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Unraveling the Dual Nature of GPx4: From Ferroptosis Regulation to Therapeutic Innovation in Human Pathologies

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ABSTRACT

GPx4 (Glutathione peroxidase 4) is a Sec (selenocysteine)-dependent monomeric antioxidant enzyme capable of maintaining cellular redox homeostasis by catalyzing the reduction of lipid peroxides by GSH (glutathione). As a core regulatory node of the ferroptosis pathway, GPx4 not only directly affects apoptosis, but also deeply participates in tumorigenesis, cellular senescence, and other key biological processes by inhibiting the lipid peroxidation cascade; at the same time, GPx4 also exhibits a key targeting value in neurodegenerative diseases, metabolic disorders, and cardiovascular pathologies.The aim of this paper is to analyze the protein structure and biological function of GPx4, to systematically explore the core regulatory role of this enzyme in the ferroptosis pathway and its molecular mechanism in various diseases, and ultimately to break through the existing therapeutic bottlenecks based on the current progress of research, and to provide a new idea for the precise intervention strategy targeting GPx4.

Keywords: GPx4; Ferroptosis; Disease

Introduction

The GPx family is a family of selenium-containing antioxidant enzymes, and the common feature of the proteins in the family is the presence of cysteine as a key functional residue in redox reactions in the center of their catalytic activity[1,2].The GPx proteins were first identified in 1982, when Ursini's team isolated a novel peroxidation inhibitory protein with a molecular weight of 20 kDa for the first time from porcine liver cytosol, and found that the protein in the presence of GSH (glutathione), it significantly inhibited peroxidative damage to phosphatidylcholine liposomes and biological membranes[3]. The human GPx family contains eight isoforms, which differ significantly in tissue distribution, structural features, functional localization, and substrate selectivity[4], including gastrointestinal-type GPx2, which is localized in the gastrointestinal tract[5], plasma-type GPx3[6], and phospholipid peroxidation-type GPx4, etc. GPx4 is a key antioxidant enzyme in the organism[7] and GPx4 once known as PHGPx, is the star molecule in the GPx family and has a special status due to its unique ability to reduce phospholipid peroxidesreduction ability[8].

1 GPx4 Overview

The GPx4 gene is located at the position of sub-band 3 in the main band 13 of the short arm of chromosome 19 in the human genome and the full length of the GPx4 gene is 2865 bases[9]. From this study using X-rays it was resolved that GPx4 is a monomeric protein containing four α-helices and seven β-strands, and the most critical finding was that it lacks a surface loop structural domain, which explains why GPx4 is able to contact complex lipid substrates. Moreover, this study found that the catalytic triad of GPx4 is located on a flat surface surrounded by basic amino acid patches, K48/K135/R152/T139, and this particular conformation supports its broad-spectrum substrate specificity[10], and several studies have demonstrated that the molecular weight of GPx4 proteins is 19-22 kDa[11,12], Moreover, we compared the amino acid sequences of GPx4 protein in various model organisms using sequence analysis software (SNAPGENE, 6.0.2, San Diego, CA, US) and found that it was highly conserved (Figure 1) , making it a cross-species universal model for studying ferroptosis mechanisms and accelerating the clinical translation of anticancer and neuroprotective drugs targeting this protein.

