BCa, one of the ten most common cancer types in the world, can be divided into nonmuscle-invasive BCa and muscle-invasive BCa. Radical cystectomy and lymphadenectomy, and neoadjuvant immunotherapy, can be used to treat patients, but the efficacies of these various treatments are not ideal. Therefore, new therapeutic strategies are needed for this disease.[5]

Worldwide, RCC accounts for 5% and 3% of all diagnosed cancers in men and women, respectively, making it the sixth most frequently diagnosed cancer in men and the tenth in women.[7] However, after first- and second-line treatments for RCC, there are limited effects of therapeutic treatment, and drug resistance and severe side effects begin to appear.[6]

Therefore, it is vital for us to excogitate ancillary therapeutic strategies or alternative treatments to strengthen conventional chemotherapeutic methods. Among the current ancillary therapeutic strategies, ferroptosis induction has been used as a novel and effective treatment to enhance the curative effects against urological cancers.

In 2012, Dixon et al.[7] introduced ferroptosis as a peculiar iron-dependent type of nonapoptotic cell death, with accumulating lipid reactive oxygen species (ROS) and being induced by erastin (an oncogenic *RAS*-selective lethal compound) at the earliest phase. Ferroptosis also features iron accumulation, glutathione (GSH) deprivation, and lipid peroxidation.[8] Ferroptosis-inducing factors can affect GSH peroxidase by various direct or indirect pathways to lessen antioxidant capacity and aggrandize lipid ROS, which results in an oxidative cell death process.[9] There are four main categories of ferroptosis inducers in the present study. The first category comprises erastin, the archetype ferroptosis inducer, which induces ferroptosis by suppressing cystine/glutamate exchange transporter (system Xc^-) and voltage-dependent anion channels (VDACs) and augmenting lysosomal-associated membrane protein 2a.[10] The second category comprises *RAS*-selective lethal 3 (RSL3) and DPI7, which inhibit glutathione peroxidase 4 (GPX4). The third category includes ferroptosis inducer 56 (FIN56), which facilitates GPX4 degradation and combines with the enzyme squalene synthase, leading to the depletion of the endogenous antioxidant coenzyme Q10 (CoQ_{10}).[9] The last category comprises $FINO_2$, which triggers ferroptosis by inactivating GPX4 and the first oxidation reaction of labile iron.[11]

Mechanisms of ferroptosis

Ferroptosis is another form of regulated cell death (RCD) characterized by GSH deprivation and severe iron-dependent lipid peroxidation in a Fenton-like manner, resulting in ROS production and cell death.[12,13] In the Fenton reaction, polyunsaturated fatty acids (PUFAs) are oxidized by H_2O_2 and Fe^{2+} to release ROS and phospholipid hydroperoxide (PLOOH). This is oxidized into radicals in the cell membrane and then triggers ferroptosis.[14,15] Oxidative stress raises the expression levels of the system Xc^-[16] and promotes cystine uptake and its reduction to cysteine. GSH, the most abundant intracellular antioxidant, comprises cysteine (limiting the rate of synthesizing GSH), glycine, and glutamate.[17,18] GSH eliminates ROS by its antioxidant function as a cofactor to multiple antioxidant proteins, such as GSH peroxidases (GPXs) and glutaredoxins (GRXs).[19]

Decreased intracellular GSH and suppressed GPX4 levels facilitate the generation of lipid peroxides by the GPX4-catalyzed reaction, and lipid-OOH induces a plentiful accumulation of ROS and can trigger ferroptosis.[20,21] GPX4, which reduces lipid peroxides to alcohols, suppresses the accumulation of lipid peroxides, and works as an endogenous suppressant of ferroptosis.[11,15,22] There are three main pathways involved in ferroptosis modulation: the GPX4, GTP cyclohydrolase-1-(GCH1-) tetrahydrobiopterin (BH4), and nicotinamide adenine dinucleotide phosphate (NADPH)-FSP1-CoQ_{10} pathways.[23] A targeted therapy that modulates cystine uptake could cause cysteine depletion and lead to cancer cell ferroptosis.[7,24] In addition, the flavoprotein FSP1, the current name of apoptosis-inducing factor mitochondria-associated 2 (AIFM2), can repress ferroptosis through the mediation activity of CoQ_{10} and has been shown to be parallel to the PLOOH-reducing enzyme GPX4.[25,26] Finally, BH4 expression is upregulated by GCH1, and BH4 can possibly act as a direct antioxidant or facilitate the synthesis of CoQ_{10} to inhibit lipid peroxidation and ferroptosis.[27] In addition to the previously mentioned mechanisms of ferroptosis-like cell death, further significant research has been performed and is depicted in the ferroptosis timeline figure [Figure 1].

Ferroptosis induction may become a promising therapeutic strategy for urological cancers by acting as a monotherapy or as an additional treatment, such as cooperating with anti-androgens in PCa.[28] Thus, there is an urgent need to study the mechanisms of ferroptosis inducers (FINs) through basic science research and clinical applications.

Prostate

Enzalutamide

Androgen-targeted therapies (ATTs), usually using the androgen receptor (AR) antagonist enzalutamide, change lipid supply and remodel lipids, expounding the mechanism of multidrug tolerance and ferroptosis hypersensitivity of PCa cells.[29] In addition, when compared with enzalutamide, erastin, or RSL3 alone, a combination treatment of enzalutamide with erastin or RSL3 can more effectively kill PCa cells.[28]

It was suggested that enzalutamide might function as a FIN through three mechanisms: First, enzalutamide synergizes with RSL3 and erastin by downregulating the expression levels of heat shock proteins (HSPs). HSPs can act as negative ferroptosis regulators, such as HSPB1 and HSPA5. Increased HSPB1 levels may inhibit ferroptosis mediation by erastin, whereas rising HSPA5 expression can inhibit ferroptosis induction by repressing the GPX4 protein degradation process.[30,31] Moreover, enzalutamide can partly prevent the nuclear translocation of AR and attenuate the stabilization of AR-mediated by HSPs.[32,33] Second, FINs may enhance the efficacy of anti-androgens through their separate programmed cell death approaches, and the combined therapeutic effect is stronger than those of the individual treatments. Enzalutamide has been shown to induce apoptosis through increased Bax and decreased Bcl-2 expression levels.[33] Finally, enzalutamide can lead to lipid remodeling and PUFA enrichment in PCa, and then excess PUFAs can be oxidized into radicals to impair the cell membrane and trigger ferroptosis.

In the early phase of PCa, androgen stimulates cell proliferation, and the intracellular lipid biomass is derived from *de novo* lipogenesis (DNL) of cholesterol and FAs together with lipid uptake. Enzalutamide treatment can reduce oxidative phosphorylation and decrease multifold pivotal enzymes involved in *de novo* FA and cholesterol biosynthesis. In addition, enzalutamide use leads to a decrease in DNL and an increase in lipid uptake through cargo-selective transport mechanisms: lipid transporters, such as LDLR and SCARB1, and nonselective uptake mechanisms, such as tunneling nanotubes, TNTs, macropinocytosis, and MPC. However, saturated FAs are excluded from lipid uptake, so intracellular saturated FAs and PUFAs can be upregulated by other intake mechanisms or transporters. In addition, enzalutamide induces lipid sources mainly to take up exogenous lipids through diverse approaches. Therapy brings about lipid remodeling consisting of the mobilization of storage lipids (cholesterol esters [CEs] and triacylglycerols [TAGs]) by lipases, enhancements of entire dominating phospholipid classes, and beneficiation of PUFAs, which increases membrane fluidity, GPX4 dependence, and lipid peroxidation.[29]

It was demonstrated that vast accumulation of lipids and multidrug tolerance was strongly associated with inactive cell proliferation and reduced bioenergetic pathways. The lipid biomass is enhanced by the lipid uptake process through cargo-selective mechanisms (lipid transporters) and through nonselective cargo mechanisms like micropinocytosis and tunneling nanotubes. However, *de novo* lipid synthesis is reduced to a great extent. By using storage lipids, all dominating phospholipid species are widely remodeled by enzalutamide to increase acyl chain length and desaturation of membrane lipids.[29] Enzalutamide increases PUFA levels in phospholipids to enhance membrane fluidity,

