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Review Article

Pharmacological Targeting of Ferroptosis in Cancer Treatment

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Abstract

A non-apoptotic iron-dependent form of Regulated Cell Death (RCD) known as ferroptosis is brought on by an excess of harmful lipid peroxides and iron overload. Inhibiting the antioxidant defense system results in overwhelming of GSH dependent pathway and building up iron-dependent Reactive Oxygen Species (ROS) that react with polyunsaturated fatty acids in large quantities can both cause ferroptosis. Recent research has shown that ferroptosis holds a great deal of promise for preventing tumor cell resistance and limiting growth and spread. Emerging evidence also suggests that ferroptosis plays a dual role in human cancer. However, the precise underlying molecular mechanisms and their different role in tumorigenesis are unclear. Therefore, in this review we summarize and briefly present the key pathways of ferroptosis, its dual role as an oncogenic and as a tumor suppressor event in human cancers, paying special attention to the regulation of ferroptosis along with a variety of current medications and naturally occurring substances that may one day be used to target ferroptosis in tumor cells. Thus, addressing this sort of cell death could be seen as a potentially expanding technique in cancer treatment. Consequently, this will offer crucial viewpoints for next research on ferroptosis-based cancer treatment.

Keywords: Ferroptosis, antioxidant defense system, Cancer

INTRODUCTION:

Tumor cells innate ability to resist apoptosis and resist conventional chemotherapeutic treatments has become a serious problem for basic and clinical scientists in recent years.[1] For many years, apoptosis was thought to be the main cause of tumor cell death, even though caspase-induced tumor cell death is not the only way that tumor cells die. Cell death brought about by traditional therapies. On the other hand, an increasing amount of data indicates that inducing ferroptosis may be an additional antitumor characteristic of traditional anticancer drugs. In terms of appearance, genetics, and biochemistry, ferroptosis—a novel type of RCD that Scott Dixon originally characterized in 2012—is distinct from other RCD forms, which include apoptosis, necroptosis, and autophagy.[2]Iron-dependent lipid peroxidation and failure of the antioxidant defense system are hallmarks of ferroptosis.[2] The morphological changes that occur in ferroptotic cells include the reduction of cristae, rupture of the outer membrane, shrinkage, and elevation of the membrane density.[2,3]Research has indicated that ferroptosis is closely related towith the onset, progression, and suppression of cancer.[4-8]Thus, focusing on this type of cell death could open up new avenues for the treatment of cancer. Three basic strategies are used to accomplish ferroptosis, a process closely linked to metabolism and redox balance: modifying iron metabolism, influencing lipid peroxidation, and inhibiting the antioxidant system.[9,10] Consequently, using effective exogenous agents totarget these pathways may be a useful tactic for causing tumor cells to undergo ferroptosis. Since ferroptosis was discovered, a number of experimental drugs have been created or found that target distinct ferroptosis regulatory mechanisms. For example, the first known inducer of ferroptosis was erastin, which targets oncogenic Ras mutant tumor cells specifically.[11] In terms of mechanism, erastin works against the antioxidant defense system by permanently inhibiting system Xc, which causes glutathione (GSH) to be depleted. Subsequently, different experimental agents were progressively presented to target ferroptosis in tumor cells, including FIN56, ML162, RSL3, and others. Because of their unstable metabolism and inadequate solubility in water, none of these compounds—despite their strong pro-ferroptotic activity—are appropriate for usage in vivo. Therefore, creating new ferroptosis inducer medicines with improved pharmacokinetic conformance or repurposing existing therapeutic drugs that successfully cause ferroptosis should be of the utmost importance. This article offers a brief synopsis of the fundamental mechanisms of ferroptosis and lists some of the current medications and natural substances that may be modified for use in ferroptosis-based cancer treatments.

MOLECULAR CHARACTERISTICS OF FERROPTOSIS:

Iron accumulation: Iron absorption, utilization, recycling, and storage are among the several processes that make up iron metabolism.When iron metabolism is disrupted, intracellular iron accumulates excessively, which results in the production of free radicals and oxidative stress.[12,13] In particular, ferroptosis is primarily caused by iron, which is also a necessary component for the growth and multiplication of tumor cells.[14,15]Apart from its function in the synthesis of DNA and ATP, iron is an essential part of the electron transport chain in the mitochondria and a cofactor for metalloproteinases.Ferrithioprotein, for instance, functions as a cofactor for numerous essential enzymes in redox processes as well as for oxidoreductases in the mitochondrial electron transport chain.The transferrin–Fe3+ complex, which is reduced to Fe2+ and enters the cell through the membrane protein transferrin receptor 1, is formed when extracellular ferric ions (Fe3+) mix with transferrin.The labile iron pool accumulates Fe2+ in the cell with the help of the divalent metal transporter 1 (solute carrier family 11 member 2; SLC11A2) or Zrt- and Irt-like proteins 8 and 14 (SLC39A8 and SLC39A14, respectively).[14,15,16]To maintain the equilibrium of internal iron, Fe2+ works with iron chaperones like poly(rC)-binding proteins 1 and 2 to pump iron through membrane ferroportin (FPN) 1.[14,18] But when cells' Fe2+ levels are too high, the Fenton reaction with hydrogen peroxide takes place, producing too many ROS and causing ferroptosis (Fig.1).

Anomalous lipid metabolism: Lipids are essential for the production of cell membranes, energy storage, signal transduction, membrane development, and energy storage. Cell lipid toxicity is regulated by lipid metabolism, and anomalous lipid metabolism is thought to be a sign of malignancy and a critical component of ferroptosis.[19] Fatty acids are also crucial for the metabolism of lipids in cells. Fatty acids are classified as monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), and saturated fatty acids (SFAs) based on the degree of their saturation. Ferroptosis has been shown to be facilitated by PUFAs and MUFAs among them.[20,21]ROS can cause lipid peroxidation by attacking PUFAs on the cell membrane because of the weak C–H bond at the diallyl location.[22] The synthesis of PUFAs in this process is dependent on acyl-CoA synthetase long-chain family member 4 (ACSL4), which in turn favorably regulates ferroptosis. On the other hand, it has been observed that exogenous MUFAs, like exogenous oleic acid and palmitic acid, adversely regulate drug-induced ferroptosis.[23,24] Acyl-CoA synthetase long-chain family member 3 has the ability to activate exogenous MUFAs, which can displace PUFAs at the plasma membrane and lessen the lipids' oxidation sensitivity.[24] Furthermore, it has been discovered that cancer cell membranes have a higher ratio of MUFAs to PUFAs, which prevents lipotoxicity and ferroptosis (Fig.1).[25]

Aberrant amino acid metabolism: Amino acids are necessary for cell viability and are involved in the metabolism of ammonia, deamination, decarboxylation, and oxidative decomposition capacity. In the meantime, aberrant metabolism of amino acids results in redox imbalance, dysregulation of energy management, and dysfunction in biosynthesis, all of which promote the growth of tumors.[26] The primary cause of ferroptosis brought on by aberrant amino acid metabolism is GSH. Glutamate-L-cysteine-L-glycine (γ-glutamyl-L-cysteinyl-L-glycine) is a tripeptide that is essential for the body's elimination of free radicals and as an antioxidant.[27,28] Important regulators of GSH breakdown and biosynthesis include GPX4 and System Xc-. The light chain (SLC7A11) and heavy chain (SLC3A2) subunits that make up System Xc- are crucial for preserving the equilibrium of GSH in cells.[29,30] Glutamate is transported from inside the cell to the outside by System XC, which also enables the exchange of cystine and glutamate across the plasma membrane and regulates GSH synthesis in response to external glutamate levels.[31] Reduced GSH synthesis can result from compromised system XC function or inadequate intracellular cysteine levels, which can cause ferroptosis. However, GPX4 can employ GSH as a substrate to convert membrane lipid hydrogen peroxide to nontoxic lipid alcohols, lessen oxidative stress damage, and negatively regulate ferroptosis. GPX4 is an essential enzyme for scavenging lipid oxygen free radicals (Fig.1).[27,28]

