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Review Article

Ferroptosis Unleashed: A Bold Approach to Revolutionize Cancer Treatment

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A B S T R A C T

One of the deadliest diseases that affects world health is cancer. More than one cell death pathwayhas been found, one of which is ferroptosis. In 2012, the word ferroptosis was introduced to characterize a regulated cell death dependent on iron and arising from the build-up of reactive oxygen species derived from lipids. This particular form of cell death was discovered to possess unique molecular traits that set it apart from other types of regulated cell death. Ferroptosis characteristics have been noted. These chemical characteristics have appeared on occasion during the past few decades, but it wasn't until recently that they were identified as proof of a unique type of cell death. Here, we outline the development that led to the emergence of the idea of ferroptosis, as well as the history of data consistent with its current description. We also review the latest applications and implications of ferroptotic death pathway modifications.

Key Words: -Ferroptosis, Cancer, Iron, Reactive oxygen species, GPX4, Lipid peroxides

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INTRODUCTION

Death is the common fate of all living organisms, and so is every cell in our body. [(1)].Understanding cell death offers inherent and enormous translational potential because it offers unique opportunities to disrupt the processes involved in cell death and survival. Ferroptosis is a form of programmed cell death [(2)]

FACTS

1. Ferroptosis is often dysregulated in human cancer.
2. Ferroptosis plays a dual role in cancer.
3. Ferroptosis provides a promising strategy for cancer therapy.[(3)]
4. Excessive ionic iron will cause “iron enrichment” and cause cell death, that is, ferroptosis [(4)]

Approaches to arrest cell death have been a major focus of research on apoptosis, as it has long been considered the only form of cell death amenable to pharmacological and genetic intervention.[(5)]. Whether under physiological or pathological conditions, cell death is an unavoidable and important link in the process of life and marks the end of the life of a cell[(6)].Cell death is necessary to maintain the normal development and homeostasis of the organism and to prevent hyperproliferative diseases (such as cancer).[(7)]

Early classifications based on cell morphology in the 1970s divided cell death into apoptosis (type I), autophagy (type II), and necrosis (type III). According to the latest recommendations of the 2018 Committee on Cell Death Nomenclature, there are currently two types of cell death, namely accidental cell death (ACD) and regulated cell death (RCD). Accidental cell death is an uncontrolled and unavoidable process of cell death caused by severe chemical, physical, or mechanical stress. ACD is characterized by the immediate and catastrophic death of cells exposed to severe chemical, physical, or mechanical damage, while RCD is cell death. a process that depends on a particular molecular machine and can be modulated (accelerated or delayed) in a specific genetic way and pharmacological interventions can be modulated by pharmacological or genetic interventions[(8)]

It is essential for normal development and homeostasis, excess or insufficient RCD can contribute to the pathology of many human diseases, including neurodegeneration,

autoimmunity, and cancer.[9]. Damaged or unwanted cells can be removed from the body through regulated cell death (RCD).

RCD is further divided into apoptotic and nonapoptotic forms (e.g., ferroptosis[10], necroptosis [11], pyroptosis, and alkalosis [12][13] with different signal induction and molecular modulation properties and disease effects. RCDs depend on a specific molecular machinery that makes cells sensitive to pharmacological or genetic control. As a type of non-apoptotic RCD, ferroptosis has attracted the attention of more and more researchers and has great potential to open new avenues for effective disease treatment.[14]

Finally, in 2018, the Nomenclature Committee on Cell Death (NCCD) defined ferroptosis as "RCD caused by oxidative disturbances in the intracellular microenvironment, which is under the constitutive regulation of glutathione peroxidase 4 (GPX4) and can be prevented by iron chelators and lipophilic antioxidants. "[8]

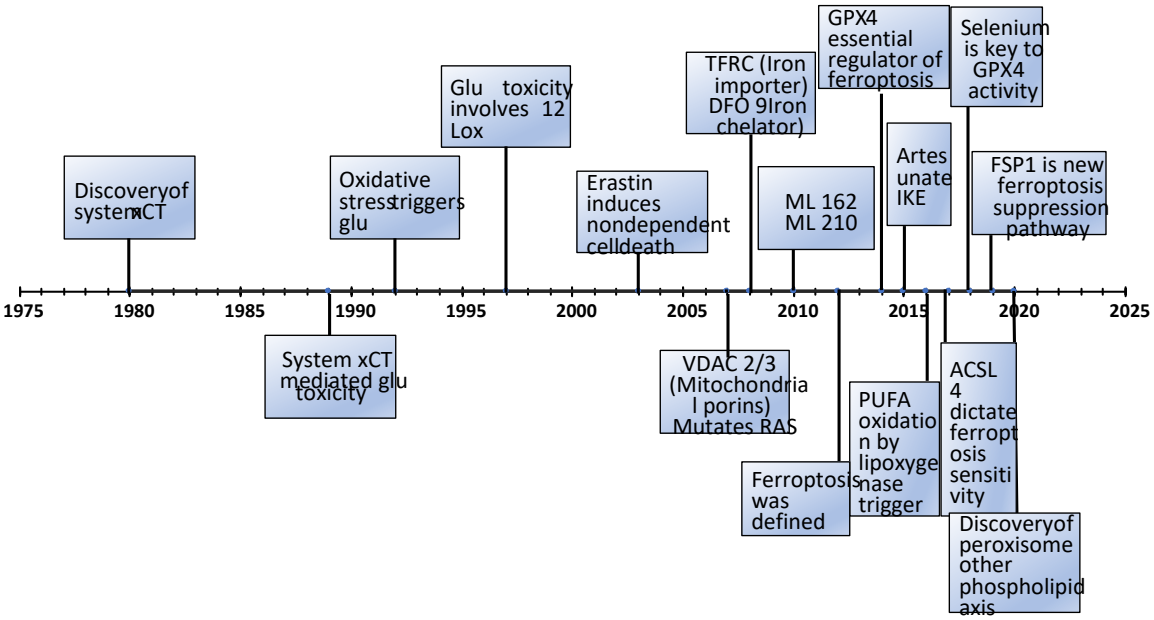
Caspase-dependent apoptosis was widely thought to be synonymous with RCD, but the discovery of several types of non-apoptotic RCD showed otherwise: apoptosis-inducing factor 1 (AIF1)-dependent parthanatos, receptor-interacting protein kinase 1 (RIPK1)-dependent. necroptosis and iron-dependent ferroptosis [15],[10][16]

This form of cell death differed from known forms of cell death in terms of morphological and biochemical characteristics. Meanwhile, iron chelators can inhibit this process and mediate cellular iron abundance. Therefore, it was called ferroptosis[17][18],[19][10]