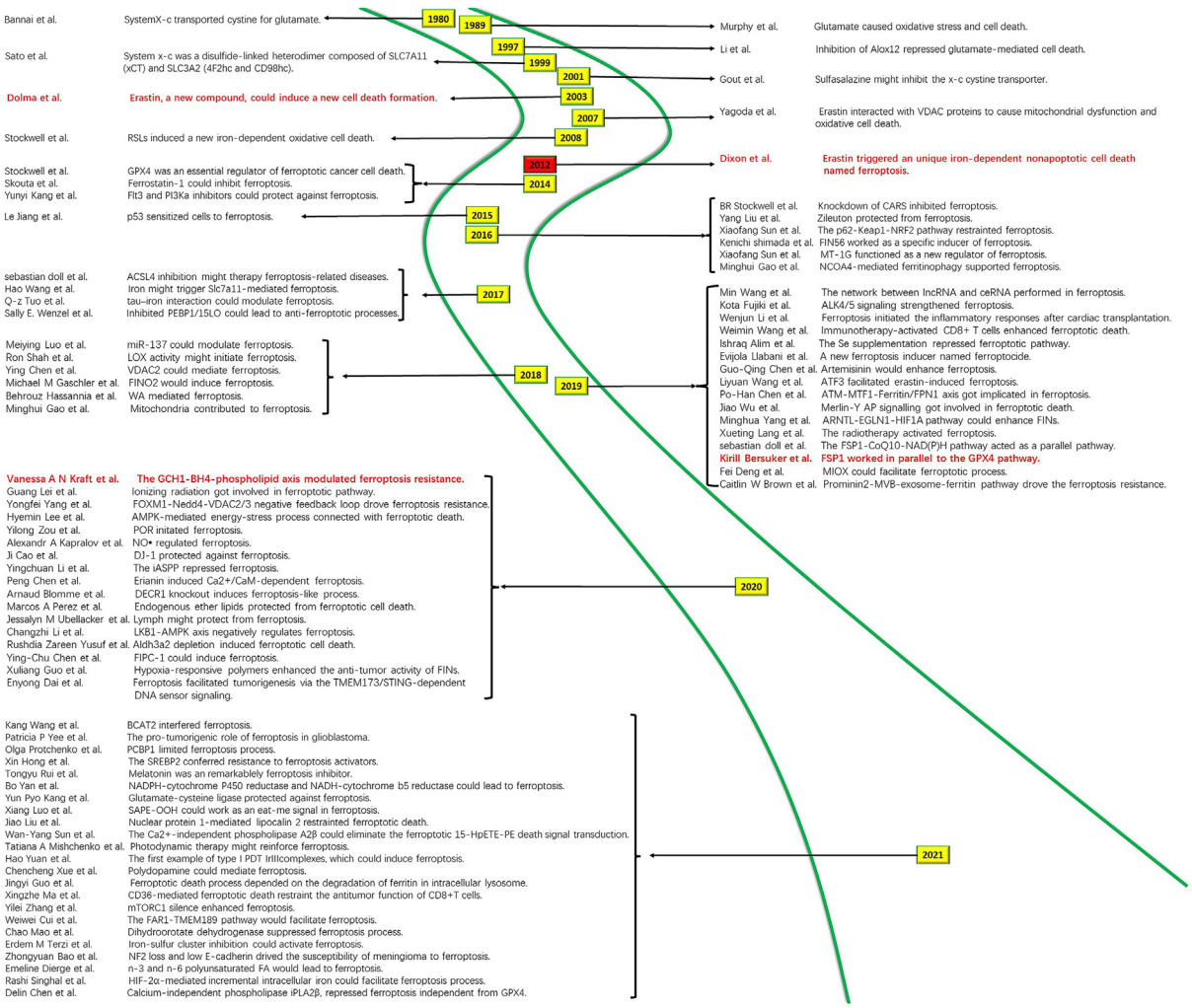

Figure 1. The history of ferroptosis research.

which promotes less sensitivity to chemotherapy reagents (multidrug tolerance),[34] augments cellular mobility along with permeability, and strengthens membrane-oriented biological reactions, including transporters, receptors, vesicle formation, and membrane fusion.[35] There would be a metabolic vulnerability for incremental PUFA capacity of phospholipids[36]: lipid peroxidation leading to oxidative damage by ROS and reactive nitrogen species (RNS). Enzalutamide results in PUFA enrichment in lipid remodeling, and thus the surplus of accumulated PUFAs is oxidized into radicals to impair the cell membrane and trigger ferroptosis.[29]

Statins

Statins, such as fluvastatin, lovastatin, and simvastatin, are classical drugs that promote ferroptosis. The pharmacologic role of statins is to induce a rate-limiting enzyme to suppress 3-hydroxy-3-methylglutaryl-coenzyme A (CoA) reductase (HMGCR) in the synthesis pathway for CoQ and GPX4 derived from acetyl-CoA.[37,38] With the catalysis of HMGCR, HMG-CoA, the downstream product of acetyl-CoA, is converted to mevalonate and the subsequent isopentyl pyrophosphate (IPP). Thereafter, there are two diverse pathways [Figure 2]: one synthesis pathway is associated with GPX4, which can be synthesized by the sec-t-RNA that stems from IPP; the other synthesis pathway involves CoQ_{10}, and geranyl pyrophosphate, the product of IPP, can synthesize CoQ_{10} through the previous synthetics farnesyl-PP and geranylgeranyl-PP.[39,40] When HMGCR is inhibited by statins, GPX4 and CoQ_{10} levels are correspondingly reduced. GPX4 can inhibit lipid-OOH generation, and lipid-OO production can be suppressed by $CoQH_2$, which is the product of the reduction of CoQ_{10} by GAD(P)H. The mechanism of ferroptosis is involved in the impairment of the cell membrane by lipid-OO, and thus statins may induce ferroptotic cell death in PCa cells.[40]

BSO and ITC-ARis

The synthesis of GSH involves two consecutive reactions that are catalyzed by glutamate cysteine ligase (GCL) and GSH synthetase. Buthionine sulfoximine (BSO) inhibits the activity of γ-GCL, which functions as the rate-limiting enzyme in the synthesis of GSH [Figure 2].[41] Thus, BSO treatment can break down GSH-dependent cellular defense mechanisms that prevent oxidative damage and ferroptosis induction. GSH acts as the reducing equivalent of GSH peroxidase. GPX4 is a vital regulatory protein of the ferroptosis-mediated process and is the sole known phospholipid peroxidase that catalyzes the conversion between lipid hydroperoxide and unreactive lipid alcohol. Decreasing GSH attenuates lipid damage repair, accumulates lipid hydroperoxide, and finally leads to ferroptosis-mediated processes.[42]

Isothiocyanate (ITC)-containing AR antagonists (ITC-ARis) are synthesized by the incorporation of an ITC moiety and an ARi. Therefore, ITC-ARi can inhibit AR and possesses diverse anti-PCa activities derived from ITC, including a decrease in both AR and AR-V7 levels.[42] Through cysteine thiocarbamoylation of Kelch-like ECH-associated protein 1

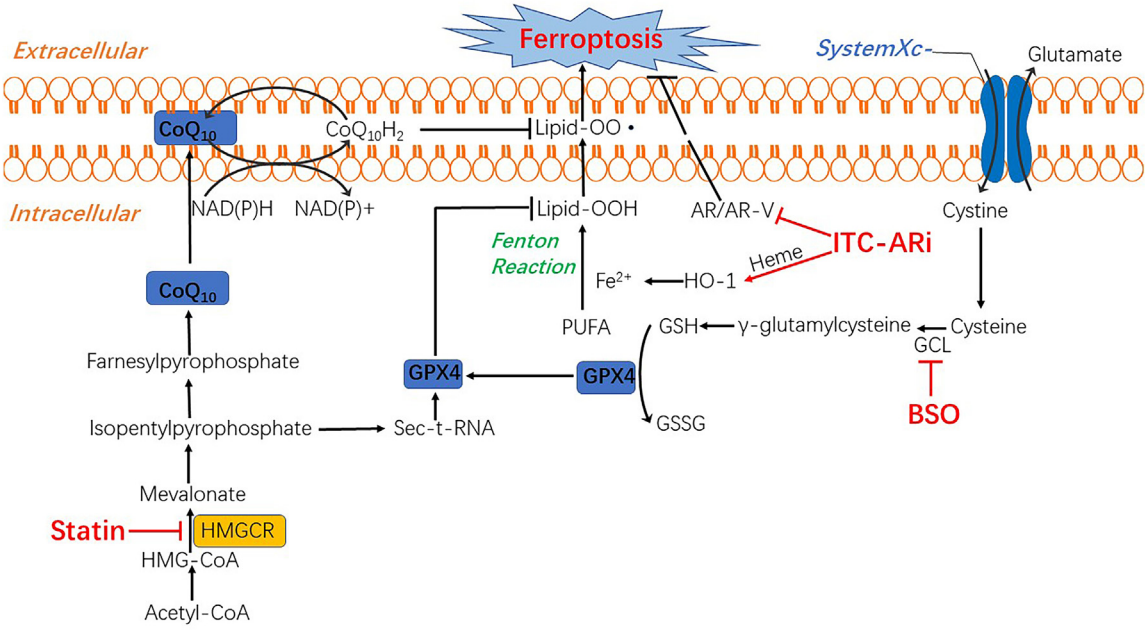

Figure 2. Mechanisms by which statins can induce ferroptosis and the synergy of BSO and ITC-ARi13.CoQ: Ubiquinone; GSH: Glutathione; PUFAs: Polyunsaturated fatty acids; PLOOH: Phospholipid hydroperoxide.