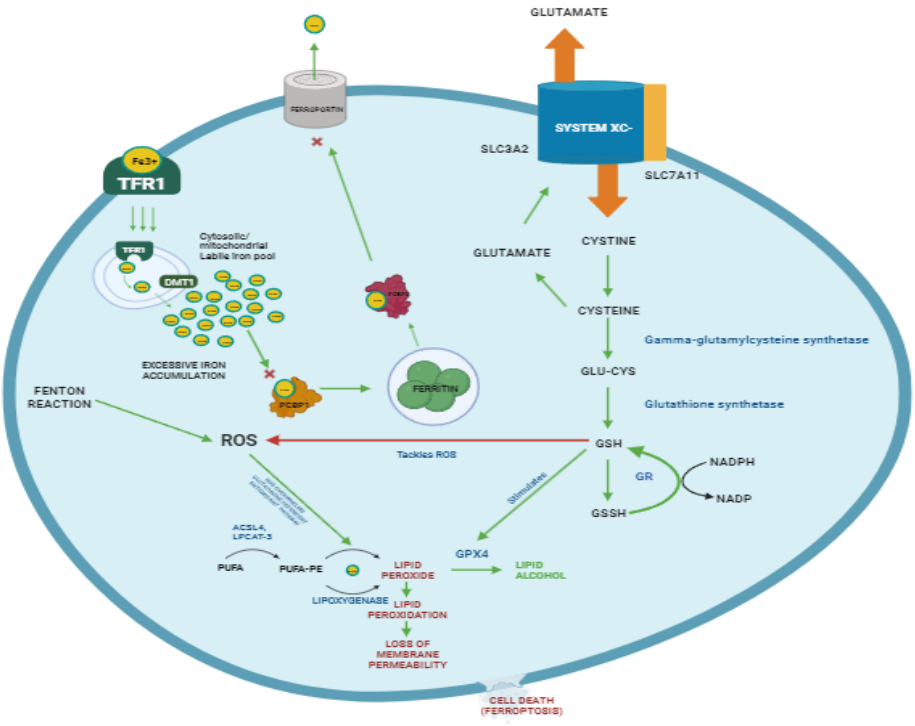

Figure 1: Merged diagrammatic representation of molecular characteristics of ferroptosis including excessive iron accumulation, anomalous lipid metabolism, and aberrant amino acid metabolism.

REGULATION OF FERROPTOSIS IN CANCER

Ferroptosis can be regulated by a variety of mechanisms, especially by the transcription of genes and post translation of proteins.

Noncoding RNAs (ncRNAs) induced ferroptosis in cancer

ncRNAs have been shown in numerous studies to stimulate ferroptosis in a variety of malignancies. For instance, it has been shown that miR-15a-3p and miRNA-15a-15a target GPX4 to enhance ferroptosis in colorectal and prostate cancer, respectively.[32-33] Furthermore, by raising the levels of miR-4715-3p, which are downregulated in malignancies of the upper gastrointestinal tract, GPX4 inhibition causes ferroptosis to become sensitive.[34]Non-small cell lung cancer has been found to operate via a comparable mechanism. By inhibiting GPX4 expression, miR-324-3p leads to cisplatin resistance,[35] whereas miR-302a-3p targets FPN to positively regulate ferroptosis.[36] A study by Bai et al. has demonstrated that miR-214-3p the GSH axis in hepatoma and so functions as a tumor inhibitor, in addition to causing ferroptosis via GPX4.[37] Certain long non-coding RNAs (lncRNAs) in different malignancies can speed up ferroptosis, just like miRNAs do. As an illustration, it has been noted that suppression of the lncRNA plasmacytoma variant translocation 1 markedly raised ROS and Fe2+ levels, which was followed by a reduction in cell viability in liver cancer.[38] SLC16A1-AS1 suppression in renal carcinoma led to a considerable reduction in SLC7A11 expression and a GSH/glutathione disulfide (GSSG) ratio reduction in cells.[39] Wang et al. previously reported similar outcomes, showing that in acute myeloid leukemia, the long intergenic nonprotein-coding RNA 618 triggers ferroptosis by upregulating SLC7A11 and downregulating ACSL4.[40] Mechanistically, the lncRNA ARHGEF26-AS1 functions as a sponge for miR-372-3p, causing ferroptosis and preventing esophageal squamous cell carcinoma cells from proliferating and migrating.[41] The cytosolic p53-related lncRNA consistently inhibits the growth of lung cancer by inducing ferroptosis by increasing ROS and intracellular iron buildup.[42] Furthermore, metallothionein 1D, pseudogene has been shown through preclinical studies and bioinformatics analysis to augment erastin-induced ferroptosis in nonsmall cell lung cancer by blocking nuclear factor erythroid 2-related factor 2 (NRF2).[43]It has also been revealed that a variety of circular RNAs contribute to the promotion of ferroptosis. Jiang et al.'s research specifically found that overexpression of circ0000190 expedited the process of ferroptosis in gastric cancer cells by elevating levels of malondialdehyde, lipid ROS, and Fe2+.[44] Furthermore, following circ0007142 knockdown, cells in colon cancer displayed growth suppression and ferroptosis signals.[45] Furthermore, knockdown of the circular RNA glial cell line-derived neurotrophic factor family receptor alpha-1 (circGFRA1) resulted in upregulation of the GSH/GSSG ratio and apoptosis-inducing factor mitochondria-associated 2 and GPX4 expression, indicating that circGFRA1 promotes ferroptosis in breast cancer via two distinct pathways.[46] Notably, studies conducted both in vivo and in vitro have demonstrated that the circular RNA LIM domain just 1 increases ferroptosis through upregulating ACSL4 expression, hence inhibiting the proliferation and spread of cervical cancer cells.[47] Additionally, hepatocellular carcinoma (HCC) has been shown to overexpress the circular RNA IARS (circIARS) according to RNA-sequencing research; yet, a detailed investigation has revealed that cells silenced by circ-IARS exhibit a considerable rise in intracellular GSH and a significant drop in Fe2+. Consequently, it is possible that circ-IARS will stimulate ferroptosis in HCC cells.[48] Nonetheless, there are numerous obstacles to overcome and the connection between ferroptosis and ncRNAs is not well understood. For instance, further research is required to clarify the underlying regulatory mechanism regulating the interaction between ferroptosis and ncRNAs. There is yet no proof that ncRNAs that directly bind to ferroptosis are involved in the development and prognosis of cancer. Thus, greater research into the functions of ferroptosis-related ncRNAs in various malignancies is important. Furthermore, the in vivo validation of ferroptosis-related ncRNAs is still limited. It's clear that more research using extensive human tissue samples is necessary to ascertain whether these ncRNAs may be utilized as clinical targets.