In addition to the difference between apoptotic and non-apoptotic pathways, a clear difference is a special mechanism called "suicide" and those that occur when an essential cellular process is interrupted are called "sabotage."[20][21]

Apoptosis, necroptosis, and pyroptosis are examples of cell suicide programs executed by dedicated pathways involving key pro-death effector proteins such as BCL2-associated X protein (BAX), mixed lineage kinase domain-like protein (MLKL), and gastrin D, respectively.[22][23][24][25]

Cancer is the second leading cause of death worldwide, accounting for approximately 10 million deaths each year [26]. The production of anticancer drugs stimulates cell apoptosis as one of the main methods of killing cancer cells. However, in recent years, it has been discovered that cancer cells are resistant to drugs and have some resistance to apoptosis. Therefore, targeting other forms of non-apoptotic cell death has become a new therapeutic approach to eliminate cancer cells and reduce drug resistance in cancer cells. [27, 28]



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1. Autosis-Autosis is an autophagy-established non-apoptotic form of cell death, characterized via way of means of improved cell-substrate adhesion, focal ballooning of the perinuclear space, and dilation and fragmentation of endoplasmic reticulum. Autosis is prompted via way of means of autophagy-inducing peptides, starvation, and neonatal cerebral hypoxia-ischemia That significantly is predicated on plasma membrane Na+/K+-ATPase.[30]
2. Cellular senescence. Senescence is taken into consideration to be a particularly dynamic, multi-step manner and strong cell cycle arrest that may be precipitated in everyday cells in reaction to diverse intrinsic and extrinsic stimuli, Cellular senescence can compromise tissue restore and regeneration, thereby contributing in the direction of aging. Removal of senescent cells can attenuate age-associated tissue disorder and expand fitness span [31]. Irreversible lack of proliferative ability is related to precise morphological and biochemical features, which include the senescence-related secretory phenotype (SASP). Cellular senescence no longer represents the shape of RCD.
3. Efferocytosis. It is an anti-inflammatory process sensitive to adenosine 3, 5'-monophosphate and it is the effective clearance of apoptotic cells by phagocytosis [32]. The mechanism whereby dead cells and fragments thereof are taken up by phagocytes and disposed of defect in it results in anti-inflammatory disorders.[33]
4. Entotic cell death. A kind of RCD that originates from actomyosin-established cell-in-cell internalization (entosis) and is accomplished through lysosomes. A homotypic invasion of an epithelium cell into the cytoplasm of any other epithelial cell via way of means of deforming the personal cell of the host cell which includes the nucleus and the internal cell survives inside the host cell for 12 hours in the long run ends in dying of the invading cell.[34]

OVERVIEWOFFERROPTOSIS:-

5. Ferroptosis is an iron-dependent, non-apoptotic form of cell death that was defined in 2012. It is characterized by excessive accumulation of lipid peroxides and reactive oxygen species (ROS) intracellular iron ion accumulation, and reactive oxygen species (ROS)-induced lipid peroxidation.[35] Ferroptosis can occur in many organ systems, including testes, kidneys, heart and brain.

Brent R. Stockwell	As iron-dependent cell death is mediated by lipid reactive oxygen species (ROS) (36–38) and is significantly different from other regulated cell death forms.
Yang et al.	Renal cell carcinoma is particularly sensitive to ferroptosis and identified glutathione peroxidase 4 (GPX4) as a key regulator of ferroptosis.[39]
Alvarez et al	It also showed that resistance to ferroptosis is important for the survival of lung adenocarcinoma in a high-oxygen environment. Alvarez et al. Increasing the intracellular lip by inhibiting nfs1 has been shown to sensitize lung cancer cells to ferroptosis and reduce lung tumor growth in vivo. In addition, the et al. discovered that bay 11-7085, a known ικbα inhibitor, activates heme oxygenase-1 and increases ferroptosis in cancer cells by increasing lip.[40]
Ubellacker et al	Showed that melanoma cells prefer to metastasize via lymph nodes rather than blood to avoid ferroptosis [41]
Viswanathan et al.	Found that the therapy-resistant high-mesenchymal cell state depends on the GPX4-regulated lipid-peroxidase pathway that protects against ferroptosis [42]

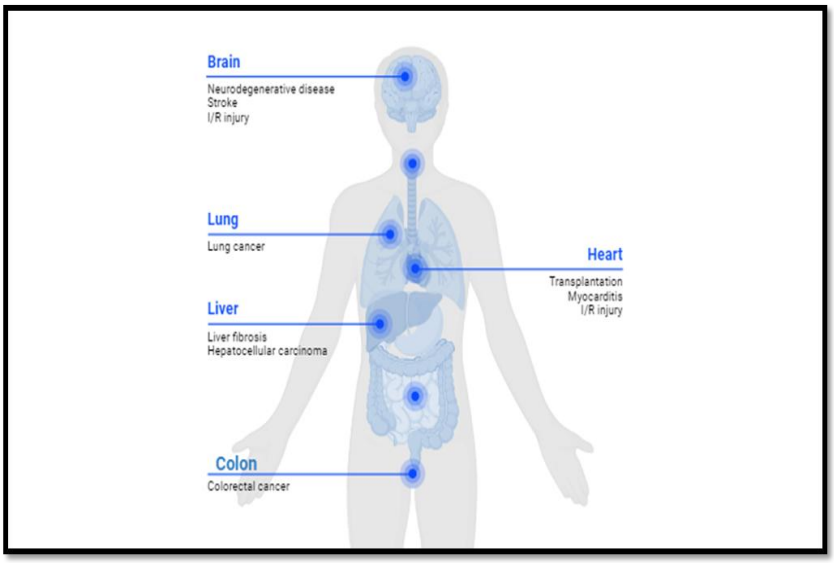

Figure 2: The involvement of ferroptosis in various human diseases. The ferroptosis process is implicated in the pathogenesis of a variety of human diseases including ischemia-reperfusion (I/R) injury diseases, neurodegenerative diseases, stroke, myocarditis, and malignant diseases (e.g., lung cancer, pancreatic cancer, colorectal cancer, clear cell renal cell carcinoma, and gastric cancer).

Molecular Principle of Ferroptosis

Biochemical features:

IRON ACCUMULATION:

Intracellular iron metabolism and homeostasis are below sensitive regulation. A state-of-the-art network, related to iron-binding and mRNA-regulatory proteins IRP1 and IRP2, can immediately experience the attention of loose iron (Fe2+) in cells, and reply with the aid of changing the synthesis of a sequence of proteins governing iron export, import, garage, and release[43].