(Keap1), ITCs inhibit the ubiquitination of nuclear factor erythroid-2 related factor 2 (Nrf2) by Cul3 E3 ligase, which can heterodimerize with sMaf, induce Nrf2 translocation into the nucleus, and trigger transcription of antioxidant genes that encode HO-1, GSH synthesis enzymes, and the Xc^- system.[43]

The synergy between BSO and ITC-ARi 13 can be seen in several ways, including inhibiting colony formation and PCa, suppressing AR/AR-V, and boosting HO-1, together with triggering ferroptosis. Furthermore, BSO may enhance the anti-PCa function of ITC-ARi 13 in numerous ways. First, the GSH conjugate impedes ITC binding to cellular targets and facilitates ITC export by efflux pumps in the cell membrane.[44] BSO-induced GSH deficiency can increase cellular drug levels and promote ITC-ARi 12b or ITC-ARi 13 to target proteins, like FL AR and Keap1, which induce AR antagonism and HO-1. Second, HO-1 is upregulated by a GSH deficiency. Through HO-1 catalysis, heme is decomposed into biliverdin, carbon monoxide, and Fe^{2+}, which facilitate ferroptosis through the Fenton reaction.[45] Third, BSO can block GSH-dependent cellular pathways that prevent oxidative damage and ferroptosis. GSH is the reducing equivalent of GSH peroxidase. Fourth, Nrf2-induced GSH synthesis can be repressed by BSO by suppressing γ-GCL. Simultaneously, BSO inhibits NAC-induced GSH synthesis. Therefore, BSO could counteract GSH synthesis to facilitate ferroptosis induction.[42]

Erastin

Erastin can trigger ferroptosis through multiple pathways [Figure 3]: activating VDAC, inhibiting the cystine-glutamate transport of system Xc^-, and activating tumor protein P53 (p53). First, by binding the VDAC protein, erastin leads to mitochondrial oxidative injury, which induces ferroptosis.[46] VDAC proteins control the flow of metabolites and respiratory substrates through the outer mitochondrial membrane. VDACs can be blocked by cytoplasmic free tubulin, which can be prevented and reversed by erastin treatment to keep VDAC open.[47] This leads to two independent but simultaneous processes. First, both increasing oxidative phosphorylation and adenosine triphosphate (ATP) synthesis and decreasing glycolysis to reverse the Warburg effect. Second, increasing ROS levels to induce oxidative stress.[48,49] The anti-Warburg effect can kill cancer cells or reduce their proliferation.[50] Furthermore, erastin can hyperpolarize mitochondria and induce subsequent depolarization quickly in cancer cells, causing mitochondrial dysfunction.[50] Therefore, erastin could induce ferroptosis by opening VDACs, leading to three dominant biological processes: increasing mitochondrial metabolism (enhanced $\Delta\psi$), decreasing glycolysis and increasing ROS levels.[50,51] Then, by triggering the phosphorylation of AMP-activated protein kinase (AMPK) and the subsequent phosphorylation of Beclin1 (BECN1), erastin can form the BECN1-SLC7A11 complex to suppress system Xc^- and inhibit the import of extracellular cystine, which leads to a subsequent intracellular decrease in GSH levels.[52] Then, the decrease in GSH leads to reduced GPX4, which influences redox homeostasis and leads to the accumulation of lipid-OOH, causing ferroptosis. Finally, activated p53 significantly reduces the expression levels of SLC7A11 in cells to generate ROS, which subsequently activates the downstream targets of p53. In turn, this process creates a feedback loop and augments the ferroptosis induction effects of erastin.[53]

Flubendazole

In the present reports, flubendazole is described as a neoteric antitumor drug that efficaciously inhibits cell propagation and facilitates apoptosis in CRPC cells by suppressing the cell cycle and inducing ferroptosis [Figure 3]. Moreover, flubendazole reportedly has a neoteric application in neoadjuvant chemotherapy and could be used for synergistic antiproliferative effects with 5-fluorouracil.[54]

Under conditions of low or basal ROS levels, p53 suppresses the accumulation of fatal levels of ROS in cells while repairing moderate oxidative damage and facilitating survival. However, when it encounters higher or toxic ROS levels, such as the levels in cancer cells, p53 instead facilitates the death of advanced cancer cells by ferroptosis.[55] Flubendazole is a novel p53 activator that triggers ferroptosis through the p53/SLC7A11/GPX4 pathway in CRPC cells. Flubendazole treatment results in p53 overexpression, which downregulates SLC7A11 transcription, thus restraining the activity of the system Xc^-. This then lessens cystine by interfering with its uptake and reduction to cysteine, ultimately reducing GPX4 levels.[54,56] Because GPX4 is downregulated, ferroptosis is induced in CRPC cells. Current reports have demonstrated that 5-fluorouracil therapy, one of the classic chemotherapy agents, treats hormone-refractory PCa and leads to p53 assembly and cell death

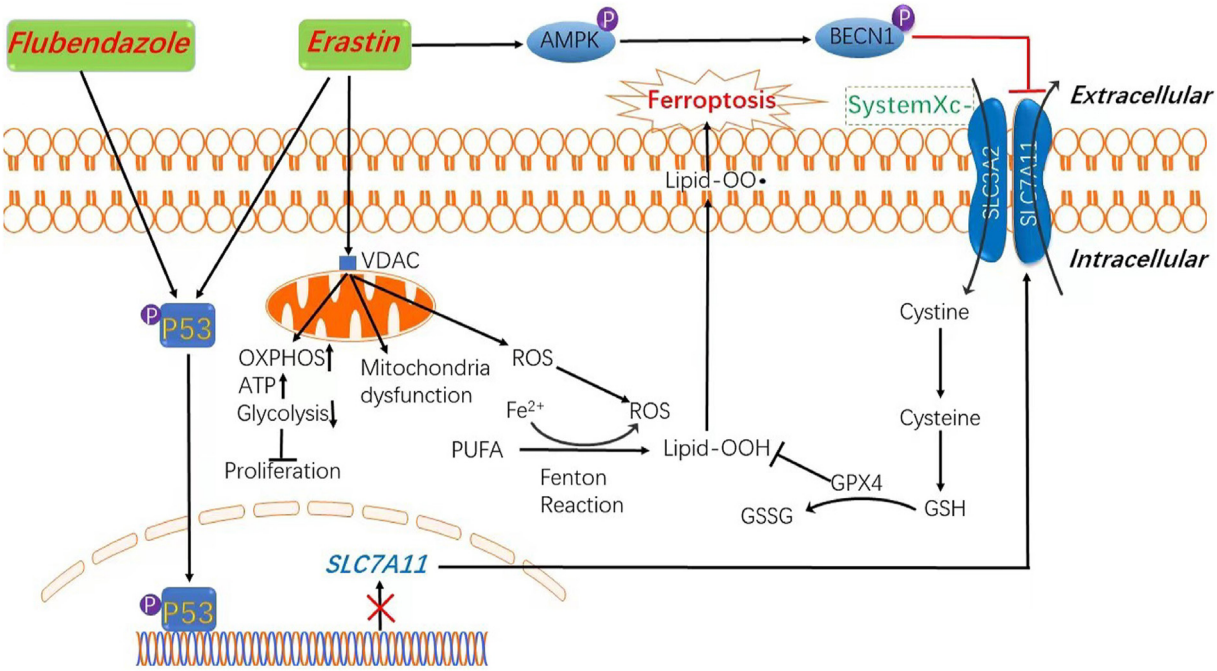

Figure 3. Ferroptosis induction-associated pathways of erastin and flubendazole. The three pathways by which erastin can induce ferroptosis are as follows: activating VDAC, inhibiting the cystine-glutamate transport of system Xc^-, and activating p53. Flubendazole can activate p53 to trigger ferroptosis.GSH: Glutathione; ROS: Reactive oxygen species; PUFAs: Polyunsaturated fatty acids; VDACs: Voltage-dependent anion channels; PLOOH: Phospholipid hydroperoxide.