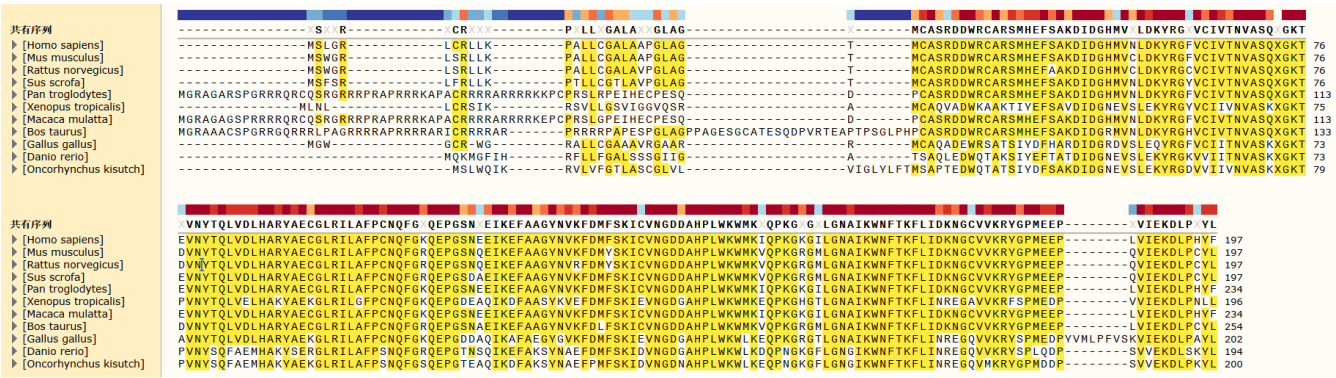

Fig 1: Sequence conservation of GPx4 in multiple model organisms.[1]

GPx4 is a selenocysteine-containing glutathione peroxidase whose core biochemical property is to utilize glutathione to specifically reduce phospholipid hydroperoxides in cell membranes[13-15]. This unique lipid-repairing ability makes it a key molecular defender in inhibiting lipid peroxidation and preventing ferroptosis, which is essential for cell survival and organismal development[16-18].

In general, the GPx4 gene is capable of expressing three isoforms, which are generated by selective promoter or mRNA splicing to generate different isoforms [19,20]. The three isoforms are cytoplasmic (c-GPx4), mitochondrial (m-GPx4) and nuclear (n-GPx4)[20,21]. The classification of the three subtypes of proteins is closely related to their functions, for example, c-GPx4 plays an important role in the defense against ferroptosis, which can scavenge intracytoplasmic lipid peroxides, maintain intracellular redox homeostasis, and participate in the regulation of cell proliferation, differentiation, and antiferrodeath[22]. m-GPx4 has a mitochondrial signal at its N-terminal end, so that the m-GPx4 protein targeting localizes to the mitochondria, with its main function is to protect the mitochondrial membrane from lipid peroxidation damage and maintain the structural integrity and function of mitochondria[22], and it also has the unique function of maintaining energy metabolism and preventing mitochondria-derived ferroptosis[23-25]. n-GPx4 mainly maintains chromatin cohesion and genetic integrity. n-GPx4 protects the lipids and genetic material in the nucleus from oxidative damage[26,27], and some studies have found that n-GPx4 also has the special function of sperm nuclear maturation and safeguarding male reproductive function[28-30]. According to the structure and catalytic mechanism of GPx4 protein, it can also be classified into selenium-dependent and non-selenium-dependent; and by species and evolution, it can be classified into mammalian and non-mammalian GPx4 homologs.

2 GPx4 and the regulation of ferroptosis

2.1 GPX4'S CENTRAL ROLE IN FERROPTOSIS

As a selenium-dependent glutathione peroxidase, the core function of GPx4 is to directly block the lipid peroxidation chain reaction through the selenocysteine-substituted cysteine in its active center by using reduced GSH to specifically reduce phospholipid hydroperoxides ,e.g phosphatidylcholine hydroperoxides

1 The highlighted parts are the identical amino acid sequences of GPX4 in various model animals.

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in the cell membrane system[31-33]. This function plays a key role in protecting the integrity of the plasma membrane, mitochondrial membrane and nuclear membrane, and is a central antioxidant mechanism for maintaining cellular redox homeostasis[34].When it comes to the non-classical functions of GPx4, these include the ability to scavenge lipid hydroperoxides to prevent iron-dependent cell death[35]; also reproductive-specific functions, such as the aforementioned nGPx4 catalyzing sperm protein disulfide bond formation in the nucleus of spermatocytes to drive chromatin densification[28]; and involvement in the repair of ischemia/reperfusion injuries through the inhibition of ferroptosis, as well as in the modulation of drug resistance in cancer cells[36,37].We summarize the bidirectional role of GPx4 in Table 1.

Table 1: Bidirectional action of GPx4.