Dual role of transcriptional factors in ferroptosis (suppressive and inductive effect)

An increasing body of research suggests that transcriptional regulators have two opposing effects on the regulation of ferroptosis. For instance, it has been revealed that p53, a tumor suppressor, has a dual function in ferroptosis. Specifically, it has been shown that p53 causes ferroptosis by directly suppressing SLC7A11 expression and raising lipid peroxidase. Notably, it has been shown that p53 activation inhibits cystine uptake, limits intracellular GSH synthesis, and activates ferroptosis, which in turn inhibits tumor growth.[49] On the other hand, it has also been suggested that p53 functions to prevent ferroptosis in human cancer cells. Mechanically, nutlin-3, a small molecule inhibitor, was able to boost p53 expression while reducing ROS buildup and GSH consumption, which in turn suppressed ferroptosis. In HT-1080 fibrosarcoma cells, there is a concurrent increase in cell viability.[50-51]Additionally, in a variety of malignancies, activating transcription factor (ATF) 4 regulates ferroptosis either positively or negatively. ATF4 has the ability to cause sorafenib resistance in HCC by preventing ferroptosis,[52] however it has also been demonstrated that sevoflurane can cause ferroptosis in Glioma cells by activating ATF4.[53] Likewise, it has been documented that ATF3 induces ferroptosis and possesses tumor-suppressive properties.[54] Furthermore, the aberrant expression of two essential transcription factors of the Hippo pathway, transcriptional co-activator with PDZ-binding motif (TAZ) and yes-associated protein (YAP), leads to chemotherapy resistance and cell proliferation in a variety of malignancies.[55-56] Additionally, a preclinical investigation has shown that YAP's transcriptional regulatory function targets the transferrin receptor and ACSL4 to cause ferroptosis. In summary, ROS levels rise and cell viability falls when YAP is overexpressed.Additionally, in colon cancer cells, YAP is more vulnerable to ferroptosis at high cell densities.[57] This conclusion is supported by the observation that in some cancer cell lines treated with erastin, loss of TAZ decreases sensitivity to ferroptosis.[58] Furthermore, it is thought that hypoxia-inducible factor 1 alpha (HIF1A), a transcriptional regulator of the homeostatic response of cells to hypoxia, prevents the death of cancer cells by encouraging the accumulation of lipids. However, it has been demonstrated that HIF1A deletion favorably regulates ferroptosis in mouse models treated with RSL3 via controlling lipid metabolism and consequently efficiently inhibits tumor growth.[59-60] Conversely, there are transcription regulators that, through blocking ferroptosis, encourage the growth of tumours. The most obvious evidence is that NRF2 has been demonstrated to upregulate SLC7A11, which shields tumor cells from undergoing ferroptosis .[61] However, it has also been observed that NRF2 induces ferroptosis in lung cancer and renal cell carcinoma (RCC) cells by upregulating HMOX1 expression. In particular, 4, 4'-dimethoxychalcone (DMC), which is taken from the plant Angelica keiskeikoidzumi, have the ability to activate NRF2. NRF2 activation directly increased the expression of HMOX1, which in turn caused iron overload and ferroptosis.[62-63] It will be interesting to learn more about the precise mechanism behind ferroptosis, given the dual function transcription factors play in this process. Screening a greater number of transcription factors that target ferroptosis will be interesting as well. Moreover, the specificity of these transcription factors is

unknown because of the intricate regulatory network of ferroptosis. Thus, there is an urgent need for comprehensive research on the specificity and preclinical trials.

Post translational modification in ferroptosis

The control of ubiquitination, phosphorylation, methylation, and acetylation is significantly influenced by ferroptosis. A number of deubiquitinases, such as ubiquitin-specific protease (USP)11, USP14, and OTU domain-containing ubiquitin aldehyde-binding protein 1, as well as ubiquitinases, such as neural precursor cell expressed developmentally downregulated protein 4 (NEDD4), NEDD4 ligase, and so on, can regulate the key ferroptosis regulatory genes, including SLC7A11, GPX4, and voltage-dependent anion-selective channels (VDACs).[64-66] It is anticipated that NEDD4 is the primary E3 ligase causing VDAC1 degradation in melanoma among the ubiquitinases. It has been confirmed by another investigation that endogenous VDAC1 interacts with NEDD4, and that treatment with erastin strengthens this interaction. However, erastin-induced ferroptosis was averted by VDAC2/3 inactivation. It's interesting to note that these effects increased after NEDD4 silencing. Furthermore, a comprehensive analysis has demonstrated that the VDAC subtype's K63, K90, and K163 are essential for NEDD4-mediated ubiquitination.[67] Furthermore, direct phosphorylation of ACSL4 or concomitant phosphorylation of SLC7A11 can control the activity of ferroptosis. Precisely, phosphorylating ACL4 at Thr328 directly through protein kinase C βII speeds up ferroptosis and improves the effectiveness of immunotherapy in melanoma patients.[68] Phosphorylation of beclin 1 at S90/93/96 was found to be involved in its complexation with SLC7A11 and subsequent lipid peroxidation in ferroptosis, which extended the survival of pancreatic cancer-stricken mice in a preclinical investigation.[69] According to the aforementioned research, a large number of genes have been shown to control ferroptosis via methylating the SLC7A11/GPX4 axis. Clinically, poor DNA methylation in a number of malignancies may be connected to elevated GPX4 expression. Additionally, it has been shown that acetylation of histone H3 on lysine 27 and trimethylation of histone H3 on lysine 4 are abundant in the upstream site of GPX4 in various cancer tissues, suggesting that methylation may be the cause of the high expression of GPX4.[70] The multiple myeloma cell lines MM1S and MM1R treated with the GPX4 inhibitor RSL3 underwent changes in total DNA methylation levels. An additional investigation assessed these alterations and found that both MM1S and MM1R converge towards a similar methylation profile under conditions of ferroptosis.[71] Furthermore, the ferroptosis inhibitor sulfasalazine, which targets SLC7A11, has been shown in a prior work by the Hasegawa group to induce DNA methylation on the mucin 1 gene (MUC1) promoter to regulate MUC1 gene transcription in triple-negative breast cancer.[72] Furthermore, it has been shown that acetylation has a role in controlling ferroptosis. For instance, Jiang et al. have shown that p533KR (K117/161/162) causes ferroptosis and controls the expression of SLC7A11.[29] What's more intriguing is that p53's transcriptional activity is unaffected by the absence of acetylation at position K98. But when the P533KR and K98 mutations are combined, P53 is completely unable to control SLC7A11, suggesting that p53's K98 acetylation is crucial for inhibiting SLC7A11 production and p53-mediated ferroptosis.[73] However, more investigation is necessary to fully understand the precise mechanism underlying the acetylation-mediated regulation of ferroptosis. Thus, to elucidate their functions in cancer, the identification of new regulators of acetylation and ferroptosis will be required.

POTENTIAL COMPOUNDS TO TARGET FERROPTOSIS BASED CANCER THERAPY

Ferroptosis can be induced by suppressing antioxidant defence components such as systems Xc–, GSH, and GPX4, or by precisely controlling various endogenous elements like intracellular iron concentration and PUFA-containing phospholipids.[74] Up till now, the potential effectiveness of a variety of naturally occurring substances and clinically utilized medications in inducing ferroptosis has been investigated.