in colon cancer cells. This suggests that 5-fluorouracil plays an antineoplastic role in part through the p53 signaling pathway. In addition, it has been demonstrated that the synergistic antiproliferative roles of flubendazole can be used with 5-fluorouracil *in vitro* and *in vivo*. Furthermore, a lower concentration of flubendazole can exert substantial repressive activity in CRPC cells.[54]

ALZ003

ALZ003, a curcumin analog, leads to F-box/LRR-repeat protein 2 (FBXL2)-mediated AR ubiquitination, which downregulates AR expression.[57] Androgens binding to AR can activate AMPK, the metabolic regulator AMP-activated kinase, and expedite oxidative phosphorylation.[58] Subsequently, phosphorylated AMPK acts as a stimulator to increase glucose transporter type 1 (GLUT1) levels, which significantly augments reduced GSH. Therefore, AMPK and GLUT1 can be downregulated by decreased AR, and GSH is consequently reduced.[59] ALZ003 can decrease AR, downregulate GPX4 expression, facilitate lipid peroxidation, and cause ferroptotic cell death by reducing AR-regulated GPX4 expression [Figure 4]. In addition, ALZ003 also induces apoptosis by modulating caspase activity.[57]

DECR1

2,4-dienoyl CoA Reductase 1 (DECR1) acts as a *de novo* direct androgen-repressed gene, and thus androgen (5α-dihydrotestosterone) evidently decreases DECR1 expression in PCa cells at both the mRNA and protein levels. DECR1, robustly overexpressed in PCa tissues, encodes the rate-limiting enzyme in an auxiliary pathway for PUFA β-oxidation, selectively promotes β-oxidation of PUFAs, and promotes the proliferation and migration of PCa cells, including treatment-resistant cell lines. Thus, DECR1 has been a promising novel therapeutic target for treating PCa.[60]

In addition to the *de novo* synthesis of FAs, extracellular FAs, such as those in the circulation and stromal adipocytes, are the major contributor to lipid synthesis in PCa cells.[61–63] In these cells, fatty acid β-oxidation (FAO) is the major bioenergetic pathway and a promising novel therapeutic target. The dominant metabolic reaction occurs in the mitochondria, where FAs are converted into acetyl-CoA and undergo the β-oxidation reaction. Then, acetyl-CoA participates in the tricarboxylic acid cycle (TCA) and generates ATP and nicotinamide adenine dinucleotide (NADH) to supply the cell with energy.

Long-chain acyl-CoA species are converted to the corresponding long-chain acylcarnitine species by carnitine palmitoyl transferase 1 (CPT1), then FAs subsequently enter the mitochondria. There, they undergo a dehydrogenation reaction through acyl-CoA dehydrogenase (ACAD) to yield trans-2-enoyl-CoA, the only molecule that the following enzymes can catalyze in the downstream β-oxidation reaction.[60] Different from saturated FAs, all unsaturated FAs whose double bonds are derived from even sites require three auxiliary enzymes, DECR1, enoyl CoA isomerase (ECI1), and dienoyl CoA isomerase (ECH1). These enzymes produce intermediates that suit the normal β-oxidation pathway,[64] as do some unsaturated FAs whose double bonds are derived from odd sites. FAs with unsaturated bonds either on an odd carbon or in the cis-configuration produce enoyl-CoA intermediates that the subsequent β-oxidation pathway enzymes cannot directly catalyze. They can be converted to trans-2-enoyl-CoA by three downstream auxiliary enzymes: DECR1, ECI1, and ECH1. The transformation between 2-trans,4-cis-dienoyl or 2-trans,4-trans-dienoyl-CoA, and 3-trans-enoyl-CoA is catalyzed by DECR1. In the mitochondrial β-oxidation pathway, DECR1 catalyzes the rate-limiting portion and supplies reducing equivalents to enhance the ATP yield.[60,65] An integrated β-oxidation cycle produces the first acetyl-CoA to generate ATP through the TCA cycle, whereas fatty-acyl-CoA loses two carbons. The shortened fatty-acyl-CoA is the same reactant beginning with the ACADs to produce trans-2-enoyl-CoA either directly or through the ancillary enzymes with the double bonds. This process is not complete until all carbons of the FA are converted to acetyl-CoA.[60]

DECR1 knockdown increases PUFA levels and the levels of certain lipids, such as phosphatidylethanolamine (PE) and phosphatidylinositol (PI) phospholipid species. DECR1 knockdown also dramatically upregulates mitochondrial oxidative stress, especially lipid peroxidation. In parallel with monounsaturated fatty acids (MUFAs), PUFAs heighten free radical production and lipid peroxide accumulation from strong susceptibility to peroxidation.[66] Intracellular overaccumulation

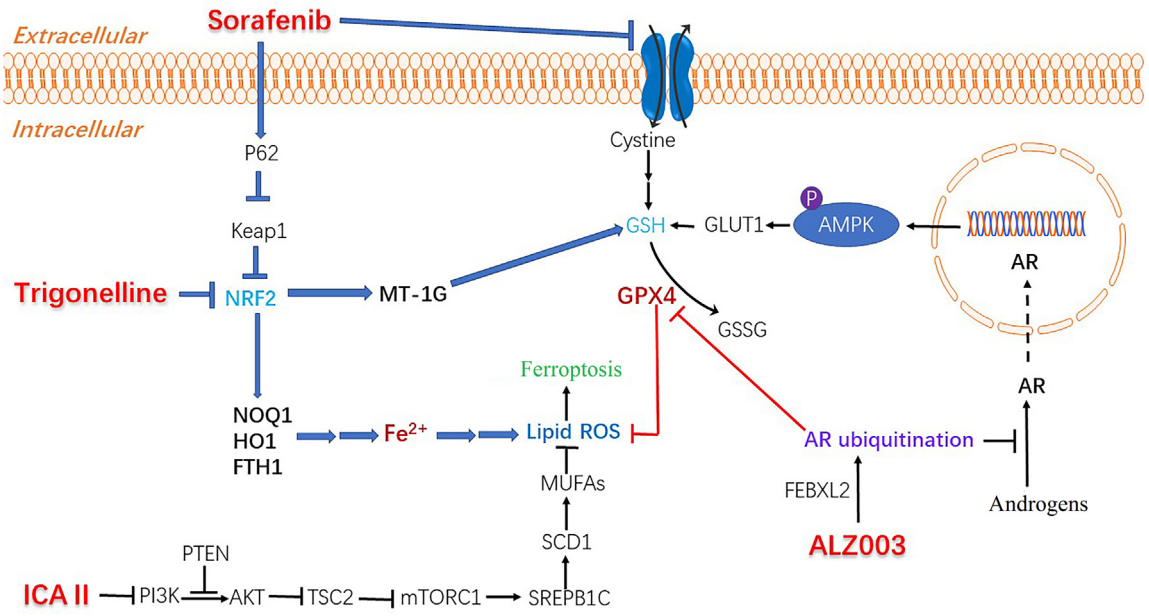

Figure 4. Signaling pathways by which sorafenib and ALZ003 can induce ferroptosis. Sorafenib induces ferroptotic cell death through two mechanisms: inhibiting system Xc^- and activating the p62-Keap1-Nrf2 pathway. In addition, trigonelline can enhance sorafenib-mediated ferroptosis by inhibiting Nrf2. ALZ003 leads to ferroptotic cell death through FBXL2-mediated AR ubiquitination. ICA II activates ferroptosis–regulatory pathways, including the PI3K-AKT-mTORC1 pathway, and the subsequent SREBP1/SCD1-mediated lipogenesis process.GSH: Glutathione; AR: Androgen receptor; AR: Androgen receptor; Keap1: Kelch-like ECH-associated protein 1; Keap1: Kelch-like ECH-associated protein 1; NQO1: Quinone oxidoreductase 1; FTH1: Ferritin heavy chain 1; PI3K: Phosphatidylinositol 3-kinase; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; mTORC1: Mechanistic target of rapamycin C1; SCD1: Stearoyl-CoA desaturase-1; ICA II: Icariside II; AMPK: AMP-activated protein kinase, Nrf2: Nuclear factor erythroid-2 related factor 2.