Specific role	Mechanism of action	References
Neurodegenerative diseases: Protect neurons, delay progression	Reduces phospholipid peroxides and inhibits neuronal ferroptosis	[77,78,79]
Ischemia-reperfusion injury: Alleviate organ damage	Scavenges lipid ROS in the heart/kidneys and reduces cell death	[36]
Atherosclerosis: Delay plaque progression	Inhibits lipid peroxidation in vascular endothelial cells and reduces foam cell formation	[83,84]
Male infertility: Ensure sperm motility	Maintains sperm cell membrane integrity and prevents oxidative damage	[28-30]
Malignant tumors: Enhance drug resistance, promote metastasis	Scavenges lipid ROS in tumor cells and inhibits ferroptosis	[67,68]
Chemotherapy-resistant tumors: Cause chemotherapy failure	Resists ferroptosis inducers (e.g., erastin) through the System Xc^--GSH-GPx4 axis	[69,71]

Ferroptosis is an iron-dependent, lipid peroxidation-driven form of programmed cell death, the execution of which centers on the uncontrolled accumulation of PL-OOH (phospholipid hydroperoxides)[38,39], and Unlike the accidental necrosis caused by severe external insults, ferroptosis is a form of programmed cell death [40,41].GPx4 plays an irreplaceable defense role in ferroptosis, as the only selenoprotein that can directly reduce membrane phospholipid hydroperoxides, GPx4 blocks the lipid peroxidation chain reaction by utilizing GSH to convert toxic PL-OOH into harmless lipid alcohols[17,42].This unique repair capacity makes GPx4 the ultimate barrier to inhibit ferroptosis, for example, when GPx4 is targeted by the inhibitor RSL3, genetically deficient, or when upstream GSH synthesis is blocked, PL-OOH accumulates in bursts in cell membranes, especially mitochondrial membranes(Figure 2), triggering membrane integrity disintegration and iron-dependent free radical reactions that directly trigger ferroptosis[21,43,44]. Thus, GPx4 activity is a central molecular switch in the ferroptosis pathway, and the System Xc-GSH-GPx4 axis is also a central pathway in the ferroptosis pathway, in which a key member, inhibitory SLC7A11 (solute carrier family 7 member 11), inactivates GPx4 and increases lethal reactive oxygen species by blocking the entry of cysteine into the cell. thereby reducing GSH synthesis and ultimately inducing ferroptosis[45-47].