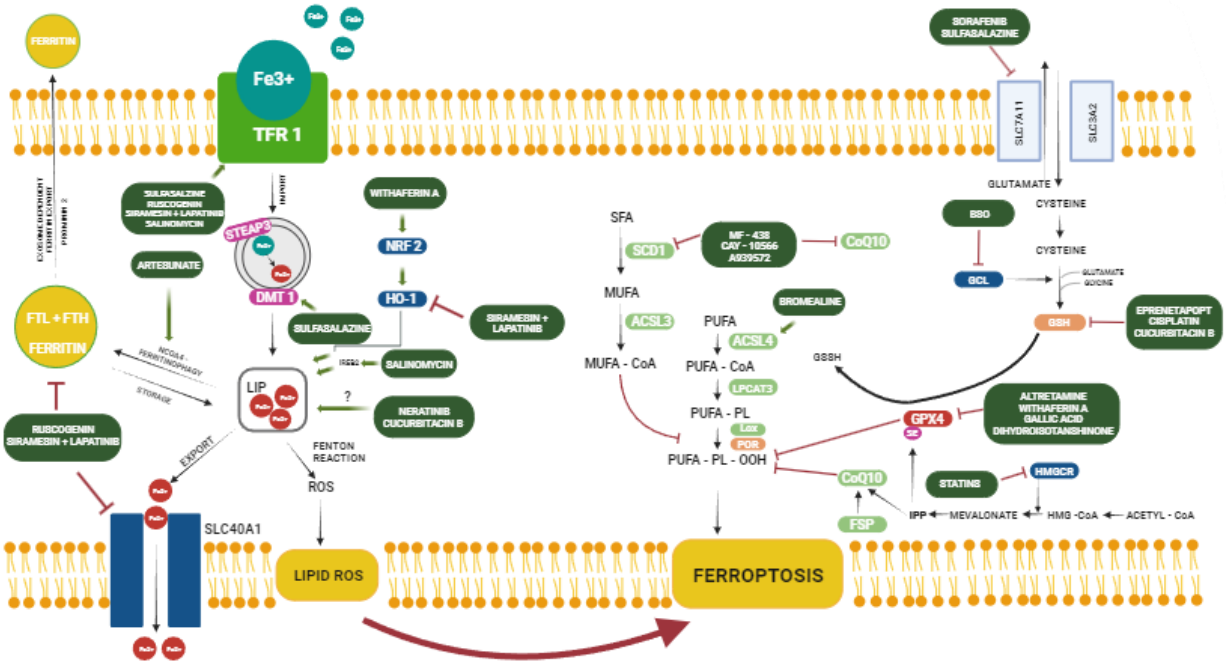

Figure 2: schematic illustration of the mechanisms of action of potential compounds involved in the ferroptosis induced cancer therapy

While some of these drugs are already FDA-approved, others are still in the preclinical and clinical trial stages (Table 1). Here, we are reminded of the substances already on the market for various purposes that could be converted to ferroptosis-based cancer therapy. We have divided these potential medications and substances into four major categories of ferroptosis inducers in the sections that follow; group 1 focuses on intracellular iron concentrations; Group 2 targets system Xc-, GSH, and GPX4, Group 3 targets β HMG-CoA reductase, and Group 4 targets system SCD1 and ACSL4.

Table 1. Potential compounds associated with ferroptosis induced cancer cell death.

Drugs/Compounds	Targeted Pathway	Cancer Types	FDA Approval	Exact Mechanism	Ref
Salinomycin	Intracellular iron levels	Breast cancer	NO	Degradation of ferritin, downregulation of NRF2, and increases in TFRC and IREB2	84-86
Lapatinib +Siramesine	Intracellular iron levels	Breast cancer, Glioblastoma, Lung cancer	YES	Elevate transferrin expression, downregulate HO-1, ferroportin, and ferritin, and increase intracellular iron concentration	96-98
Artesunate	Intracellular iron levels	Head and neck cancer, Pancreatic cancer, Hepatocellular carcinoma	YES	Depletion of GSH, activation of ATF4-CHOP-CHAC1, Degradation of ferritin, and NCOA4-mediated ferritinophagy	111-113
Ruscogenin	Intracellular iron levels	Pancreatic cancer	NO	Downregulation of ferroportin and upregulation of transferrin	115
Neratinib	Intracellular iron levels	Breast cancer	YES	Increase intracellular iron level	118
Sulfasalazine	Xc-, GSH, and GPX4	Head and neck cancer, Breast cancer, Fibrosarcoma, Glioma	YES	System Xc- inhibition and prevention of cystine absorption, which results in an increase in TFRC and DMT1 expression levels	125,142
Sorafenib	Xc-, GSH, and GPX4	Fibrosarcoma, Hepatocellular carcinoma, Renal cell carcinoma, Pancreatic cancer	YES	Inhibiting system Xc- and preventing theabsorption of cystine	123-127
Cisplatin	Xc-, GSH, and GPX4	Colorectal cancer, Lung cancer	YES	Depletion of GSH and deactivation of GPXs	132
Eprenetapopt	Xc-, GSH, and GPX4	Acute myeloid leukemia, Oesophageal cancer, non-small cell lung cancer	NO	Depletion of GSH and suppression of thioredoxin	147
Buthionine sulfoximine	Xc-, GSH, and GPX4	Colorectal cancer, Lung cancer	NO	Inhibition of the production of GSH	125
Dihydroisotanshinone I	Xc-, GSH, and GPX4	Glioblastoma, Breast cancer, Lung cancer	NO	GPX4 inactivation and GSH attenuation	162,164
Withaferin A	Xc-, GSH, and GPX4	Neuroblastoma	NO	Direct inactivation of GPX4, targeting the Nrf2-HO1	172
Gallic acid	Xc-, GSH, and GPX4	Neuroblastoma, Breast cancer, Melanoma, Colorectal cancer, Cervical cancer	NO	suppression of GPX4	177,179
Cucurbitacin B	Xc-, GSH, and GPX4	Nasopharygeal carcinoma	NO	Depletion of GSH, GPX4 downregulation, and elevated intracellular iron levels	183
Altretamine	Xc-, GSH, and GPX4	Human diffuse large B cell lymphoma	YES	GPX4 inhibition	185
Statins	HMG-CoA reductase	Fibrosarcoma	YES	Inhibition of HMG-CoA reductase	190
MF-438, CAY10566, and A939572	SCD1, and ACSL4	Ovarian cancer	NO	Suppression of SCD-1	197
Bromelain	SCD1, and ACSL4	Colorectal cancer	NO	Upregulation of ACSL4	201

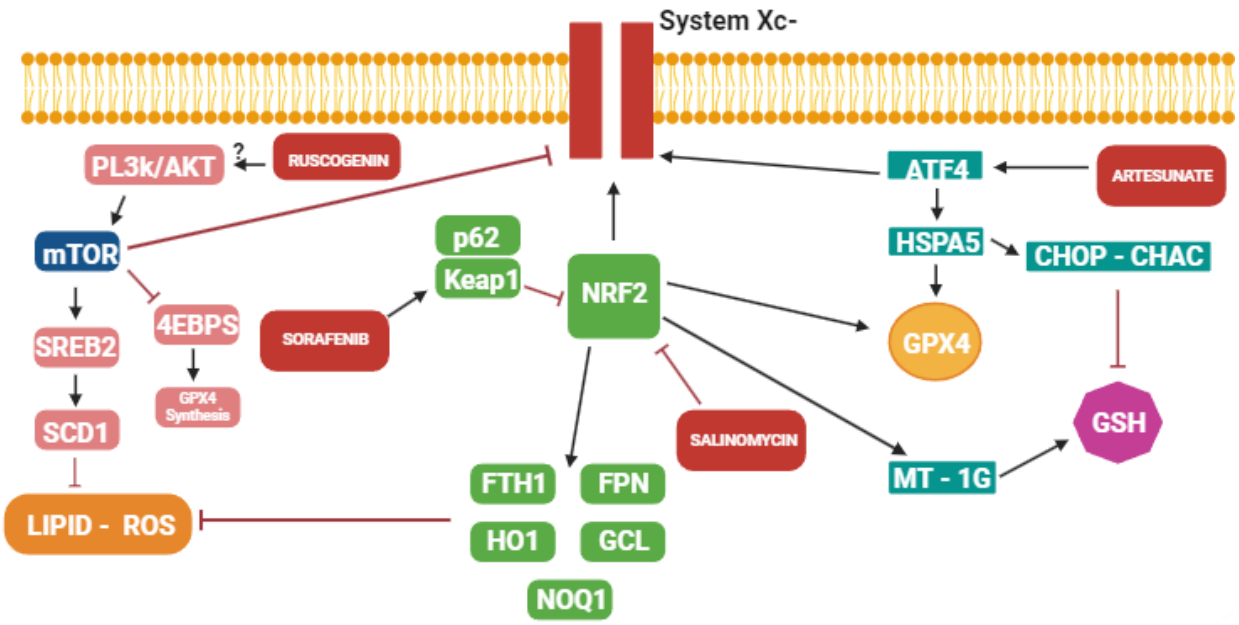

Figure 3: The ferroptosis process is negatively regulated by the master transcription factor NRF2. NRF2 controls oxidative stress-induced ferroptosis by regulating the expression of numerous genes involved in the antioxidant defense system. ATF4 has the ability to activate HSPA5, which prevents GPX4 degradation and mediates ferroptosis resistance. Through GSH depletion, artesunate-induced ATF4-CHOP-CHAC1 activation initiates ferroptosis. Lipid peroxide limitation mediated by SCD1 mediates ferroptosis resistance through the PI3K-AKT-mTOR signaling cascade. 4EBPs is implicated in the synthesis of GPX54 protein, and mTOR suppresses it as well.