of lipid peroxides can lead to ferroptosis. In addition, ferroptotic cell death-corresponding inhibitors like deferoxamine and ferrostatin and relevant inducers such as ML210, erastin, and FIN56, respectively facilitate and suppress the function of DECR1 in ferroptosis in PCa cells.[67]

Previous therapeutic drug strategies have aimed to suppress CPT1. However, it is currently believed that DECR1 should be targeted rather than CPT1 for PCa treatment. Unlike CPT1 suppressants that can inhibit the β-oxidation reaction of all long FA species, including PUFAs, MUFAs, and saturated FAs, DECR1 targets PUFAs.[60]

Bicalutamide-iron combination

Bicalutamide and other anti-androgen drugs enhance the beneficial effects of iron, whereas iron toxicity can impair PCa cell growth.[68]

Many cell types suffer from lipid damage and ferroptotic cell death upon exposure to iron. In contrast, iron can enhance oxidative stress and ferroptosis in combination with bicalutamide compared with iron alone. The high iron sensitivity of PCa cells mainly depends on large amounts of free iron along with the oxidation state. This is in accordance with mitochondrial metabolic activity and depends on androgen signaling,[69,70] so androgen metabolic activity may be parallel to iron sensitivity. Furthermore, PCa cells with active androgen signaling could be intrinsically sensitive to iron. This could be related to castration-resistant tumors with active AR signaling. Simultaneously, when the androgen signaling pathway of castration-resistant tumors is inactive or absent, they become iron-sensitive when the iron is in combination with anti-androgens.[68]

PCa cell proliferation is downregulated by the bicalutamide-iron combination, which is much more effective than any single therapy. Both aldo-keto reductase 1C (AKR1C) 1 and AKR1C2, upregulated by bicalutamide, belong to the AKR1C superfamily. These are steroid hormone-transforming enzymes that function as reductases in the physiological environment when the cellular biological levels of NAD(P)H inhibit their oxidative activity.[71] In prostate cells, AKR1C1 and AKR1C2 both catalyze the reduction of 5α-dihydrotestosterone to 3α-diol or 3β-diol to inhibit the activity of 5α-dihydrotestosterone. In addition, 3α-diol is characterized by low AR affinity as a steroid hormone, but 3β-diol acts as a ligand of estrogen receptor β with a high affinity that suppresses PCa cell proliferation.[72,73] Thus, bicalutamide can upregulate AKR1Cs to weaken PCa cell viability. AKR1Cs, acting as reductases, can be induced by ROS to form an antioxidation product.[74] The pro-oxidant iron contributes to the consumption and antioxidant capacity of GSH to minimize toxicity. Therefore, high levels of AKR1Cs, regulated by anti-androgens, can enhance the affinity with NADP + to act as oxidases to produce oxidative lesions.[68]

Inhibiting Pannexin 2 or Nrf2

The existing evidence shows that Pannexin 2 (PANX2) functions as a latent marker and indicates the progression of prostate tumors.[75] Nrf2, a crucial gene regulating oxidative stress in tumorigenesis, can act in a pro-tumorigenic manner by inducing its downstream targets in PCa cells.[76–79] Genes containing antioxidant response elements (AREs) in their promoters are primarily modulated by Nrf2.[80] Under oxidative stress conditions, PANX2 is enriched. Furthermore, PANX2 enhances the malignant phenotypes of PCa cells and upregulates the levels of ferrous iron and MDA. In PCa cells, overexpressed PANX2 activates Nrf2 to trigger AREs, inhibiting ferroptotic cell death and facilitating the malignant characteristics of PCa cells, such as proliferation, migration, and invasiveness.[75] Therefore, inhibitors of PANX2, such as carbenoxolone, probenecid, staurosporine, IL-1β, and IFNγ, may regulate Nrf2, making this a potential therapeutic approach for treating PCa. In addition, suppressors of Nrf2, like puerarin, may generate a similar therapeutic effect in prostate tumors.[81–84]

Kidney

FH inactivation and iron chelators

Hereditary leiomyomatosis and renal cell cancer (HLRCC), a hereditary cancer, is triggered by the loss-of-function mutations of the Krebs cycle enzyme fumarate hydratase (FH) and is often incurable after it evolves into renal carcinoma with type 2 papillary morphology.

FH inactivation can make HLRCC cells tumorigenic, and HLRCC cells would die from ferroptosis. FH inactivation ($FH^{-/-}$) was shown to be sensitive to inducers of ferroptosis because of dysfunctional GPX4. In $FH^{-/-}$ cells, the C93 residue of GPX4 can be post-translationally modified by fumarates to suppress GPX4 activity. However, FH inactivation might trigger Nrf2 as well.[85] The intracellular labile iron pool can be coordinately downregulated by Nrf2 through the upregulation of ferritin and ferroportin which can export and stockpile iron, respectively.[86] Furthermore, Nrf2 can upregulate GPX4 levels and facilitate the expression of GSH. Therefore, Nrf2 may act in an opposing manner to the decreased GPX4, where Nrf2 and GPX4 can form a balance and make the FH-inactivated cells vulnerable.[85] In current studies, iron chelators, such as Triapine, can downregulate ferritin and enhance ferroptotic cell death in HLRCC cells.[87]

Erastin or BSO

Clear cell RCC (ccRCC), the most common type of RCC, is mainly characterized by metabolic reprogramming and mutations in the Von Hippel–Lindau (VHL) gene. VHL-inactivation could reportedly render ccRCC cells more sensitive to ferroptosis inducers, and inhibition of GSH synthesis or GSH peroxidases could suppress ccRCC cell proliferation without affecting the nonmalignant renal epithelial cells. From the current experiments, ccRCC cells could be suppressed by erastin or BSO through inhibition of GSH biosynthesis to induce ferroptosis, whereas the CPT1 inhibitors etomoxir or oligomycine can inhibit β-oxidation in the mitochondria to enhance ferroptosis induction.[88]

HIF-HILPDA pathway

Hypoxia-inducible factors (HIF)-2α can activate hypoxia-inducible lipid droplet-associated protein (HILPDA) in renal clear cell carcinomas (CCCs) via the HIF-HILPDA pathway. HILPDA can then selectively upregulate the expression of most PUFA-PE/ePEs and PUFA-TAGs, with effects on SFA/MUFA-lipids. Moreover, G0 switch 2 (G0S2)-overexpression increases the levels of whole phospholipids and TAGs.[89] The elevated PUFA-lipid levels are vital to impact factors that can enhance ferroptosis sensitivity in CCCs.[90]

Porous yolk–shell Fe/Fe_3O_4 nanoparticles

Recently, a new therapeutic strategy has been developed that uses the porous yolk–shell nanoparticles (PYSNPs) of Fe/Fe_3O_4 to induce zero-valent iron-catalyzed Fenton reactions in HepG2 cells. In a neutral physiological environment, the PYSNPs of Fe/Fe_3O_4 can stabilize zero-valent iron (Fe^0) and prevent it from being oxidized. However, in a weakly acidic tumor microenvironment, it will release Fe^0.[91] The Fenton reaction of Fe^0 can then convert hydrogen peroxide (H_2O_2) into ROS and be catalyzed by Fe^{2+}.[92] In addition, iron accumulation inactivates GPX4, which subsequently induces ferroptosis.[12,93] Both ROS and ferroptosis induction can inhibit HepG2 cells. Moreover, there are minimal side effects of Fe_3O_4 fragments in kidneys. In addition, through modification with iRGD (a tumor-targeting and penetrating peptide), the iRGD-PYSNPs-2 can suppress HepG2 cells more effectively.[91]

The NCOA4 gene

In ccRCC tumor tissues, nuclear receptor coactivator 4 (*NCOA4*) levels are downregulated. *NCOA4* can facilitate ferroptosis, whereas *NCOA4* depletion can suppress ferroptotic cell death by decreasing the intracellular free iron levels, GSH production, and ROS.[94] Mechanistically, *NCOA4* acts as an autophagosome component in the ferritinophagy procedure.[95] Ferritin heavy chain 1 (FTH1) can characteristically bind *NCOA4* and combine with lysosomes through nascent autophagosomes to promote ferroptosis. In addition, *NCOA4* deficiency can affect the IFN-γ signaling pathway, which acts as a dominant effector of activated T cells and facilitates ferroptotic cell death in the immunotherapy process.[96]