During ferroptosis, this fine-tuned iron homeostasis might be disrupted, and an undesired growth of loose mobile iron contents (additionally recognized as “labile iron portion” or “LIP”) occurs. Such unusual growth of LIP calls for transferrin and transferrin receptor (to import iron from the extracellular environment), in addition to autophagic-lysosomal degradation of ferritin (to launch the saved intracellular iron)[44,45]

Iron is a hint detail and one of the maximum considerable metals determined inside the human body, it performs a vital position in mobile processes, inclusive of the synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and proteins, inside the delivery of electrons, in mobile respiration, in mobile differentiation and proliferation and the law of gene expression[46]

Iron is an important constituent of some of the proteins concerned with oxygen shipping or metabolism. It should additionally be transported across the body, stored, and made to be had for the synthesis of iron proteins. The potential of iron to go through cyclic oxidation and discount is a crucial element of its function. Iron can sell radical formation from physiological or xenobiotic compounds, e.g., via way of means of catalyzing autoxidation, it may provoke lipid peroxidation, and react with hydrogen peroxide to supply extra notably reactive and poisonous species.[47]

Ion metabolism law in ferroptosis in mitochondria, iron, and calcium are essential ions involved in ferroptosis. Mitochondria are the middle of cell iron metabolism, and iron ions are imported into mitochondria through the transferrin receptor at the mitochondrial membrane.[48]

Fenton Reaction:-[47]

a. Iron and hydrogen peroxide canoxidizean extensive variety of substrates and inflict organic damage. The reaction called the Fenton reaction, is complicated and able to produce each hydroxyl radical and better oxidation states of the iron.

b. The Haber-Weiss reaction is a specific example of the Fenton reaction. This term refers to the reaction between hydrogen peroxide and ferrous salts to produce a reactive species capable of oxidizing a wide variety of organic substrates. If Fe^{2+}can be recycled from Fe3+ iron can act catalytically. This is likely to be necessary under physiological conditions, where iron availability is low. Superoxide is one potential iron reductant. Hydrogen peroxide is produced in a vast majority of biologically relevant free radical reactions. Although on its own it is not particularly toxic, there are numerous examples of damage to biological molecules, in which hydrogen peroxide and iron are implicated

c. The simplest representation of the Fenton reaction is (1) in which there is an initial electron transfer with no bonds formed or broken in the process, and hydroxyl radicals are produced. This is termed an outer sphere mechanism.

d. $Fe_{2+} + H_2O_2 = Fe^{3+} + [H_20_2^-] = OH + OH^-$

Iron Metabolism:-

a. Iron chelating retailers inhibit ferroptosis via way of means of restricting iron overload, and growing exogenous iron can sell ferroptosis[49].

b. Insufficient or immoderate quantities of iron can damage cells or even the frame due to the fact it's miles one of the

essential hint factors in humans. Cellular ferroptosis is basically due to abnormalities in mobile iron metabolism, especially iron excess. The manner of iron metabolism is how iron is absorbed, stored, transformed, and excreted with the aid of using dwelling organisms[50]

c. Ferrihemoprotein is concurrently a crucial cofactor of oxidoreductases inside the mitochondrial electron shipping chain and a cofactor of many crucial enzymes in redox reactions. Extracellular ferric ions (Fe3+) integrate with transferrin to shape the transferrin–Fe3+ complex[51][52]

d. The trivalent iron ions (Fe3+) in the peripheral circulation bind to transferrin (TF) to form a complex and then enter the cellular endosome by binding to the TF receptor (TFR1) on the cell membrane. Simultaneously, Fe3+ is reduced to Fe2+ (divalent iron ions) by the iron oxygen reductase six-transmembrane epithelial antigen of the prostate (STEAP3). Subsequently, Fe2+ is released from the endosome into the cytoplasm, mediated by divalent metal ion transporter protein 1 (DMT1). Some Fe2+ released into the cytoplasm is stored in the unstable iron pool (labile iron pool [LIP]). Excess iron is stored as ferritin, and the remaining Fe2+ is oxidized to Fe3+, which is transported outside the cell by ferroportin (FPN) and participates in iron recirculation in vivo. LIP and Fe2+ formed by the degradation of ferritin can participate in the intracellular Fenton reaction, which is involved in oxidative stress [53]

Iron ions in the intracellular LIP can react with hydrogen peroxide in a Fenton reaction, which leads to the overproduction of reactive oxygen radicals, such as hydroxyl radicals. The peroxide reaction between hydroxyl radicals and phospholipids containing polyunsaturated fatty acids (PUFAs) occurs on the cell membrane and can lead to a series of changes in the cell membrane, such as the thinning of the cell membrane and the formation of protein pores. Such changes in cell membranes affect the balance of the intracellular environment and further cause cell damage [54]

Therefore, modifications inside the intracellular iron degrees via numerous pathways can affect ferroptosis. Ferritin, every other intracellular iron storage, additionally performs an essential position inside the onset of ferroptosis. Nuclear receptor coactivator-4 (NCOA4) mediates the phagocytic degradation of ferritin. NCOA4overexpression complements ferritin degradation via way of means of binding to ferritin and transporting it from the cytosol to lysosome, main to the accelerated launch of unfastened Fe2+ and ultimately accelerated lysosomal ROS production[55],[56], [57]

In addition, indirectly enhancing intracellular ferric ion concentration by increasing the expression of TF and TFR1 can also promote the occurrence of ferroptosis in cells (58)However, various interventions that lead to intracellular iron ion depletion can inhibit the occurrence of ferroptosis. Heat shock protein beta-1 (HSPB1) was recently found to inhibit ferroptosis by suppressing the expression of TRF1 to reduce intracellular iron ion concentration. [59]

Cancer cells were proven to have multiplied iron necessities for survival in assessment to regular cells.[60]

Lipid Per Oxidation:

- **Lipid metabolism-**

  In the process of ferroptosis, the disorder of lipid metabolism is a signal of cell death. The accumulation of lipid peroxidation products plays a key role in the occurrence of ferroptosis and ultimately induces ferroptosis. The intracellular lipid peroxidation products accumulate mainly through non-enzymatic lipid peroxidation and enzymatic lipid peroxidation.