Potential compounds to target intracellular iron levels

One of the key characteristics of ferroptosis is iron overload. The following is a description of the medications and substances that cause ferroptosis by raising the amount of iron within cells: salinomycin, artesunate, neratinib, lapatinib+siramesine, and, ruscogenin are some of these agents.

Salinomycin

A polyether ionophore molecule called salinomycin was discovered from the bacterium Streptomycin albus. It exhibits a broad spectrum of antibacterial activity against viruses, gram-positive bacteria, fungi, and parasites.[75]Salinomycin's capacity to fight cancer has drawn more attention from researchers worldwide throughout the last ten years. Salinomycin has antitumor effects that significantly reduce the growth of breast tumors in the mice xenograft model,[76] according to a 2009 study by Gupta et al.Studies have shown that salinomycin dramatically reduces the ability of docetaxel-resistant prostate cancer cells to form colonies.[77] Additionally, the resistance of ovarian cancer cells to chemotherapy medicines based on platinum is substantially eliminated by salinomycin and its derivatives.[78] More research is still needed to determine the precise method by which salinomycin kills tumor cells. By focusing on the hypoxia-inducible factor 1-α (HIF-1α)/vascular endothelial growth factor (VEGF) signaling pathway, salinomycin significantly inhibits the angiogenesis and development of breast cancer cells.[79]Preclinical research findings demonstrated that salinomycin considerably inhibits the migration of cancer cells by disrupting the integrity of actin stress fibers.[80]Tumor cells treated with salinomycin have been shown to undergo apoptosis and autophagy caused by endoplasmic reticulum (ER) stress.[81-82] Additionally, it has been discovered that salinomycin increases intracellular ROS levels and downregulates NRF2 expression, hence improving the radiosensitivity of nasopharyngeal cancer cells.[83]Salinomycin treatment for colon cancer cells may cause ROS production and mitochondrial dysfunction.[84]An effective synthetic salinomycin derivative, ironomycin (AM5), has been shown to have enhanced anticancer activity against breast cancer stem cells. Researchers have discovered that administering salinomycin and AM5 to cancer stem cells prevents iron transport from the lysosome lumen to the cytosol. This, in turn, causes cytosolic iron depletion, which is shown by ferritin degradation and an increase in IREB2 and TfR.[85-86]By causing lipid peroxide buildup and inducing ferroptosis, delivery of salinomycin-loaded gold nanoparticles (SalAuNPs) to breast cancer stem cells can efficiently kill tumour cells.[87] To support these results, the ferroptosis-specific inhibitor ferrostatin-1 (Fer-1) remarkably prevented cell death caused by salinomycin or Sal-AuNPs.[87] In conclusion, it appears that causing ferroptosis may be an additional salinomycin anticancer effect.

Lapatinib

Lapatinib, which is often referred to as TYKERB®, is a synthetic derivative of 4-anilinoquinazoline that has been shown to have a reversible inhibitory impact on the activation and autophosphorylation of HER1 and HER2.[88] In 2007, the Food and Drug Administration (FDA) approved the use of lapatinib in conjunction with capecitabine for patients with advanced HER2 overexpression breast cancer.[89] It has recently been discovered by researchers that lapatinib therapy may prevent low-dose doxorubicin from having a promigratory effect on breast cancer cells.[90] A piperidine analogue, siramesine is a ligand for the sigma-2 receptor that was first developed to treat depression and anxiety.[91] It has been demonstrated that siramesine increases liposomal membrane permeabilization, which causes cathepsin leakage, the generation of ROS, and eventually the death of cancer cells.[92] By inhibiting the activity of acid sphingomyelinase, siamesine can also cause tumor cells to die.[93] Treating triple-negative breast cancer cells with siramesine as a lysosomotropism drug dramatically eliminates their resistance to CDK4/6inhibitors.[94] According to a study by Liu and colleagues, siramesine's anticancer activity was enhanced in vitro when it was delivered to breast cancer cells via a metal-organic framework-based nanoplatform known as ZIF-8@Sira/FA.[95] According to a study by Ma and colleagues,

co-treating breast cancer cells with siramesine and lapatinib simultaneously causes ferroptotic cell death by interfering with iron metabolism and so causing the generation of reactive oxygen species.[96] The authors additionally demonstrated that [siramesine + lapatinib]-induced synergistic mortality was independent of its conventional targets. By lowering HO-1 levels.[97] Rodriguez and colleagues discovered that siramesine and lapatinib together can also cause ferroptosis in tumor cells. They found that HO-1 overexpression produced by cobalt protoporphyrin chloride (CoPP) effectively decreased lipid ROS reactions and cell death brought on by [lapatinib + siramesine].[98] While the exact mechanism of [lapatinib + siramesine]-induced ferroptosis is yet unknown, it appears that combining the two drugs may provide a fresh approach to going after refractorytumor cells.

Artesunate

For the treatment of malaria infection, doctors frequently administer artesunate, a semisynthetic water-soluble derivative of artemisinin.In May 2020, the FDA approved artesunate as a treatment for severe malaria in both adult and paediatric patients. Apart from its ability to fight malaria, artesunate has demonstrated promise as a means of eradicating cancerous cells. According to research, artesunate inhibits the expression of VEGF and angiopoietin 1 to perform an antiangiogenic activity.[99-100] Furthermore, by changing the expression of a number of regulatory proteins, artesunate causes cell cycle arrest in tumour cells.[101-102] By suppressing RAD51 recombinase, artesunate can also hinder ovarian tumour cells ability to repair DNA double-strand breaks.[103] By blocking nuclear factor (NF)-κBsignalling, the combination therapy of artesunate and anti-androgen belumenutamide inhibits the growth of tumours in castration-resistant prostate cancer cells.[104] According to recent research, artesunate can cause ferroptotic cell death in a wide range of cancers by focusing on different molecular elements.[21,105-108] Artesunate therapy induces lysosomal iron-dependent ferroptosis in K-Ras mutation-activated pancreatic ductal adenocarcinoma, which can be effectively counteracted by the ferroptosis inhibitors deferoxamine, trolox, and fer-1.[108] Moreover, it has been discovered that artesunate increases the production of ROS in tumour cells via increasing ferritin breakdown and lysosomal function.[109] Additionally, Kong and associates have demonstrated that in hepatic stellate cells, artesunate stimulates NCOA4-mediated ferritinophagy.[110] According to a recent publication, low-dose sorafenib in combination with artesunate treatment synergistically increases ferroptosis in hepatocellular carcinoma cells both in vitro and in vivo.[111] Another theory for how artesunate-induced ferroptosis works is to target the unfolded protein response.It has been discovered recently that the administration of artesunate to Burkitt lymphoma cells activates the ATF4-CHOP-CHAC1 signalling cascade, hence inducing ferroptosis. Additionally, they have shown that in tumour cells, downregulating CHAC1 expression raises GSH levels and reduces lipid peroxidation. It is important to note that CHAC1 is essential for GSH degradation, which is likely a factor in artesunate-mediated ferroptosis.[112] Notably, ferroptosis resistance in head and neck cancer cells is mediated by the NRF2-ARE pathway, which can be activated by artesunate therapy.[113] Because artesunate inhibits the NRF2 cascade, HNC cells are especially susceptible to artesunate-mediated ferroptosis in vitro and in vivo.[113] All things considered, the therapeutic repurposing of artesunate may offer a chance to treat anti-apoptotic tumour cells by inducing ferroptosis.