SUV39H1 deficiency inducing ferroptosis

Chaetocin acts as an inhibitor of the suppressor of variegation 3–9 homolog 1 (SUV39H1), which encodes a histone H3 lysine 9 methyltransferase. This enzyme can tri-methylate histone 3 lysine 9 (H3K9me3) and is responsible for heterochromatin formation and transcriptional repression of target genes. Chaetocin can induce the H3K9me3 status of the dipeptidyl-peptidase-4 (DPP4) gene promoter and increase its expression levels. By combining with NADPH oxidase 1 (NOX1), DPP4 can produce the DPP4-NOX1 complex to boost intracellular lipid peroxidation and induce ferroptosis. Overall, inhibiting SUV39H1 and inducing ferroptosis may become a therapeutic strategy for treating ccRCC in the future.[97]

Bladder

Quinazolinyl-arylurea derivatives

Quinazolinyl-arylurea derivatives can induce three different cell death mechanisms, including autophagy, apoptosis, and ferroptosis, depending on the concentration and incubation time. Apoptosis will occur with lower concentrations and shorter incubation times. With higher concentrations and longer incubation times, ferroptosis will occur through the induction of the Sxc/GPX4/ROS signaling pathway. Autophagy can also occur through the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR)/Unc-51-like kinase 1 (ULK1) pathways. Cell death from the quinazolinyl-arylurea derivatives specifically occurs from the production of ROS and reduction of the mitochondrial membrane potential. In summary, quinazolinyl-arylurea derivatives may become a promising treatment for BCa.[98]

AuNRs&IONs@Gel

In recent studies, a triple-therapy strategy was effective against BCa and its recurrence via intravesical instillation. AuNRs&IONs@Gel, a gel system, could lead to the target delivering a joint treatment of ferroptotic death, immune therapy, and photothermal via intravesical instillation. This system includes a gel platform, iron oxide nanoparticles (IONs), and gold nanorods (AuNRs). The delivery platform can bind collagen molecules in cancer cells via dextran aldehyde. Under imaging-guided near-infrared radiation, AuNRs can implement photothermal therapy. Meanwhile, IONs are absorbed and induce ferroptosis in BCa cells by augmenting the labile iron pool (LIP). In addition, by repolarizing an immune-suppressive phenotype into an antitumor phenotype, tumor-associated macrophages can directly fight the tumor by presenting tumor antigens to induce an immune response.[99]

Other cancers

Sorafenib

Sorafenib can induce ferroptosis through two mechanisms [Figure 4].[100] First, sorafenib can inhibit system Xc^- to suppress the cystine uptake process, which triggers the following outcomes:

endoplasmic reticulum stress, GSH depletion, and the iron-dependent accumulation of lipid ROS, thus inducing ferroptosis.[101] The second mechanism involves p62-Keap1-Nrf2 pathway activation.[102] With sorafenib stimulation, the activated p62 protein can inhibit Nrf2 degradation and facilitate its nuclear accumulation by inactivating Keap1.[102] Subsequently, musculoaponeurotic fibrosarcoma oncogene homolog G (MafG) can be activated by Nrf2 to induce multiple genes, including quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), and ferritin heavy chain 1 (FTH1).[103] These genes can trigger the Fenton reaction by upregulating Fe^{2+} to induce ferroptosis. Moreover, high levels of Nrf2 can also upregulate metallothionein-1G (MT-1G) expression, which inhibits ferroptotic cell death by interfering with lipid peroxidation mediated by GSH depletion.[104] In summary, through the p62-Keap1-Nrf2 pathway, Nrf2 can inhibit sorafenib-induced ferroptotic cell death by affecting redox and iron metabolism.[104] Furthermore, trigonelline could be an adjuvant therapy to enhance sorafenib-mediated ferroptosis by inhibiting Nrf2.[102]

ICA II

Several experiments have indicated that when the PI3K-AKT-mTORC1 pathway is activated, it can inhibit ferroptosis through the following sterol regulatory element-binding protein 1 (SREBP1)/stearoyl-CoA desaturase-1 (SCD1)-mediated lipogenesis process in cancer cells [Figure 4].[105] Because of incremental metabolic and proliferative events, cancer cells often suffer from enhanced oxidative damage.[106,107] Thus, more cascade reactions are triggered to prevent oxidative stress, such as Nrf2 signaling[108] in cancer cells. mTORC1 regulates cellular redox homeostasis through the Nrf2-mediated signaling pathway and SREBP1/SCD1-mediated MUFA synthesis. The mTOR pathway consists of two signaling branches, mTORC1, and mTORC2. However, ferroptosis is primarily inhibited by mTORC1 but not mTORC2.[105,109] SREBP1/SCD1-mediated MUFA synthesis is vital for inhibiting oxidative stress from lipid peroxidation, which leads to ferroptosis. The PI3K-AKT-mTOR pathway is one of the most common signaling pathways[109–111] in which mutations can allow cancer cells to resist ferroptosis.

Activating mutations in PI3K can induce the downstream PI3K-AKT-mTOR signaling axis by suppressing the activation of AKT by PI3K. This resistance to ferroptosis requires mTORC1 to be constitutively activated, after which SREBP1 is activated by mTORC1. SCD1, a transcriptional target of SREBP1, mediates the ferroptosis-suppressing activity of SREBP1 by producing MUFAs. The suppressive ferroptotic function of SREBP1 is mediated by the activity of SREBP1 as a critical transcription factor in modulating lipid metabolism. SCD1, an iron-dependent enzyme catalyzing and desaturating FAs, is directly transcriptionally targeted by SREBP1 to generate MUFAs that decrease ROS levels to inhibit ferroptosis. Furthermore, Torin can suppress mTORC1 to induce ferroptosis, which could possibly be used to treat PCa through the previously mentioned pathway.[105]

In summary, the present evidence suggests that activating mutations in the PI3K-AKT-mTOR axis can downregulate lipogenesis through SREBP1 and SCD1 to lessen oxidative stress and ferroptosis. Thus, joint treatment with the flavonol glycoside icariside II (ICA II), inhibition of PI3K-AKT-mTOR signaling, and induction of ferroptosis could become a potential therapeutic strategy for patients.[105]

Sulfasalazine

As a novel ferroptosis inducer, sulfasalazine triggers ferroptotic signaling pathways by one of the following four mechanisms [Figure 5]. First, through the transferrin receptor (TFR), sulfasalazine can facilitate the process by which circulating Fe^{3+} enters the cells and is converted to Fe^{2+} under the catalysis of Steap3 in the endosome.[112] Through the Fenton reaction, excessive intracellular enrichment of Fe^{2+} can upregulate lipid ROS levels, which ultimately leads to ferroptosis.[7] Second, the phosphorylation of BECN1 is mediated by sulfasalazine by inducing AMPK phosphorylation. Phosphorylated BECN1 can block system Xc^- by forming the BECN1-SLC7A11 complex. Mechanistically, ferroptosis can be triggered by sulfasalazine to block system Xc^-, which upregulates GSH and suppresses lipid peroxidation.[52] Third, sulfasalazine activates ferritinophagy and increases cellular labile iron levels. High levels of cellular labile iron consequently lead to rapid accumulation of cellular ROS.[113] ROS can induce ferroptosis by activating lipid peroxidation.[113] Finally, AMPK phosphorylation mediated by ROS consequently inhibits the nuclear translocation of SREBP1, which then suppresses the transcription of branched-chain aminotransferase 2 (BCAT2), its direct target gene.[114] By catalyzing the branched-chain