- **Lipid storage-**

  Lipid droplets are ubiquitous in cells and can buffer and store excess lipids. They are very dynamic organelles composed of triglycerides and cholesteryl esters, with a hydrophobic core surrounded by a monolayer of phospholipids and various related proteins. In particular, lipid droplets interact with various organelles such as the endoplasmic reticulum (ER), peroxisomes, mitochondria, and lysosomes, making their functions more complex. In general, lipid droplets are formed from the cytoplasmic leaflets of the ER membrane, which are involved in the synthesis of neutral lipids, mainly triacylglycerols and sterols. Lipid droplet formation prevents palmitic acid-induced lipotoxicity by sequestering damaged membranes. Thus, this physical barrier function of lipid droplets can protect against different types of cell death(61)

- **Lipid utilization-**

  FAO fatty acid catabolism, which occurs in the mitochondria, involves a series of reactions that lead to the shortening of fatty acids, producing acetyl-CoA, NADH, and FADH2 in each round, from which acetyl-CoA enters the Krebs cycle, while NADH. and FADH2. FADH2 enables the production of ATP through the transport chain. The first step in FAO is fatty acid activation acyl-CoA synthetase, which produces long-chain acyl-CoA as an end product but cannot penetrate the inner mitochondrial membrane, requiring L-carnitine as a cofactor. This acylcarnitine is then imported into mitochondria (solute carrier family 25 members 20) by SLC25A20/CACT and finally converted back to acyl-CoA (carnitine palmitoyl transferase. Overexpressed CPT1 is closely associated with tumor CPT1 inhibition) by the inner mitochondrial membrane enzyme CPT2 (carnitine membrane enzyme CPT2). palmitoyl transferase). inhibits cancer cell growth Etomoxir is a CPT1 inhibitor that enhances RSL3-induced ferroptosis, suggesting that storage of PUFA for oxidation may promote ferroptosis.(62)

- **Lipid peroxidation-**

Lipid peroxidation is an indicator of ferroptosis and is due to a complicated system of lipid metabolism, related to non-enzymatic Fenton response and enzymatic response pathways. In contrast, the fatty acid beta-oxidation (FAO) in mitochondria commonly consumes the maximum of the fatty acids, accordingly main to a discount inside the charge of lipid peroxidation. [63]

PUFAs are the main targets of lipid peroxidation, which is caused by H-atom extraction of PUFAs by free radicals.

PUFAs can be acylated to phospholipid polyunsaturated fatty acids (PUFA-PL), which is regulated by acyl-CoA synthase long-chain family member 4 (ACSL4) and Lys-phosphatidylcholine acyltransferase 3 (LPCAT3). Considerable evidence indicates that ACSL4 is a susceptibility factor for ferroptosis[64,65]

ACSL4 and LPCAT3 are two types of enzymes involved in phospholipid metabolism and play an important role in the synthesis of cell membranes. The former catalyzes the esterification of PUFAs to give acyl-coenzyme A (CoA) derivatives (such as AA/AdA-CoA), while the latter incorporates them into cellular phospholipids (Dixon et al., 2015), where AA-CoA is converted to AA-CoA-CoA see MM-FRI. This is because the upregulation of ACSL4 and LPCTA3 generally promotes ferroptosis. Similarly, reducing the expression levels of ACSL4 and LPCAT3 can reduce the accumulation of lipid peroxide substrates (peroxidation to produce lipid hydroperoxides (LOOH) and subsequent reactive aldehydes (e.g., 4-HNEs or MDAs) damage the lipid bilayer and affect membrane function thereby inhibiting ferroptosis[66–69].

Enzymatic lipid peroxidation is largely mediated by the controlled activity of the arachidonate lipoxygenase (ALOX) family. The mammalian ALOX family consists of six members (ALOX3, ALOX5, ALOX12, ALOX12B, ALOX15, and ALOX15B) For example, ALOX5, ALOXE3, ALOX15, and ALOX15B are responsible for ferroptosis in human cell lines derived from different cancer types (BJeLR, HT-1080 or PANC1 cells), while ALOX15 and ALOX12 mediate the development of non-small cell lung cancer. (NSCLC) p53 induced ferroptosis in H1299 cells in which ALOX12 induced ferroptosis via TP53-mediated downregulation of SLC7A11[65,70–72]

OXIDANT SYSTEM

Free radicals, including ROS and reactive nitrogen species (RNS), are oxidants produced by redox reactions and participate in the regulation of cell survival and death. Both ROS and RNS are considered to be important signals in ferroptosis.[73]

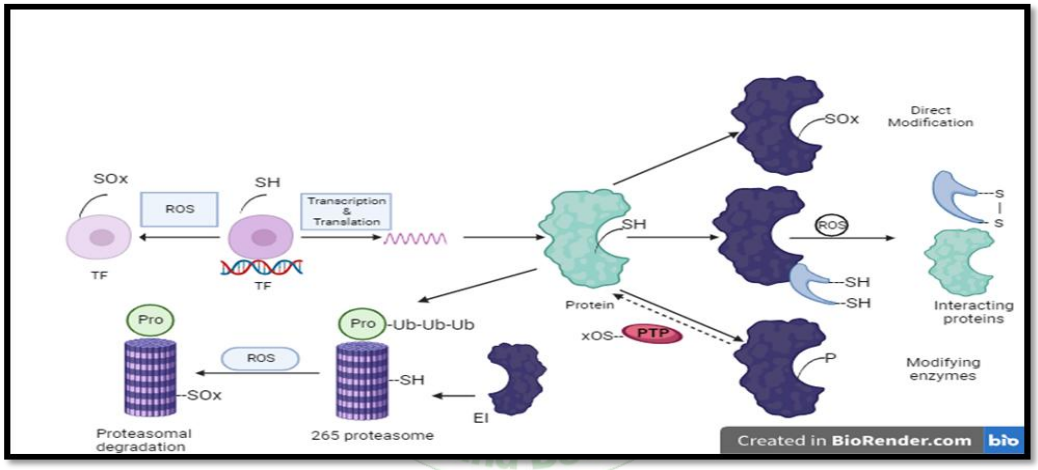

Figure 3: Mechanism of ROS

ROS=

Reactive oxygen species (ROS) are generally defined as reactive chemical compounds that contain oxygen. There are two types of ROS: free radicals, which contain one or more unpaired electrons in their outermost molecular orbitals, and non-radical ROS, which have no unpaired electrons but are chemically reactive and can be converted to radical ROS. Examples of radical ROS radicals commonly found in biological systems include superoxide, nitrous oxide, and hydroxyl radicals. Non-radical ROS compounds include hydrogen peroxide, ozone, peroxy nitrate, and hydroxide. ROS are involved in cell growth signaling and differentiation, regulate the activity of enzymes (such as ribonucleotide reductase), and mediate inflammation by stimulating cytokine production and eliminating pathogens and foreign particles. Mild increases in ROS levels can cause transient cellular changes, while severe increases in ROS in cells can cause irreversible oxidative damage leading to cell death. Cancer cells in advanced tumors often show multiple genetic alterations and high oxidative stress, suggesting that these cells can be eliminated mainly by pharmacological ROS insults.[74]