Ruscogenin

A naturally occurring steroidal sapogenin, ruscogenin was first identified from the shrubs Ruscus aculeatus. There have been reports of anti-inflammatory, antithrombotic, and anti-neoplastic effects of roscogenin. Its underlying therapeutic actions are unclear, nevertheless. Recent studies have shown that blocking tumour cell invasion and migration with ruscogenin therapy substantially suppresses the metastasis of hepatocellular carcinoma.[114] Through altering the PI3K/AKT/mTOR signalling cascade, they found that ruscogenin dramatically downregulates the production of matrix metalloproteinase-2 (MMP-2), MMP-9, urokinase-type plasminogen activator (uPA), VEGF, and HIF-1α.[114] According to a recent study by Song et al., ruscogenin both in vitro and in vivo induces ferroptosis, which slows the growth of pancreatic tumours.[115] By upregulating transferrin expression and downregulating FPN expression;roscogenin therapy increases intracellular ferrous levels and ROS production.[115] Ferric ammonium citrate increased and deferoxamine inhibited the effects of roscogenin-induced cell death.[115] All things considered, more research is necessary to assess ruscogenin's pro-ferroptotic function in various cancer models.

Neratinib

The FDA approved neratinib, also marketed as NERLYNX®, an oral panHER kinase inhibitor, in 2017 for patients with HER2-positive breast cancer that is in the early stages of treatment.[116] Neratinib attaches itself mechanistically and irreversibly to the tyrosine kinase domain of HER1, HER2, and HER4. Thus, downstream signalling cascades are suppressed and autophosphorylation is reduced.[116] By reducing growth factor receptor expression and phosphorylation, neratinib significantly increases the anticancer activity of vorinostat in combination with sorafenib in pancreatic tumour cells.[117] Remarkably, neratinib was shown to function as a pro-ferroptotic drug in some metastatic breast cancer cells for the first time.[118] This conclusion was supported by research that shown liproxstatin-1, an inhibitor of ferroptosis, may stop cell death brought on by neratinib.[118] Treatment with neratinib also increases intracellular iron content in a manner that is dose-dependent.[118] More thorough research is necessary to determine the particular process by which neratinib raises iron levels, as the exact mechanism of neratinib's contribution to ferroptosis induction remains unclear.

Potential compounds to target system Xc-, GSH, and GPX4

Sorafenib

NEXAVAR, commonly known as sorafenib, is an oral bioavailable multitarget kinase inhibitor that is being used to treat patients with thyroid, liver, and advanced renal cell carcinoma.[119]

By targeting Raf serine/threonine kinases and various cellsurf ace receptor tyrosine kinases, suchas VEGFR1-3, PDGFRβ, cKit protein, FMSlike tyrosine kinase 3 (FLT3), and platelet derived growth factor receptor β (PDGFRβ)derived growth factor receptor β (PDGFRβ), sorafenib is able to exert its antineoplastic activity.[120] It has been discovered that sorafenib not only causes apoptosis but also activates autophagy in cancer cells.[121-122] Additionally, it has been discovered by researchers that sorafenib's anticancer effect can also be mediated by ferroptosis induction, which is separate from its conventional kinase inhibitory function.[123-124] By inhibiting system Xc and subsequently depleting GSH, sorafenib mechanistically causes ferroptosis.[125] Furthermore, research indicates that sorafenib-mediated ferroptosis is also modulated by the expression of a few genes, such as NRF2, retinoblastoma (RB), and MT-1G.[126-127] In hepatocellular carcinoma cells, sorafenib-induced ferroptotic cell death is negatively regulated by MT-1G, a transcriptional NRF2 targetgene, which inhibits GSH depletion-mediated lipid peroxidation.[126] Significantly, sorafenib's anticancer effectiveness is enhanced by decreasing MT-1G both in vitro and in vivo.[127]

Furthermore, the interaction between p62 and Keap1 is made worse by sorafenib therapy, which prevents NRF2 degradation and enhances NRF2 nuclear accumulation.It is interesting to note that NRF2 heterodimerizes with MafG, the V-maf avian musculoaponeurotic fibrosarcoma oncogene, and subsequently induces the transcription of several genes related to antioxidant defence, such as FTH1, HO-1, and NQO1.[128] Furthermore, a recent study showed that sorafenib-induced ferroptosis is significantly influenced by ACSL4, a positive regulator of ferroptosis.[129] Hepatocellular carcinoma cells are susceptible to mitochondrial dysfunction when treated with sorafenib.[130] In conclusion, it appears that blocking MT-1G or NRF2 in conjunction with sorafenib therapy may be a viable therapeutic strategy for ferroptosis-based cancer therapy.

Cisplatin

A platinum coordination anti-neoplastic agent called cisplatin(cisdiamminedichloroplatinum II) is frequently used to treat a variety of solid tumours, such as pancreatic, ovarian, lung, and esophageal malignancies.The primary mode of action of cisplatin is its binding to nuclear DNA and interaction with various cytoplasmic elements, such as mitochondrial DNA (mtDNA) and cytoplasmic proteins. This ultimately results in the creation of cytotoxic species, damage to DNA, and apoptotic cell death.[131] Cisplatin was found to cause ferroptotic cell death in A549 and HCT116 cancer cells in addition to its proapoptotic action.[132] Ferroptosis caused by cisplatin mostly stems from GSH depletion and subsequent GPX4 inactivation.[132] Furthermore, compared to their individual administration, the combination therapy of cisplatin and erastin demonstrated notable antitumor effectiveness.[132] According to reports, medications based on platinum exhibit a strong affinity for interacting with biomolecules that include sulphur, such as thioredoxin, metallothionein, and GSH.[133] It appears that cisplatin's primary non-DNA target in cells is GSH.[133] The Pt-GS complex is produced when about 60% of the cytoplasmic cisplatin combines with GSH. It's interesting to note that cisplatin resistance in ovarian cancer cells is connected with elevated GSH levels.[134] In conclusion, combining cisplatin with additional ferroptosis-inducing glutathione depleters may be a viable method of eliminating tumour cells.

Sulfasalazine

An FDA-approved anti-inflammatory drug called sulfasalazine is created by mixing the antibiotics sulfapyridine and salicylate. It is frequently used to treat inflammatory bowel illness and rheumatoid arthritis.[135] Sulfasalazine has been shown to have both immunomodulatory and anti-inflammatory properties, yet its exact route of action is still unknown. Furthermore, it has been demonstrated that sulfasalazine possesses anticancer capabilities against tumours. For example, it has been shown that sulfasalazine inhibits NF-κB activity, making pancreatic tumour cells more sensitive to gemcitabine.[136] Additionally, studies using glioblastoma rat xenograft models have shown that sulfasalazine enhances the antitumor efficacy of gamma knife radiosurgery.[137] Additionally, it has been shown that sulfasalazine inhibits the proliferation of certain tumour cell types by depleting GSH and inhibiting system Xc–.[137-140] Accordingly, sulfasalazine may be a viable option for inducing ferroptosis. According to Ma et al., by lowering GSH and increasing cellular platinum levels, sulfasalazine dramatically increases the lethal action of cisplatin on colorectal cancer cells.[141] Additionally, by triggering iron metabolism, sulfasalazine encourages ferroptosis.[142] Studies show that in breast cancer cell lines, sulfasalazine increases the expression of DMT1 and TFRC.[142] All things considered, sulfasalazine seems like a good option to target ferroptosis; still, more research is required to assess the therapeutic effectiveness of sulfasalazine-induced ferroptosis.