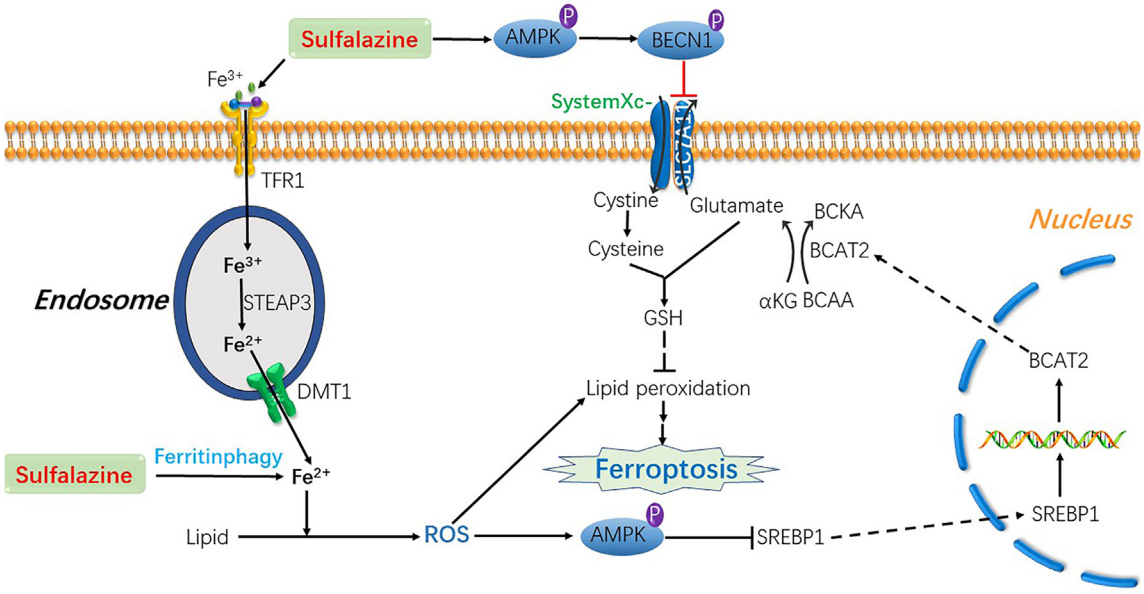

Figure 5. Sulfasalazine can trigger ferroptosis through four mechanisms. Sulfasalazine can activate the TFR and inhibit system Xc^- simultaneously. Moreover, sulfasalazine can activate ferritinophagy and upregulate cellular labile iron levels to induce two pathways. ROS levels can be upregulated by Fe^{2+} to induce ferroptosis by facilitating lipid peroxidation and mediating AMPK phosphorylation, which consequently inhibits the nuclear translocation of SREBP1 and suppresses the transcription of BCAT2.GSH: Glutathione; AMPK: AMP-activated protein kinase; ROS: Reactive oxygen species; TFR: Transferrin receptor.

Table 1
Summary of nanoparticles in ferroptosis applications.

Nanoparticles	Compositions	Mechanisms	Reference
Arginine-rich manganese silicate nanobubbles	Arginine; nanobubble	Reducing GSH level	117
FeGd-HN@Pt@LF/RGD2	Cisplatin-loaded Fe_3O_4/Gd_2O_3 hybrid nanoparticles; lactoferrin;	Fe^{2+} facilitated the Fenton reaction and cisplatin generated ROS	118
SRF@FeIIITA	Tannic acid; sorafenib	SRF inhibited GPX4 enzyme; TA might reduce the Fe^{2+}	119
CSO-SS-Cy7-Hex/SPION/Srfn	Cy7-Hex; Superparamagnetic iron oxide nanoparticles; sorafenib	Cy7-Hex produced ROS; SPION released Fe^{2+} and catalyze Fenton reaction; Sorafenib enhanced lipid peroxidation	120
UCNP	Up-conversion nanoparticle; doxorubicin; oxidized starch-based gel nanoparticle	Fe^{2+} could react with H_2O_2 to generate ROS	121
Nanoparticle ferritin-bound erastin and rapamycin	Ferritin; erastin; rapamycin	Downregulating GPX4 and accumulating lipid per-oxidation	122
SRF@Hb-Ce6	Hemoglobin; chlorin e6; Sorafenib	Hb furnished oxygen; Sorafenib inhibited system Xc^-	123
Zinc oxide nanoparticles	ZnO	ZnO NPs inhibit GPX4 and GSH: ZnO NPs orchestrate iron uptake, storage and export; ZnO particle remnants and dissolved zinc ion both enhance ferroptosis	124
Hybrid core–shell vesicles	An ascorbic acid core and iron oxide nanocubes embedded poly lactic-co-glycolic acid shell layer	Ascorbic acid lead to the redox reaction of IONCs	125
Fe_3O_4-SAS @ PLT	Sulfasalazine; mesoporous magnetic nanoparticles; platelet	"Inhibiting system Xc^- pathway; Fe_3O_4 nanoparticles induce ferroptosis	126
NLC/H(D + F + S) NPs	doxorubicin ferrocene, and TGF-β receptor inhibitor	DOX and Fc raised intracellular ROS level	127
PFP@Fe/Cu-SS	Perfluoropentane; Fe^{3+} and Cu^{2+}; metal organic framework	Increased ·OH levels; disulfide–thiol exchange to deplete GSH; Fe^{3+} and Cu^{2+} inhibited the GPX4	128
UPDA-PEG@$Fe^{2+}/^{3+}$ nanoparticles	PEG; ferrous ions and ferric ions;	UPDA-PEG@Fe^{2+} nanoparticles induce ROS-dependent ferroptosis; UPDA-PEG@Fe^{3+} nanoparticles induce LPO-dependent ferroptosis	129
SRF@MPDA-SPIO nanoparticles	Sorafenib; superparamagnetic iron oxide nanoparticles: mesoporous polydopamine	SPIO supply ferroptosis with iron; SRF deactivate GPX4; MPDA NPs offered a moderate PTT	130
LDL-DHA	Low-density lipoprotein nanoparticles; Omega-3 fatty acid; docosahexaenoic acid	Increased tissue lipid hydroperoxides and suppressed GPX4 expression	131
Pt&Fe_3O_4@PP	Polypeptide vehicles; cisplatin; Fe_3O_4 nanoparticles	$Fe^{2}/^{3+}$ activate the cascade reaction to generate sufficient •OH	132
Sal-AuNPs	Gold nanoparticles; salinomycin	Eliciting ROS, mitochondrial dysfunction, and lipid oxidation	133
Lipid-coated MIL-100(Fe) MOF nanoparticles	Iron; trimesic acid; Hybrid metal organic framework nanoparticles	Introduce iron ions into cells	134
FePt@MnO@DSPE-PEG_{5000}-FA	Folic acid; iron platinum nanoparticles; MnO; DSPE-PEG_{5000}-FA	Catalyzing intracellular H_2O_2 into ROS	135
Zero-valent iron nanoparticles	Zero-valent iron	Induced mitochondrial lipid peroxidation and reduced glutathione peroxidases; induced mitochondrial membrane potential loss	136
Folate/Pt-si-GPX4@IONPs	Iron oxide nanoparticles; cisplatin; folate; small interfering RNA targeting glutathione peroxidase 4	IONPs increased Fe^{2+} and Fe^{3+} levels; IONPs increased H_2O_2 levels; si-GPX4 inhibited GPX4	137
SPFeN	Fe^{3+}; semiconducting polycomplex	SPFeN could generate hydroxyl radicals	138
PEGylated single-atom Fe-containing nanocatalysts	Single-atom Fe; nitrogen-doped carbon	Triggered the Fenton reaction	139
Fe(III)-GA/GOx@ZIF-Azo(FGGZA)	Ferric-gallic acid coordination polymer nanoparticles; glucose oxidase; zeolitic imidazolate framework	FGGZA modulates the Fenton reaction	140
FePt/BP-PEI-FA NCs	FePt nanoparticles; Black phosphorus nanosheets; polyethylenimine	FePt could transform H_2O_2 into ROS	141
FePt/MoS_2-FA	FePt nanoparticle; folic acid; MoS_2 nanosheets	FePt catalyzed the Fenton reaction	142
Fe(III)-ART NPs	Artemisinin; Fe^{3+}	Reduction-induced GSH depletion	143
FaPEG-MMSNs@DHA	Folate grafted PEG; manganese-doping mesoporous silica; dihydroartemisinin	Inhibited GPX4; enhanced the accumulation of PL-PUFA-OOH	144
DFTA	Doxorubicin; ferric chloride	DFTA	145
FePtMn–Ce6/FA	Folic acid; chlorin e6; FePtMn	Fe^{2+} could catalyze H_2O_2 into •OH	146
TMB-F4TCNQ		Inhibited the intracellular biosynthesis of GSH	147
2,3-Dimercaptosuccinic acid-coated Fe_3O_4 nanoparticles	2,3-Dimercaptosuccinic acid; Fe_3O_4	Facilitating ROS generation	148
GBP@Fe_3O_4	1H-perfluoropentane; Fe_3O_4	Fe_3O_4 produce potent ROS	149
API-Fe_2O_3/Fe_3O_4@mSiO_2-HA	Apigenin; Hyaluronic acid; Fe_2O_3, Fe_3O_4; mesoporous SiO_2	Upregulating COX2 and p53; downregulating GPX4 and FTH1	150
MIL-101(Fe)@sor	Sorafenib; MIL-101(Fe) nanoparticles	Increasing lipid peroxidation and malondialdehyde; reducing GPX4	151
Fe_3O_4-PLGA-Ce6 nanosystem	Poly(lactic-co-glycolic acid); ferrous ferric oxide; chlorin e6	Ferrous/ferric ions and hydrogen peroxide could produce •OH; Ce6 increased ROS	152
PDA NPs@Fe/DOX	Doxorubicin; Fe^{3+}; polydopamine nanoparticles	Fe^{3+} was reduced to Fe^{2+} and formed free radical	153
ZnONPs		Zinc ions could damage mitochondrial and increase mtROS	154
Nano-activator (DAR)	Doxorubicin; tannic-acid and IR820	DOX activated NADPH oxidases reaction and TA triggered disproportionation reaction and Fenton reaction; IR820 could increase ROS	155
SL-IONPs-Ac	Iron oxide nanoparticles; stealth liposomes	Promoting mitochondrial dysfunction	156
PEG-Fns	Ferrihydrite nanoparticles; PEG	Triggered Fe^{2+} to generate excessive ROS	157