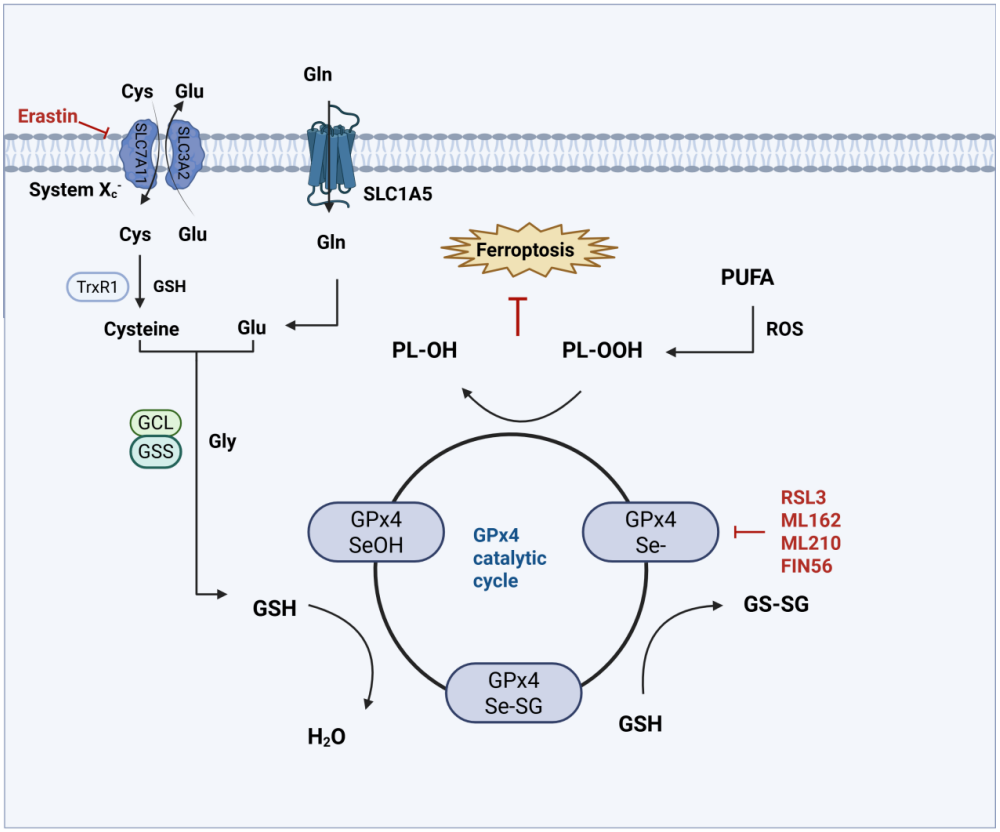

Fig 2 The role of GPx4 in ferroptosis.

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2.2 REGULATORY MECHANISMS OF GPX4

The function of GPx4 is precisely regulated at multiple levels, with post-translational modification being the most rapid response mechanism. CKB (Creatine kinase B) exhibits a non-classical function under oxidative stress rather than a classical metabolic enzyme role, directly phosphorylating the Thr136 site of GPx4 and significantly enhancing its enzymatic activity to resist ferroptosis[48]. It has been shown that AC binds to and promotes ubiquitination of GPx4 protein, leading to degradation of GPx4 via the proteasome pathway, thereby reducing its protein expression level and synergizing with autophagy activation to induce ferroptosis[49]. In addition to the common phosphorylation and ubiquitination, there are also examples of GPx4 being palmitoylated.GPx4 undergoes palmitoylation at the cysteine 66 site, a modification that enhances the protein stability of GPx4 and reduces cellular sensitivity to ferroptosis[50].

Further, transcriptional regulation remodels GPx4 expression levels through key factors. For example, Nrf2, in this paper, GPx4 is a downstream target of the transcription factor Nrf2, which acts as a transcription factor that influences the ferroptosis process by regulating the expression of GPx4, and the absence of Nrf2 leads to a reduction in the expression of GPx4, which exacerbates ferroptosis and liver injury. In a CCl4-induced acute liver injury model, knockdown of Nrf2 further impaired the protective effect of bicyclol[51]. In p53-mutant colon cancer cells, MDM4 (murine double minute 4) inhibits ubiquitinated degradation of GPx4 by upregulating the expression of the E3 ubiquitin ligase TRIM21, a regulatory mechanism that allows GPx4 to maintain high protein levels in p53-mutant colon cancer cells, which, in turn, inhibits the occurrence of ferroptosis[52].

At a longer-term epigenetic level, methylation, histone modifications, and non-coding RNAs can collectively influence the epigenetic phenomenon of GPx4. PRMT5 (Protein arginine methyltransferase 5)-mediated symmetric dimethylation of GPx4 at arginine position 152 significantly prolongs the half-life of GPx4 by blocking the ubiquitination degradation pathway of the FBW7 E3 ligase, which enhances the resistance of tumor cells to ferroptosis[53,54].HDAC9 mediates the deacetylation and ubiquitination of the transcription factor Sp1 through its histone deacetylase activity modification, leading to Sp1 degradation, which inhibits the transcriptional expression of GPx4, a key factor in resistance to ferroptosis, and ultimately drives neuronal ferroptosis in models of cerebral ischemia[54]. Several studies have shown that in many diseases, miRNAs are able to directly target the 3'UTR of GPx4 mRNA to drive its degradation. e.g., in hepatocellular carcinoma, miR-214-3p targets binding to GPx4, which represses GPx4 expression and promotes ferroptosis[55]; miR-211-5p also protects GPx4 indirectly by repressing P2RX7, whose downregulation ultimately lead to the inhibition of GPx4, which in turn induces ferroptosis and aggravates epilepsy[56]. CircRNAs (circular RNAs) such as Circ0060467 can act as ceRNAs (competitive endogenous RNAs) to adsorb these miR-6805 and deregulate their inhibition of GPx4[57]. In addition to non-coding RNAs, RBPs (RNA-binding proteins) are also able to regulate GPx4 expression, e.g., Staphylococcal nuclease SND1 (structural domain-containing protein 1) promotes the degradation of GPx4 by destabilizing HSPA5 (heat shock protein family A member 5) mRNAs and repressing HSPA5 expression to promote ferroptosis of osteoarthritic chondrocytes[58].