Eprenetapopt

Also referred to as APR-246 and PRIMA-1Met, eprenetapopt is a tiny, new medicinal chemical that selectively reactivates mutant p53 and encourages cancer cells to undergo apoptosis. The process that turns eprenetapopt into the reactive species methylene quinuclidinone (MQ) involves covalent bonding with cysteine residues in the p53 core domain.[143] There is considerable uncertainty regarding the exact underlying mechanism by which eprenetapopt/MQ restores mutant p53 function. Several studies have demonstrated that eprenetapopt therapy efficiently reduces tumour growth in a variety of malignancies, either when used alone or in conjunction with other anticancer medications.[144] Apart from its ability to target mutant p53, eprenetapopt has also demonstrated the ability to reduce intracellular GSH levels and inhibit the thioredoxin and glutaredoxin systems.[145-146] It might therefore be a good fit for ferroptosis induction. Birsen et al. discovered that eprenetapopt can cause ferroptosis in acute myeloid leukaemia cells, regardless of the presence of P53 mutations.[147] Treatment with eprenetapopt substantially reduces GSH levels and increases the buildup of lipid-ROS, which Fer-1 can prevent significantly.[147] Additionally, they demonstrated that eprenetapopt therapy and SLC7A11 inhibition worked in concert to reduce the tumour cell burden in the bone marrow of mice used as xenograft models.[147]

Buthionine sulfoximine

The rate-limiting stage in the synthesis of GSH is blocked by the strong irreversible GCL enzyme inhibitor buthionine sulfoximine (BSO).[148] It has been suggested that BSO may function as a possible pro-ferroptotic agent because the ferroptosis inhibitors Fer-1, α-tocopherol, and deferoxamine can prevent BSO-mediated cell death, but not the apoptosis inhibitor zVAD-fmk.[149-150] Research has demonstrated that BSO can efficiently make cancer cells susceptible to popular chemotherapeutic medications.[151-152] Recent work has shown that BSO and Ce6-based photodynamic treatment together efficiently reduce HCT116 colorectal cancer cells ability to proliferate.[153] They also propose that intracellular GSH levels are a prerequisite for the effectiveness of this synergistic action.[153]

Additionally, combining BSO with a thioredoxin reductase inhibitor such as auranofin or sulfasalazine suppresses tumour growth both in vivo and in vitro in a synergistic manner.[154] It has been demonstrated that BSO increases the anti-inflammatory medication sulindac sulfide's inhibitory impact on ATP-binding cassette subfamily C member 1 (ABCC1).[155] Notably, ABCC1 is an ATP-dependent pump that plays a major role in the development of multidrug resistance. Co-administering BSO with APR-246 substantially decreased tumour growth in mice xenografts carrying JJN3 multiple myeloma cells when compared to the control group.[156] By directly targeting the GCL enzyme, alternate antioxidant defence pathways may be activated, thus reducing the anticancer efficaciousness of BSO.[157] Therefore, in ferroptosis-based anticancer therapy, combining BSO with other antioxidant-targeting ferroptosis inducers may be a useful tactic.

Dihydroisotanshinone I

A bioactive substance called dihydroisotanshinone I (DHI) was isolated from Salvia miltiorrhiza Bunge's root and has antitumor properties against several cancer models. According to certain research, DHI causes autophagic cell death and apoptosis in order to have its therapeutic benefits.[158-159] DHI triggers the c-Jun N-terminal kinase/P38 signalling cascade, which in turn causes stomach tumour cells to undergo apoptosis.[160] Furthermore, by causing DNA damage and blocking the release of C-C motif chemokine ligand 2 (CCL2), combined treatment with radiation therapy and DHI dramatically reduces cancer migration.[161] Recent investigations have indicated

that DHI can also induce ferroptosis in many tumour cell types.[162-163] Wu and colleagues discovered that DHI administration causes ferroptosis and apoptosis, along with GSH attenuation, GPX4 inactivation, and lipidROS build-up.[164] It also suppresses the proliferation and spread of lung cancer cells. Another group also found that DHI causes ferroptosis, which inhibits the growth of human glioma cells. It was discovered that DHI inhibits the expression of the GPX4 protein to carry out its pro-ferroptotic action.[163]

Withaferin A

Steroid lactone Withaferin A (WA) is derived from the herb Withania somnifera. Numerous investigations have clarified that WA has antitumorigenic qualities against a range of cancer models.[165] Furthermore, it has been shown that using WA with other chemotherapeutic medications might enhance therapeutic results and circumvent drug resistance. Nevertheless, the fundamental therapeutic mechanisms of WA in the management of cancer remain incompletely understood. Researchers discovered that papillary and anaplastic thyroid cancers responded synergistically to combined treatment with WA and lower dosages of sorafenib, which enhanced anticancer efficacy.[166]WA has been shown to reduce the infiltration of tumor cells by focusing on indicators of the epithelial-mesenchymal transition (EMT).[167-168]In order to prevent tumour cells from entering the cell cycle, WA can also target certain modulatory enzymes.[169-170] By inducing ER stress-induced autophagy and death, the combination treatment of colon cancer cells with WA and 5-fluorouracil substantially inhibited tumour growth.[171] According to a study by Hassannia and colleagues, WA may target two different molecular pathways to cause ferroptotic cell death in high-risk neuroblastoma cells.[172] By directly inactivating GPX4, treatment of neuroblastoma cells with a high WA concentration, but not a medium concentration, facilitated the conventional ferroptosis induction. It's interesting to note that WA directly targeted the NRF2-HO-1 pathway at a medium dose but not at a high concentration, leading to elevated liable iron levels and, eventually, ROS-mediated cell death.[172] Additionally, they showed that neuroblastoma xenograft models' growth and relapse rate were successfully suppressed by WA-mediated ferroptosis.[172]

Gallic acid

Natural herbal polyhydroxyl phenolic chemical gallic acid (GA) is frequently present in a variety of food items.GA has been extensively researched for its anticancer qualities using a variety of methods. GA can cause cell cycle S/G2- and G2/M-phase arrest, which can start apoptosis and stop tumour growth.[173-174] Moreover, by causing mitochondrial dysfunction and blocking the PI3K/AKT/NF-κB signalling cascade, GA prevents bladder tumour cell invasion in vitro.[175] In cervical cancer, it was demonstrated that GA improved paclitaxel's antitumor activity.[176] The ferroptotic effects of GA on tumour cells have recently been investigated.[177] Khorsandi et al.'s study demonstrated that GA treatment decreased GPX4 activity, which led to lipid peroxidation.[178] Furthermore, treatment of colorectal cancer cells with GA was shown by Hong et al. To strongly suppress the expression of GPX4 and SCL7A1.[179] Additionally, they discovered that, in comparison to the control group, the GSH levels in tumour cells treated with GA had dramatically dropped and the intracellular lipid ROs content had noticeably increased. The effects were reversed after Fer-1 therapy to further support these findings.[179]