RNS =

O2 •– can react with nitric oxide (NO) and cause nitrosative stress by forming the highly reactive RNS, peroxynitrite (ONOO•). Consequences of nitrosative stress can be mitochondrial dysfunction and cell death, including ferroptosis. Nitric oxide synthases (NOSs) are a family of enzymes that catalyze the production of NO from L-arginine. In addition, inhibition of NOS2/iNOS increases the susceptibility of M1 macrophages to ferroptosis, which increases brain damage or creates a pro-inflammatory tumor microenvironment 26. The antiferroptotic effect of NOS2 may depend on the ability of NO• to inhibit ALOX15-mediated lipid peroxidation activity.

ANTIOXIDANTSYSTEM: -

System Xc: -

The cystine/glutamate counterporter (system Xc-) is a heterodimeric complex consisting of the light chain xCT

(SLC7A11) and the heavy chain 4F2 (SLC3A2). xCT Amino acids cannot diffuse directly into cells but must be transported through the cell membrane by specific transport proteins. The amino acid antiporter system Xc− is one of the transporters and consists of two main components: the light chain SLC7A11 (xCT) and the heavy chain SLC3A2 (4F2hc). This results in extracellular oxidized cysteine and cystine replacing intracellular glutamate. When cystine enters the cell, it is reduced to cysteine, and cysteine participates in the synthesis of GSH (an important endogenous antioxidant). Inhibition of the SLC7A11 pathway is the most critical downstream mechanism for inducing ferroptosis. A variety of ferroptosis inducers can inhibit cystine absorption by inhibiting system XC−, resulting in reduced GPX activity. a decrease in cell antioxidant capacity, accumulation of lipid ROS, and ultimately the occurrence of oxidative damage and ferroptosis. In addition, P53 can also inhibit system Xc uptake of cystine by downregulating the expression of SLC7A11, thereby affecting the activity of GPX4, resulting in a reduction in cell antioxidant capacity, accumulation of lipid ROS, and ferroptosis.[53]

GPX4:-

Among the many members of the GPX family, GPX4 plays a central role in the occurrence of ferroptosis.[53] GPX4 plays a key role in the regulation of ferroptosis due to its peroxidative activity. It uses GSH to eliminate lipid peroxidation and reduce membrane L-OOH to non-toxic lipid alcohols (L-OH) (79–81). GPX plays an important role in maintaining redox homeostasis and protecting cells from lipid oxidative stress, which leads to death. Because GPX4 is the only enzyme class in the human body capable of converting lipid peroxides to the corresponding alcohols, it plays a more important role than others in the development of ferroptosis.[53]

GSH deficiency leads to GPX4 dysfunction and massive lipid ROS accumulation, which is a marker of ferroptosis triggering ferroptosis. System Xc - GSH-GPX4 pathway imbalance may affect GPX4 homeostasis and ferroptosis activity found that cells with reduced expression of GPX4 were more sensitive to ferroptosis, while increased expression of GPX4 inhibited ferroptosis. RSL3, an inducer of ferroptosis, acts directly on GPX4 and inhibits its activity, which reduces cellular antioxidant capacity and accumulates ROS, causing ferroptosis.[39]

NADPH: -

NADPH, one of the most important reductants, is mainly produced by the pentose phosphate pathway (PPP) and limits peroxidative damage caused by ferroptosis. NADPH can also be synthesized by phosphorylation by NAD-post-NAD kinase (NADK). NADK silencing reduces NADPH and enhances ferroptosis induced by erastin, RSL3, and FIN56. Changes in the NADP/NADPH ratio may determine sensitivity to ferroptosis, while ferroptosis-resistant cell lines may have higher NADPH basal levels or lower NADP/NADPH ratios.[83]

AKR1C: -

Aldosterone reductase family 1 (AKR1), including the AKR1C and AKR1D subfamilies, is a family of Aldo-keto reductase enzymes that are involved in steroid metabolism. In erastin-resistant cancer cells (DU-145, CHL-1, and SK-Mel5), an increased expression of AKR1C (including AKR1C1, AKR1C2, and AKR1C3) prevents ferroptosis by reducing the end products of lipid peroxides (AA/ AdA-PE-OOHs) to the corresponding nontoxic lipid-derived alcohols (AA/AdA-PE-OHs).

Peroxiredoxin: -

Peroxiredoxins (PRDXs) are a family of selenium-independent glutathione peroxidases that contribute to the inhibition of ferroptosis. PRDX6 is recruited to the peroxidized cell membrane after oxidative stress, where it reduces and hydrolyzes the oxidized sn-2-fatty acyl or sn-2-ester (alkyl) bond of oxidized phospholipids. PRDX6 inhibits LOOH production and ferroptosis induced by erastin or RSL3 through calcium-independent PLA2 activity.[85]

Thioredoxin: -

Thioredoxin is a 12-kDa ubiquitous oxidoreductase that is central to the thioredoxin antioxidant system, which consists of thioredoxin, NADPH, and thioredoxin reductase. Ferroptoside rapidly induces ferroptosis-like cell death in various cancer cells by inhibiting thioredoxin enzymatic activity, although there is no direct evidence that ferroptosis induces lipid peroxidation.[86]

p53 PARTICIPATESIN FERROPTOSIS

p53 the tumor suppressor gene TP53 (p53) has been widely studied since its discovery decades ago (87). The ability of p53 to mediate cell-cycle arrest, senescence, and apoptosis is widely assumed to be accountable for its function in tumor suppression[88].Activation of p53 was found to significantly decrease the expression of SLC7A11 in cells, and upregulation of p53 decreased the expression. In addition, Xie et al found that in colorectal cancer (CRC) cells, p53 can also inhibit ferroptosis by combining with dipeptidyl peptidase4 (DPP4).(89)To date, p53 is believed to be at the center of a powerful signaling network during ferroptosis. p53 can increase the sensitivity of cells to ferroptosis to eliminate abnormal cells and prevent tumor formation, while on the other hand, p53 has another important function to protect normal cells from various stressors. When metabolic stress occurs, p53 can both reduce the sensitivity of cells to ferroptosis and protect them, allowing them to maintain normal physiological functions. [90]