2.3 INTERACTION OF GPX4 WITH OTHER KEY PROTEINS FOR FERROPTOSIS

The precise regulation of ferroptosis relies on a highly synergistic molecular network. As the central antioxidant enzyme of the process, GPx4 does not function in isolation, but together builds a multilayered defense system through close interactions with the System xc^--GSH axis, the FSP1-CoQ10 pathway, and ACSL4-mediated lipid metabolism.

Ferroptosis inhibitory protein 1 (FSP1), once named AIFM2, was first found to compensate for the enzyme-catalyzed system of GPx4 deficiency, and the discovery of FSP1 revealed an ferroptosis inhibitory pathway that is independent of the GPx4-GSH pathway[59].FSP1 is localized at the plasma membrane, and utilizes NADPH to reduce ubiquinone (CoQ10) to ubiquinol ($CoQ10H_2$).$CoQ10H_2$ acts as a potent lipid-soluble antioxidant that directly neutralizes lipid radicals (L-) and blocks the chain reaction of lipid peroxidation[60]. The functional relationship with GPx4 is reflected as complementary and compensatory, with GPx4 scavenging formed PL-OOH and forming a repair mechanism, whereas FSP1-$CoQ10H_2$ prevents lipid radical generation and forms a preventive mechanism; transcriptional up-regulation of FSP1 significantly inhibits ferroptosis in GPx4-deficient cells[61].Long-chain lipoyl coenzyme A synthetase 4 (ACSL4) generates esterified forms of PL-PUFAs (phospholipid-polyunsaturated fatty acids) by catalyzing the binding of PUFAs to coenzyme A[62]. PL-PUFAs are highly susceptible to oxidation by LOXs (lip oxygenase enzymes) to PL-OOH because of their double-bond-rich structure, and become a key substrate for GPx4 action[63,64].

3 Disease Associations and Treatment

3.1 GPX4 AND CANCER

GPx4, a key inhibitor of ferroptosis, presents a distinct duality in tumor biology.

On the one hand, for normal tissues, GPx4 maintains cell membrane stability and protects normal tissues from oxidative damage by reducing phospholipid peroxides, e.g., the homeostasis of liver and kidney is dependent on its activity[65], and GPx4 is an important component of the mitochondrial sheath of mammalian spermatozoa[50,66]; on the other hand, in a variety of malignant tumors, the abnormally high expression of GPx4 scavenges lipid ROS, inhibits ferroptosis[50] and promotes tumor cell survival and proliferation[67]. Clinical studies have shown that GPx4 overexpression is significantly associated with shorter overall survival in pancreatic cancer patients, highlighting its cancer-promoting properties[68].This paradoxical role stems from the hijacking of oxidative stress defense mechanisms by the tumor microenvironment, which transforms GPx4 from a protector to an accomplice in malignant progression.GPx4-mediated inhibition of ferroptosis is a

common mechanism of tumor resistance to conventional therapy, e.g., the accumulation of lipid ROS induced by drugs such as cisplatin can be neutralized by GPx4, weakening its killing effect[69].

Lipid peroxides generated by ionizing radiation depend on GPx4 scavenging to protect tumor stem cell survival, and in head and neck squamous carcinoma GPx4 expression positively correlates with radiotherapy failure[70].EGFR inhibitor-triggered oxidative stress is mitigated through the GPx4 compensatory pathway and promotes the expansion of drug-resistant clones, as seen in KRAS-mutant colorectal cancer. This broad-spectrum resistance makes GPx4 a key target for overcoming treatment resistance[71].Therapeutic strategies targeting GPx4 focus on selectively inducing tumor ferroptosis, with small molecules such as RSL3[72], covalently binding to the selenocysteine active center of GPx4 and directly degrading its function[73]. In an in vivo model, RSL3 significantly inhibited lung metastasis in triple-negative breast cancer[74].Cutting off GPx4 substrate supply by inhibiting the cystine/glutamate reverse transporter SLC7A11 or depleting glutathione[75]. Erastin combined with a PD-1 antibody remodels the immune microenvironment and enhances anti-tumor response[76].Despite the promise of cancer treatment by targeting GPx4, its tissue selectivity remains a central challenge. Current innovative strategies are dedicated to balancing efficacy and toxicity, developing tumor microenvironment-responsive prodrugs, and reducing off-target damage to testicular and neural tissues.The dual nature of GPx4 reveals the pivotal role of ferroptosis regulation in cancer therapy. The clinical potential of GPx4 as a "tumor Achilles' heel" needs to be unlocked through precise intervention strategies in the future to facilitate the translation from pathogenesis to therapeutic innovation.