(*continued on next page*)

Table 1 (*continued*)

Nanoparticles	Compositions	Mechanisms	Reference
Iron-bearing nanoparticles	γ-Fe_2O_3 and Fe_3O_4 NPs	Upregulating intracellular iron level and lipid peroxidation	158
MnO_2@$HMCu_2$-xS nanocomposites	$HMCu_2$-xS; MnO_2	Mn^{2+} might produce ROS	159
FePt@COP-FA nanocomposites	FePt@COP NCs; folic acid	FePt could catalyze the H_2O_2 to hydroxyl radicals	160
MON-p53	Metal–organic network; p53 plasmid	Inhibited the glutathione synthesis pathway and produced abundant lipid peroxide	161
MMSNs@SO	Sorafenib manganese doped mesoporous silica nanoparticles (manganese-silica nanoparticles)	Decreasing GSH and increasing lipid peroxide to induce ferroptosis	162
FeIIPDA@LAP-PEG-cRGD	Polydopamine; Fe^{2+}; b-lapachone; PEG; cRGD	Upregulated NQO1 and enhanced H_2O_2 level	163
CSO-BHQ-IR780-Hex/MIONPs/SOR	CSO-connected BHQ-IR780-Hex; magnetic iron oxide nanoparticles; sorafenib	Triggering the xCT/GSH/GPX-4 system and producing numerous LPO	164
TA-Fe/ART@ZIF	Tannic acid; ferrous ion; zeolitic imidazolate framework-8; artemisinin	Upregultating ROS and MDA; downregulating GSH and GPX4	165
Tf-LipoMof@PL	Piperlongumine; metal–organic framework: transferrin	Piperlongumine provided H_2O_2	166
DS@MA-LS	Doxorubicin and sorafenib	Increasing ROS generation and impairing GSH synthesis	167
Pt-FMO	Cisplatin; manganese-deposited iron oxide nanoplatform	Triggering intracellular cascade reactions and generating ROS	168
mFe(SS)/DG	Metal organic framework; glucose oxidase; doxorubicin	Downregulating GPX4	169

API: Apigenin; ART: Artemisinin; AuNPs: Gold nanoparticles; Bax:BCL2-Associated X; Bcl-2:B-cell lymphoma-2; BP: Black phosphorus; Ce6: Chlorin e6; Cu: Copper; DFTA: Direct fluorescent treponemal antibody; DHA: Docosahexaenoic acid; DOX: Doxorubicin; DS: Doxorubicin and sorafenib; FA: Folic acid; Fc: Ferrocene; Fe: Iron; Fe2O3: Iron(III) oxide; Fe3O4: Iron(II,III) oxide; FeIII: Iron(III) nitrate nonahydrate; FGGZA: Fe(III)-GA/GOx@ZIF-Azo; (Fe(III)-GA:Ferric-gallic acid coordination polymer nanoparticles; Gox: glucose oxidase; ZIF: zeolitic imidazolate framework); FTH1: Ferritin heavy chain 1; GAD(P)H: glyceraldehyde-3-phosphate dehydrogenase; Gd: Gadolinium; Gd2O3: Gadolinium(III) oxide; GPX: Glutathione peroxidase; GPX4: Glutathione peroxidase 4; GSH: Glutathione; HA: Hyaluronic acid; Hb: Hemoglobin; HM: Hollow mesoporous; HN: Hybrid nanoparticles; IONC: Iron oxide nanocube; IONP: Iron oxide nanoparticles; LAP: b-lapachone; LDL: Low-density lipoprotein; LDLR: low-density lipoprotein receptor; LF: Lactoferrin; MDA: Malondialdehyde; MIONP: Magnetic iron oxide nanoparticle; MMSN: Manganese-silica nanoparticle; Mn: Manganese; MnO: Manganese monoxide; MnO2: Manganese dioxide; MOF: Metal organic framework; MON: Metal organic network; MoS2: Molybdenum disulfide; MPC: macropinocytosis; MPDA: Mesoporous polydopamine; mSiO2: Mesoporous SiO2; NCs: Nanocomposites; NP: Nanoparticle; NQO1: Quinone oxidoreductase 1; OH: Hydroxide; p53: Tumor protein P53; PDA: Droplet-associated protein; PE: Phosphatidylethanolamine; PEI: Polyethylenimine; PFP: Perfluoropentane; PL: Piperlongumine; PLGA: Polylactic-co-glycolic acid; PLT: Platelet; PP: Pyrophosphate; Pt: Platinum; PUFA: Polyunsaturated fatty acid; ROS: Reactive oxygen species; Sal: Salinomycin; SCARB1: Scavenger Receptor Class B Member 1; SL: Stealth liposomes; Sor/SRF/Srfn: Sorafenib; SPIO: Superparamagnetic iron oxide; SPION: Superparamagnetic iron oxide nanoparticles; System Xc-: cystine/glutamate exchange transporter; TA: Tannic acid; Tf: Transferrin; TGF: Transforming growth factor; TNTs: tunneling nanotubes; UCNP: Up-conversion nanoparticle; xCT: Cystine/glutamate antiporter SLC7A11ZnO: Zinc oxide.

amino acid-branched-chain keto acid (BCAA-BCKA) shuttle, BCATs can induce the reversible transamination of substrate BCAAs and a-ketoglutarate (a-KG) to the respective production of BCKAs and glutamate.[115,116] Because of upregulated intracellular glutamate and downregulated a-KG, BCAT2 can act as an inhibitor of ferroptosis. Intracellularly, high glutamate levels strengthen system Xc^-, which can suppress ferroptosis by boosting cystine uptake.[113] In addition, a-KG can replace glutamine to induce ferroptosis, so intracellular downmodulation of a-KG inhibits ferroptosis.[93] In summary, sulfasalazine can induce ferroptosis by inhibiting BCAT2 activity through the ferritinophagy-AMPK-SREBP1 pathway.[113]

Nanoparticles

With the cooperation of nanoparticle structures, FINs can have enhanced effects on urinary system cancers. In addition to the previously mentioned nanoparticles, plentiful effective nano-drugs are potential options as single or combination therapies for tumors of the urinary tract [Table 1].

Conclusions

Clinically, it is vital to include adjuvant drugs to enhance the curative effect and restrain drug resistance in the treatment courses of urological cancers. In addition, ferroptosis inducers could become a potent adjuvant therapeutic strategy. Therefore, scientists and clinicians should be devoted to developing novel ferroptosis inducers to generate effective treatment options for urological cancers.

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Author contributions

Zhaoxiang Xie drafted the manuscript and created the figures. Cheng Qiu co-wrote the manuscript and proposed suggestions. Qianghua Zhou, Dingjun Zhu, Kaiwen Li, and Hai Huang revised the manuscript. All authors read and approved the final manuscript.

Ethics statement

None.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflicts of interest

None.

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