BIOMARKERS OF FERROPTOSIS: -

PTGS2 is generally considered a biomarker of ferroptosis, but it is not a driving factor. ACSL4 is involved in fatty acid synthesis and is considered a specific biomarker and trigger of ferroptosis.[91,92]

REGULATIONMECHANISMOF FERROPTOSIS

LIPIDMETABOLISM

Lipid metabolism regulates cellular lipid toxicity, and abnormal lipid metabolism is considered a hallmark of malignancy and an important factor in ferroptosis. Due to the weak C-H bond at the diallyl position, cell membrane PUFAs are vulnerable to ROS attack, which can induce lipid peroxidation. Acyl-CoA synthetase long-chain family member 4 (ACSL4), which positively regulates ferroptosis, is

required for the production of PUFAs in this process.(94).In contrast, exogenous MUFAs such as exogenous palmitic acid and oleic acid have been reported to negatively regulate drug-induced ferroptosis.[95,96] . Acyl-CoA synthetase long-chain family member 3 can activate exogenous MUFAs to displace PUFAs in the plasma membrane and reduce the susceptibility of plasma membrane lipids to oxidation. In addition, an increased ratio of MUFAs to PUFAs can be observed on cancer cell membranes, which prevents lipotoxicity and ferroptosis. [97]

MITOCHONDRIALMETABOLISM

A survey of the literature demonstrates unequivocally that the ultrastructural adjustments of mitochondria are taken into consideration the morpho-logical trademark of ferroptosis on the identical time, a right characteristic of mitochondrial bioenergetic metabolism is obligatory for the initiation and the accomplishment of ferroptosis [98]-[99]. Mitochondria, as the principalweb page of intracellular iron utilization, also are the principal supply of mobile RO. Ferroptosis is, indeed, related to excessive harm to mitochondrial morphology, bioenergetics, and metabolism. Cells present process ferroptosis showcase unique adjustments in mitochondrial morphology, along with a discount in the number of mitochondrial cristae and a lower in mitochondrial size.

FSP1

Ferroptosis suppressor protein 1 (FSP1) is an oxidoreductase that catalyzes the reduction of ubiquinone (also known as coenzyme Q10, CoQ10). Ubiquinone is a lipophilic free radical scavenger. FSP1 can use NAD(P)H to catalyze CoQ10 regeneration. In this way, FSP1 can protect against ferroptosis caused by loss of GPX4. The FSP1-CoQ10-NAD(P)H pathway is an independent parallel system that cooperates with GPX4 to prevent increased L-ROS-induced ferroptosis.[100]

Nuclear factor erythroid 2-related factor 2

Nrf2 is a transcription factor that plays an important role in cellular antioxidant defense, and its activity is regulated by Kelch-like ECH-related protein 1 (Keap1). Keap1 promotes the sequestration of Nrf2 in the cytoplasm and targets Nrf2 for ubiquitination and degradation in the proteasome.–[101]

Nrf2 is also an important regulator of the antioxidant response in the body. Under normal conditions, Kelch-like ECH-associated protein 1 (Keap1) promotes Nrf2 ubiquitination and proteasomal degradation. However, under oxidative stress, Keap1 is abnormally activated, leading to the destruction of the interaction between Nrf2 and antioxidant response elements, thus participating in the regulation of ferroptosis.[102–104]

INDUCERSOF FERROPTOSIS: Ferroptosis can be induced by small-molecule compounds or drugs targeting transporters or enzymes in the following ways:

- Class I FINs- Class I ferroptosis inducers (FINs) mainly consume intracellular GSH which is more than 1000 times of cancer cells than that of extracellular cells and 4 times that of normal cells. GSH plays an important role in scavenging superoxide and resisting cell death [106]. So GSH has been considered cancer's Achilles' heel [105]
- Class II and III FINs-class II FINs mainly target GPX4 and inactivate its activityclass III FINs mainly consume GPX4 and endogenous antioxidant CoQ10 through the SQS-mevalonate pathway(105)therefore, for this type of cancer cells, the targeted inactivation of the activity of GPX4 by class II and III FINs can induce ferroptosis of the cells. RSL3 can induce ferroptosis by directly targeting GPX4 which inactivates GPX4 through the alkylation of selenocysteine.

Class IV FINs Based-class IV FINs induce lipid peroxidation by increasing the LIP or oxidizing iron in the characteristics of cancer cells, which may provide new opportunities for cancer treatment [107].

Target	Drug	Tumor type	Mechanism	References
A. Class I FINs				
SLC7A11	Erastin,	Glioma, lung, cervical, breast cancer, melanoma, fibrosarcoma	Inhibit SLC7A11	(35),(17),(18)
	Piperazine,	Fibrosarcoma		(108)
	Imidazole,	Diffuse large B-cell lymphoma.		(70)
	Sulfasalazine,	Breast cancer, glioblastoma, fibrosarcoma, non-small-cell lung cancer, prostate cancer		(35), (109)
	Sorafenib,	Acute myeloid leukemia, hepatocellular carcinoma, neuroblastoma, non-small-cell lung cancer, renal cell carcinoma,		(84)
	Glutamate			(35,110)
GCL	Buthionine sulfoximine	Melanoma, neuroblastoma	Inhibit the GCL and reduce GSH synthesis	(35), (111)
GSH	Cisplatin	Ovarian cancer, pancreatic cancer, NSCLC, urothelial cancer	Combine with GSH to inactivate GPX4	(112)
B. Class II and III FINs				
GPX4	RSL3	Fibrosarcoma, NSCLC, pancreatic cancer, leukemia	Inhibit GPX4 directly	(2,113)(114)
	FIN56	Fibrosarcoma	Combine and activate SQS to reduce CoQ10	(115)(116)
	FINO2	Fibrosarcoma	Oxidize Fe2+ and PUFAs,	

			promote the accumulation of ROS; indirectly inactivate GPX4	(2), (117)
C. Class IV FINs				
Iron	Heme	Glioblastoma, leukemia	Up-regulate HMOX1 expression and increase LIP	(77)(118)
	Withaferin A	Breast cancer, Neuroblastoma	Up-regulate HMOX1 expression to increase LIP at middle dose and inactivate GPX4 at high doses	(119)(120)
	BAY 11–7085	Colorectal cancer, cervical cancer	Up-regulate HMOX1 expression and increase LIP	(121)
	Salinomycin	Various solid tumours	Decrease SLC40A1, increase transferrin, and LIP	(122)
	Siramesine, lapatinib	Breast cancer	Decrease SLC40A1, increase transferrin, and LIP	(123)
D. Others				
ROS	BAY 87–2243	non-small-cell lung cancer	Combine with the mitochondrial respiratory chain complex I	(121)