3.2 GPX4 AND OTHER DISEASES

GPx4 is deeply involved in multifaceted disease pathologies by virtue of its core functions of regulating ferroptosis and maintaining redox homeostasis. From neurodegenerative to metabolic diseases, GPx4 plays a role in all of them.

In AD (Alzheimer's disease) models, Aβ deposition and hyperphosphorylation of Tau proteins cause oxidative stress and activate neuronal ferroptosis, whereas reduced expression or activity of GPx4 exacerbates lipid peroxidation damage and promotes AD progression. Recent studies have found that the natural compound ThA binds to GPx4 and activates the AMPK/Nrf2 pathway, enhancing its antioxidant function and inhibiting ferroptosis in cellular and AD models; one study revealed that MT1 activation inhibits α-syn-induced ferroptosis through the modulation of the Sirt1/Nrf2/Ho1/GPx4 pathway and iron metabolism, exerting a neuroprotective in PD (Parkinson's disease) role[77]; In ALS (amyotrophic lateral sclerosis), GPx4 depletion is present in the spinal cord of both sporadic and familial patients and it is an early and prevalent feature in the spinal cord and brain of ALS mouse models such as SOD1G93A (Superoxide dismutase 1G93A), TDP-43, and C9 or f72, GPx4 depletion and ferroptosis are associated with impaired NRF2 signaling, glutathione synthesis and dysregulation of iron binding proteins[78,79].

In cardiovascular disease, downregulation of GPx4 expression is present in early and middle stages of myocardial infarction, and its deletion or inhibition leads to accumulation of lipid peroxides in cardiomyocytes and triggers ferroptosis[80], whereas EGCG (epigallocatechin gallate) inhibits ferroptosis and ameliorates myocardial ischemic injury through upregulation of GPx4, among other pathways[81]; and after intracerebral hemorrhage, clathrin acid improves ferroptosis through cysteine 66 modification of the GPx4 site after intracerebral hemorrhage, alteration enhances its enzymatic activity by alkylation modification, thereby inhibiting neuronal ferroptosis, and the Irg1/cleroconanic acid/GPx4 axis may be a future therapeutic strategy to protect neurons from ferroptosis after intracerebral hemorrhage[82]; In atherosclerosis, GPx4 inhibits lipid peroxidation and ferroptosis through the system xc^-/glutathione pathway, and its aberrant expression correlates with ferroptosis in plaque cells e.g., macrophages, vascular endothelial cells, whereas micheliolide inhibits macrophage ferroptosis by upregulating GPx4 and xCT levels through activation of the Nrf2 pathway, thereby reducing atherosclerotic plaque progression[83,84].