Cucurbitacin B

One steroid bioactive component that has been widely identified from the Cucurbitaceae plant family is called Cucurbitacin B (CuB). CuB has demonstrated a broad range of biological characteristics in traditional Chinese medicine, including antibacterial, antipyretic, anti-inflammatory, and antineoplastic effects. Over the past few decades, a great deal of research has been done on CuB's anti-neoplastic properties in a variety of cancer models. More research is required to determine the exact underlying processes by which CuB exerts its anticancer action. Xu and colleagues, on the other hand, discovered that CuB primarily inhibits the signal transducer and activator of transcription 3 (STAT3) signalling cascade to reduce the proliferation and invasion of stomach tumour cells.[180] Furthermore, it has been observed that CuB suppresses the growth of osteosarcoma cells by blocking the Janus kinase 2 (JAK2)/STAT3 and MAPK signalling pathways, which in turn induces apoptosis.[181] By decreasing the expression of the proteins MMP-2, MMP-9, and VEGF, CuB can also lessen migration and angiogenesis.[181] In a preclinical study, Lourenço et al. Reported that paclitaxel plus 2-deoxy-2-amine-cucurbitacin E (DACE), a semisynthetic derivative of cucurbitacin B, together effectively and without significant side effects inhibit the growth and proliferation of non-small cell lung cancer xenograft models.[182] Remarkably, a recent study demonstrated that CuB could also cause ferroptosis, which would result in the death of cancer cells.[183] Huang and colleagues discovered that in CNE1 nasopharyngeal cancer cells, CuB treatment dramatically enhances lipid peroxidation by decreasing intracellular GSH level and downregulating GPX4 as a result.[183] They also showed that CuB increases intracellular iron concentrations in a manner that is dose-dependent. Fer-1 and deferoxamine dramatically prevented these effects.[183] In summary, CuB seems to be a viable option for creating ferroptosis-based cancer treatment strategies.

Altretamine

Hexalen, a synthetic alkylating anti-neoplastic medication licenced by the FDA, is routinely used to monitor patients with ovarian cancer that is recalcitrant to treatment. It is still unclear what precise mechanism underlies its anticancer effects. Nevertheless, it appears that DNA damage and the production of reactive species occur simultaneously with altretamine oxidative N-demethylation.[184] Altretamine has been shown to directly block GPX4 function and cause lipid ROS buildup in an in vitro human diffuse large B cell lymphoma cell line. It will take further preclinical and clinical research to determine whether altretamine-induced ferroptosis is feasible and effective in vivo.[185]

Potential compounds to target HMG-CoA Reductase

Statins (Fluvastatin, Pravastatin, Lovastatin, Simvastatin)

Known for their ability to decrease cholesterol, statins are frequently administered to patients with hypercholesterolemia.Mechanistically, statins inhibit HMG-CoA reductase, an essential enzyme involved in the mevalonate pathway-mediated production of cholesterol, IPP, and CoQ10.[186] Numerous accounts exist on encouraging attempts to treat cancer with statins.[186] Statins have been shown to promote apoptosis in tumour cells and mediate cell cycle G1/S-phase arrest.[187] It was also shown that statins interfere with prenylation, which prevents G proteins like Rho and Ras from activating and translocating to the cell membrane. According to a paper, statins work in concert to enhance sorafenib's antitumor activity in vitro.[188] Furthermore, in comparison to control groups, the combination of simvastatin with lipid nanoemulsions paclitaxel considerably reduces the tumour growth and metastatic rate of melanoma-bearing animal models.[189] As was previously indicated, statins prevent IPP from being biosynthesised, which is essential for Sec-tRNA maturation and GPX4 protein synthesis. Therefore, statins may be useful in the induction of ferroptosis. Accordingly, statins may decrease intracellular GPX4 levels and increase lipid peroxidation in a manner that is dose- and time-dependent, according to Viswa-

nathan et al. When coupled with the direct GPX4 inhibitor RSL3, these effects were further amplified.[190] All things considered, more study is needed to determine the preclinical and clinical effectiveness of statin-induced ferroptosis.

Potential compounds to target SCD1 and ACSL4

MF-438, CAY10566, and A939572

SCD1, an enzyme linked to the endoplasmic reticulum, is essential for the transformation of saturated fatty acids (SFAs) into monounsaturated fatty acids (MUFAs). It's interesting to note that a rise in cellular MUFA concentration and overexpression of SCD1 have been seen in a number of cancer types. SCD1 may be a viable target for antitumor therapy since, as a wealth of data over the last ten years has demonstrated, it plays a remarkable role in encouraging tumour growth and metastasis.[191] According to Pisanu et al., pharmacological targeting of SCD1 with MF-438 dramatically increases the cisplatin susceptibility of lung cancer stem cells.[192] More research is required to determine the exact underlying mechanism by which SCD1 inhibition inhibits tumour growth. SCD1 inhibition induced by MF-438 and CAY1-0566 inhibits tumour cell growth and initiates apoptosis.[193] Moreover, administering CAY1-0566 to hepatocellular carcinoma cells induces autophagy via AMP-activated protein kinase (AMPK).[194] By suppressing YAP/TAZ activity, MF-438 has been demonstrated to eliminate lung cancer cells' capacity to form spheres.[195] Furthermore, A939572-inhibiting SCD1 prevents tumor cell migration that is driven by cancer-associated fibroblasts (CAF).[196] The ferroptosis is maintained by suppressing SCD1, which lowers MUFA and CoQ10 levels.According to Tesfay and colleagues, administering SCD1 inhibitors to ovarian cancer cells causes an increase in lipid peroxidation and ferroptosis-mediated cell death, which is prevented when Fer-1 and oleic acid are present. Furthermore, erastin, RSL3, and SCD1 inhibitors work in concert to suppress tumor growth in vivo and in vitro. Additionally, a different study demonstrated that concurrently giving erastin and A939572 improved ferroptosis and reduced the growth of the pancreatic tumor xenograft model.[197]

Bromelain

A naturally occurring complex mixture of enzymes extracted from pineapple plant stems is called bromelain. Bromelain is credited with a wide range of medicinal advantages, including anti-inflammatory, antithrombotic, and anticancer properties. Combining bromelain with cisplatin dramatically reduced the growth and metastasis rate of 4T1 xenograft tumours, according to a recent publication.[198] Treatment with bromelain induces apoptosis in colorectal cancer via activating the ERK/AKT pathway.[199] In a different investigation, bromelain was demonstrated to inhibit the growth of tumor cells by producing ROS and inducing autophagy.[200] Furthermore, by modifying the expression of ACSL4, researchers found that bromelain could efficiently stimulate erastin-mediated ferrroptosis in K-Ras mutant colorectal tumor cells.[201, 202]

CONCLUSION

The function of ferroptosis in controlling a number of cellular processes and several illnesses, particularly cancer, has been thoroughly investigated since its discovery in 2012. Because of the intricate nature of the tumor microenvironment, ferroptosis has a dual role in human carcinogenesis. Consequently, given that ferroptosis suppresses tumors, creating more targeted inducers of ferroptosis could be a viable and effective cancer treatment approach. In particular, figuring out which tumors respond better to ferroptosis-based treatments will be a focus of intense research in the next years because different cancer cells have varying susceptibilities to the treatment. To date, only some classical compounds such as erastin, RSL3, etc. are more specific for ferroptosis, while other inducers, including sorafenib (the first line drug in unresectable or advanced HCC and RCC), are not specific for ferroptosis. With this concept in mind, it is necessary and urgent to screen and develop more specific activators of ferroptosis. On the other hand, using natural compounds or nanoparticles as ferroptosis inducers may be a safe and effective cancer treatment strategy due to their properties and few side effects. More importantly, combine ferroptosis inducers with other anticancer therapies will provide new sights for cancer treatment. With the exception of directly targeting ferroptosis, other approaches should be explored, such as the induction of ferroptosis through modulation of ncRNAs, transcription factors, and post-translational modifications.It will be intriguing to investigate the physiological significance of ferroptosis in the advancement of different tumors using conditional knockout or knock-in mice models, as ferroptosis is a doubleedged sword in carcinogenesis.The discovery of particular ferroptosis promoters will be aided and improved in the future by cancer type-specific animal models of ferroptosis, and large-scale clinical trials will hasten the clinical translation of these discoveries. It is anticipated that in the near future, inducers of ferroptosis with the best possible specificity and efficacy will be created and applied to the treatment of different cancer kinds.

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