FERROPTOSISINHIBITORS

Drug	Target	Mechanism	References
Vitamin E, α-toc, trolox, tocotrienols	LOX	Restrain LOX PUFA oxygenation	(67)(124)
Deuterated polyunsaturated fatty acid Butylated hydroxytoluene, Butylated hydroxyanisole Ferrostatins, liproxstatins	Lipid peroxidation	Inhibit lipid peroxidation	Raefsky et al., 2018)(126)(127)(128)(35)
CoQ10, idebenone		Target lipid peroxyl radicals	(129)(100)
XJB-5-131, JP4-039		Nitroxide-based mitochondrial lipid peroxidation mitigators	(127)
Baicalein	LOX	Inhibit 12/15-LOX	(130)(131)
PD-146176		Inhibit 15-LOX-1	(132)
AA-861			(133)(134)
Zileuton		Inhibit 5-LOX	(92)
Deferoxamine, ciclopirox, deferiprone	Iron	Reduce intracellular iron	(35)
Glutamine deprivation, Glutaminolysis inhibitor	Glutaminolysis	Hinder the mitochondrial TCA cycle	(135) (136)
Cycloheximide	Protein synthesis	Inhibit xCT protein synthesis	(137)
β-mercaptoethanol	Reducing agent	Reduce Cys2 to Cys	(138)
Dopamine	Neurotransmitter	Increase the stability of GPX4	(139)
Vildagliptin, alogliptin, linagliptin	Dipeptidyl-peptidase-4	Reduce lipid peroxidation by inhibiting DPP4	(111)

FERROPTOSISANDCANCERS:

Ferroptosis is a new type of cell death that has been reported in many malignancies such as breast cancer, liver cancer, stomach cancer, rectal cancer, prostate cancer, and pancreatic cancer.[40][119,140].

Synthetic and Natural compounds Regulating Ferroptosis In Cancer

Drug	Tumor type	Targets	Models	The phase of clinical development	Reference
Sorafenib	AML, HCC, neuroblastomas, RCC	SLC7A11	Huh7, PLC/ PRF5, PANC-1, BxPC-3, HCT116, and HT-29 cell lines	Marketed	(141)(142)(143)
Cisplatin	Ovarian cancer, pancreatic cancer, urothelial cancer	GSH	Nude mice; A549, NCI- H460, and H1299 cell lines	Marketed	(144)
Erastin	Prostate cancer	ROS and iron	Xenograft models; DU145, PC3, 22Rv1, LNCaP, and NCIH660 cell lines	Pre-clinical	(145)
RSL3	Prostate cancer	ROS and iron	Xenograft models; DU145, PC3, 22Rv1, LNCaP, and NCI-H660 cell lines	Pre-clinical	(145)
Ketamine	Liver cancer	GPX4	Patient tumor tissues; BALB/c nude mice; HepG2 and Huh7 cell lines	Approved	(146)
6-Gingerol (natural)	Lung cancer	USP14 and GPX4	Nude mice; A549 cell line	Preclinical	(147)
Bufotalin (natural	Non-small cell lung cancer	GPX4	BALB/c nude mice; A549 cell line	Preclinical	(148)

Others Target Ferroptosis Pathways in Oncology

Drug	Tumor type	Targets	The phase of clinical development	References
Zalcitabine	AIDS-related Kaposi sarcoma	DNA stress inducer	Marketed for the treatment of HIV, preclinically for the treatment of cancer	(149)
Buthionine sulfoximine	Melanoma, neuroblastoma	GCL inhibitor	Phase I	(150)
Neratinib	Breast cancer	Iron activators	Marketed	(151)
Salinomycin	Various solid tumours		Marketed as an antibacterial drug, in preclinical studies of anticancer activity	(122)
Lapatinib	Breast cancer		Marketed	(123)
Pravastatin	Acute myeloid leukemia, hepatocellular carcinoma;	HMGCR inhibitors	Marketed as a lipid-lowering agent, in oncology phase I trials	(152)
Fluvastatin	Breast cancer		Marketed as a lipid-lowering agent, in oncology phase I trials	(153)

Ferroptosis and Radio Therapy:

- About 50–70% of patients with malignant tumors require radiotherapy during treatment.(154)
- Cobler et al found that elastin can increase the sensitivity of breast cancer cells to γ-rays in vivo and in vitro by inhibiting system XC−, and thought that elastin might prolong the duration of radiation-induced DNA damage.(155)
- Erastin enhanced X-ray-induced cell death of cervical cancer and lung cancer and demonstrated the same effect in tumor-bearing mice.(156)-(157)
- More advantageously, most normal cells do not express SLC7A11,110, so erastin may specifically increase the sensitivity of cancer cells to radiation, thereby increasing the death or proliferation of cancer cells and preventing radiation damage in normal cells.(155).

Noncoding RNAs (ncRNAs) Promote Ferroptosis in Cancer:

ncRNAs	Targets	Model	Mechanism summary	Reference
miR-15a	GPX4	LNCaP cell line	miR-15a promotes ferroptosis by inhibiting GPX4 expression	(158)
miR-15a-3p	GPX4	Patient's tumor tissues; nude mice; HCT-116, CaCo2, HT29, and KM12 cell line	miR-15a-3p positively regulates ferroptosis by directly targeting GPX4, thereby inhibiting cancer cell proliferation, migration, and invasion	(159)
miR-4715- 3p	AURKA/ GPX4	Patient's tumor tissues; MKN45 and STKM2 cell lines	miR-4715-3p mediates decreased AURKA levels, and inhibition of AURKA or recombination of miR-4715-3p inhibits GPX4 and induces ferroptosis.	(160)
miR-324-3p	GPX4	A549 cell line	miR-324-3p directly targets GPX4 to induce ferroptosis and reverse cisplatin resistance.	(161)
miR-302a3p	FPN	A549, H358, H1299, and H1650 cell lines	miR-302a-3p increases ROS accumulation, induces ferroptosis, and inhibits cell growth by targeting FPN.	(162)
miR-214-3p	ATF4/GSH	nude mice; HepG2 and Hep3B cell lines	miR-214 directly targets ATF4, reduces GSH, enhances erastin-inducedferroptosis, and suppresses tumor growth	(163)
SLC16A1- AS1	miR-1433p/ SLC7A11	HK-2, 786-O, A498, and Caki-1 cell lines	lncRNA SLC16A1-AS1 induces ferroptosis and inhibits cell viability, proliferation, and migration through miR-143-3p/ SLC7A11 signaling	(164)
ARHGEF26- AS1	miR-372-3p/ ADAM23/ GPX4/ SLC7A11	Ec9706, TE-1, and EC109 cell lines	ARHGEF26-AS1 promotes ferroptosis by inhibiting SLC7A11 but inhibits cell growth via miR-372-3p.	(165)
MT1DP	miR-365a-3p/ NRF2	Patient's tumor tissues; nude mice; A549 and H1299 cell line	MT1DP sensitizes ferroptosis by upregulating MDA and ROS levels and reducing GSH levels via the miR-365a-3p/NRF2 axis	(166)
circ0000190	miR-382-5p/ ZNRF3	Patient's tumor tissues; AGS, KATO III, MKN1, and HGC27 cell lines	circ_0000190 sponges miR-382-5p inhibits cell proliferation and promotes erastin-induced ferroptosis by targeting ZNRF3	(167)