In RA (rheumatoid arthritis), where the expression of GPx4 is elevated and the level of promoter methylation is altered, glycine can promote the methylation of GPx4 promoter by elevating the concentration of SAM (S-adenosylmethanethionine) promotes GPx4 promoter methylation and reduces its expression, which in turn enhances ferroptosis in fibroblast-like synoviocytes and attenuates synovial hyperproliferation and inflammatory injury[85], whereas Jinwu Jianbao capsule improves RA symptoms by inhibiting ferroptosis through modulation of the SLC7A11/GSH/GPx4 pathway[86]; in IBD (inflammatory bowel disease), small intestinal epithelial cells of Crohn's disease patients with impaired GPx4 activity and In IBD, Crohn's disease patients' small intestinal epithelial cell GPx4 activity is impaired and LPO (lipid peroxidation) is obvious. ω-6 PUFAs, which are rich in the Western diet, can trigger the cytokine response of epithelial cells, which can be limited by GPx4. Moreover, GZMA can enhance the transcriptional activity of GPx4, inhibit ferroptosis, promote intestinal epithelial cell differentiation, and improve the function of the intestinal barrier by activating the cAMP/PKA/CREB signaling pathway[87]. In SLE (systemic lupus erythematosus), ferroptosis occurs in neutrophils as a result of autoantibody and interferon-alpha induced binding of CREMα (cAMP response element modulator α) to the GPx4 promoter, leading to inhibition of GPx4 expression and elevation of lipid reactive oxygen species, and SLE also induces osteoclast ferroptosis through downregulation of GPx4, leading to vertebral osteoporosis[88].

GPx4 also affects metabolic diseases, such as NAFLD (non-alcoholic fatty liver disease), where cGPx4 protein expression is down-regulated and induces the non-classical transcriptional variant iGPx4, which promotes ferroptosis by interacting with cGPx4 and converting it from an active monomer to an inactive oligomer, and OSA (obstructive sleep apnea), where macrophage-secreted IL6 promotes hepatocyte MARCH3 expression, mediates GPx4 ubiquitination degradation and

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exacerbates ferroptosis and lipid accumulation[89]. In diabetic complications, PPARα can directly induce the expression of GPx4 by binding to the PPRE element in intron 3 of GPx4 and inhibit the plasma iron carrier TRF, thereby inhibiting ferroptosis and attenuating tissue damage caused by iron overload[90].These findings reveal a common regulatory mechanism of GPx4 in multi-system diseases and provide a theoretical basis for the development of cross-disease GPx4-targeted therapies.

4 Current status of GPx4 drug development

In recent years, with the continuous deepening of the research on ferroptosis mechanism, targeting GPx4, as the core protein of ferroptosis regulation, has become a highly promising therapeutic strategy.

In the field of oncology, many cancer cells rely on the high expression of GPx4 to evade ferroptosis for proliferation, migration and drug resistance, which makes GPx4 an important target for antitumor drug development. However, the development of effective drugs targeting GPx4 faces many challenges. However, as researchers continue to explore and innovate, a variety of novel therapeutic strategies for targeting GPx4 have emerged, bringing new hope for disease treatment.

In terms of covalent inhibitors, GPx4 has a unique structure with a shallow binding pocket, with which conventional small molecule inhibitors bind with limited affinity and selectivity[91,92], like the classical RSL3[93], which inhibits the growth of DRD cells when the compound is present at concentrations as low as 10 ng/mL and initiates the process of killing sensitive cells after 8 hours of treatment. It showed activity in all tested cancer cells harboring oncogenic KRAS with an IC50 of 20 ng/mL. numerous cells in the NCI-60 cell bank showed specific sensitivity to RSL3 treatment at nmol concentrations, which are sufficient to trigger growth arrest or cell death[45].

In addition to the classical RSL3, there is also ML162, a drug with a similar mechanism of action to RSL3[94], and C18, as a derivative optimized based on RSL3, not only has a significantly higher inhibitory activity, but also has a better in vivo antitumor effect and lower toxicity, C18 may be a promising covalent inhibitor of GPx4 that induces ferroptosis for the treatment of triple-negative breast cancer[95]. Novel covalent inhibitors such as ML210, which uses nitroisoxazole as a prodrug form and covalently binds GPx4 after intracellular conversion to an electrophilic moiety, have selectivity and pharmacokinetic properties superior to that of chloroacetamide inhibitors[96,97], and BCP-T.A, a thiazole analog containing an alkyne-based electrophilic moiety, has been found to have inhibitory activity on specific cells up to the low-nanomolar level with high selectivity[98,99].PROTAC-degrading agents are a new direction in drug development for targeting GPx4. dGPx4, using ML162 as a warhead and connected to CRBNE3 ligase, has an enhanced anti-tumor effect in vivo after delivery via lipid nanoparticles[100]; DC2, designed based on ML210, degrades GPx4 not only by the proteasomal pathway, but also by autophagy pathway to inhibit tumor growth in vivo The effect is superior to that of ML210[96]; 8e, as an RSL3-based PROTAC, recruits VHLE3 ligase, which not only effectively induces GPx4 degradation, but also inhibits the growth of drug-resistant tumors[101].Cell type-specific degradation agents provide a solution to reduce toxicity to normal tissues.N6F11, the first of its kind, activates the tumor cell-specific protein TRIM25, which indirectly induces GPx4 degradation, uniquely inducing ferroptosis only in tumor cells without affecting immune cells and enhancing the therapeutic efficacy of immune checkpoint inhibitors[68,102].