Role of ferroptosis in the occurrence and development of related diseases Ferroptosis and tumor:-

- **Pancreatic Cancer:-**

Found artesunate (ART) and the combination of Cotylen A (CN-A) and phenylethyl isothiocyanate (PEITC)induce ROS production and activate ferroptosis in pancreatic ductal adenocarcinoma cell lines and MIAPaCa-2 and PANC-1 cell lines). The combination of piperlongumine (PL), CNA, and sulfasalazine (an inducer of ferroptosis) significantly promotes ferroptosis in pancreatic cancer cell lines MIAPaCa-2 and PANC-135, has been found by Yamaguchi et al.[169]

- **Hepato cellular carcinoma (Hcc):**

Louandre C et al. found that the Rb-negative state of HCC cells promotes ferroptosis when exposed to sorafenib. Sorafenib is widely used in the treatment of advanced HCC, and the induction of ferroptosis in HCC cells is an important mechanism of the biological effects of sorafenib.

Inhibition of the Sigma 1 receptor (S1R), which is present in liver cells,also promotes ferroptosis in HCC cells[170(170)]. HCC has many negative regulators of ferroptosis, such as nuclear factor erythroid 2-related factor 2 (NRF2), metallothionein-1G (MT-1G), CDGSH iron-sulfur domain 1 (CISD1), and P53, which suppress ferroptosis in HCC cells. p62-Keap1-NRF2 and the RAS/Raf/MEK pathwayplay an important role in inhibiting ferroptosis in HCC cells.(104)(171). MT-1G promotes sorafenib resistance by inhibiting ferroptosis, and MT-1G knockdown increases GSH depletion and lipid peroxidation.[172]

- **Gastric Cancer (GC):**

Found that erastin can induce ferroptosis in gastric GC cells and that cysteine dioxygenase type 1 (CDO1) plays a key role by competitively absorbing cysteine and limiting the process of GSH synthesis and promoting ferroptosis. Inhibition, which restores GSH levels in cells, prevents ROS production, reduces lipid peroxide levels, and ultimately prevents ferroptosis. [173]

- **Colorectal Cancer (CRC):**

Found that erastin can induce ferroptosis in gastric GC cells and that cysteine dioxygenase type 1 (CDO1) plays a key role by competitively absorbing cysteine and limiting the process of GSH synthesis and promoting ferroptosis. Inhibition, which restores GSH levels in cells, prevents ROS production, reduces lipid peroxide levels, and ultimately prevents ferroptosis.[174]

- **Breast cancer: -**

Breast cancer is one of the leading causes of cancer-related death in women. Current ferroptosis targets in breast cancer therapy mainly focus on critical regulators of endogenous and exogenous regulatory pathways: inhibition of system xc, inhibition of GPX4, inhibition of Fe3, or inhibition of downstream regulators of ferroptosis such as p53.[175] While triple-negative breast cancer (TNBC) accounts for ~15-18% of breast cancers. TNBC currently lacks an effective targeted therapy, usually based on chemotherapy, and has a poor prognosis. Cysteine is one of the most important amino acids in TNBC. Therefore, inhibiting the function of the Xc system reduces cystine availability and causes ferroptosis.[53]

- **Lung Cancer: -**

In highly differentiated lung adenocarcinomas, the iron-sulfur cluster biosynthetic enzyme NFS1 maintains iron-sulfur cluster expression levels. Inhibition of NFS1 alone does not induce ferroptosis, but when cells produce large amounts of ROS, iron starvation induced by NFS1 inhibition promotes ferroptosis.[40]

Clear cell renal cell carcinomas (ccRCC):

ccRCC cells are highly sensitive to the depletion of glutamine and cystine, which are required for GSH synthesis. These cells are highly dependent on the GSH/GPX pathway to prevent lipid peroxidation and cell death. It has been found that inhibition of GSH synthesis in ccRCC can stimulate ferroptosis and inhibit tumor growth [176]

- **Adrenocortical Carcinomas (ACCs):**

ACCs are highly malignant cancers, and mitotane is routinely used in current treatment regimens. Significantly increasing GPX4 expression and inducing ferroptosis may be a promising approach for the treatment of ACCs.[177]

- **Ovarian Cancer:**

Massive amounts of ART cause ROS-dependent DNA mutation and cellular demise in ovarian cancer cells, which results in G2/M phase arrest and is frequently linked to ferroptosis.[178] When iron metabolism is significantly disturbed with increased iron uptake and retention, expression of TFR1 for iron uptake is increased, expression of the iron efflux pump FPN is decreased, and ferritin is relatively increased. The biological processes mentioned above can cause excessive accumulation of iron in cells, which is the basis for the development of ferroptosis.[179-181]

- **Melanoma:**

By directly affecting the glutamine transporter SLC1A5, miR-137 has been shown to negatively control ferroptosis in melanoma cells, whereas miR-137 knockdown promotes ferroptosis. It is also found that inhibition of mitochondrial complex I increases mitosis-dependent ROS levels, ultimately leading to ferroptosis in melanoma cells.[181]

- **Head and Neck Malignancies**

The primary cause of ferroptosis brought on by the buildup of lipid ROS and mitochondrial iron is GPX 4 inhibitors RSL 3 and ML-162, CISD2. ART can cause variable degrees of ferroptosis in head and neck cancer cells, lowering GSH levels and causing ROS generation.[182–184].

- **OSTEOSARCOMA: -**

Osteosarcomaisthe most common primary bone malignancy occurring in young people. The high expression of the major iron-like protein TFR1 was reported, which is very important in ferroptosis. This TFR1 produces tumors in osteosarcoma along with Cellular differentiation grade, steps, and invasion.[185-187].

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