Combination therapy strategies have also received much attention. Combining KRASG12C inhibitors, such as sotorasib, as KRAS mutant tumors are highly dependent on GPx4 for survival. Screening of sensitive patients based on lipid peroxidation imaging or GPx4 activity profiles enables individualized dosing[103].In terms of combining with ferroptosis-related targets, FSP1 inhibitors in combination with GPx4 inhibitors, for example, RSL3 in combination with NPD4928 and icFSP1 can synergistically induce ferroptosis[104,105], overcoming the compensatory resistance of the tumor cells; DHODH inhibitors in combination with GPx4 inhibitors can inhibit mitochondrial lipid peroxidation defenses, which is more effective in tumors with high GPx4 expression[106].In immunotherapeutic combination, GPx4 inhibitor combined with anti-PD-1 antibody enhanced $CD8^+$ T cell infiltration and anti-tumor immunity while inducing tumor ferroptosis[107], revealing an innovative immunotherapeutic combination strategy for refractory LAR tumors.In radiotherapy combination, Tubastatin A overcomes tumor cell radiotherapy resistance and enhances the efficacy of radiotherapy. In combination with chemotherapy or targeted drugs, RSL3, in combination with TKIs (tyrosine kinase inhibitors), was able to reverse tumor resistance to drugs such as Gefitinib and Osimertinib and synergistically kill tumor cells[108]. Table 2 provides the nature and mechanism of action of drugs related to GPx4.

Table 2: Nature and mechanism of action of drugs related to GPx4

Drug Name	Description	Mechanism of Action	Advantages	References
RSL3	A covalent inhibitor targeting GPx4	Covalently binds to the selenocysteine active center of GPx4, directly inhibiting its function and inducing ferroptosis in tumor cells [72,73].	Effective against cancer cells harboring oncogenic KRAS; induces growth arrest or cell death at nanomolar concentrations [45].	[45,72,73,74]
ML162	A covalent inhibitor with a mechanism similar to RSL3	Inhibits GPx4 function by binding to its active site [94].	Suppresses GPx4 activity and induces ferroptosis [94].	[94]

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Drug Name	Description	Mechanism of Action	Advantages	References
C18	An optimized derivative based on RSL3	Acts as a covalent GPx4 inhibitor, binding to its active site to suppress function and induce ferroptosis [95].	Exhibits significantly enhanced inhibitory activity, better in vivo antitumor efficacy, and lower toxicity [95].	[95]
ML210	A novel covalent inhibitor with a nitroisoxazole prodrug moiety	Converts to an electrophilic group intracellularly, then covalently binds to GPx4 to inhibit its function [96,97].	Superior selectivity and pharmacokinetic properties compared to chloroacetamide inhibitors [96,97].	[96,97]
BCP-T.A	A thiazole analog containing an alkyne-based electrophilic moiety	Interacts with GPx4 via its alkyne electrophilic group to inhibit function [98,99].	Achieves low-nanomolar inhibitory activity against specific cells with high selectivity [98,99].	[98,99]
dGPx4	A PROTAC degrader with ML162 as the warhead, linked to CRBN E3 ligase	Degrades GPx4 by recruiting CRBN E3 ligase through PROTAC technology [100].	Enhances in vivo antitumor efficacy when delivered via lipid nanoparticles [100].	[100]
DC2	A PROTAC degrader designed based on ML210	Degrades GPx4 through both proteasomal and autophagic pathways [96].	Shows better in vivo tumor growth inhibition than ML210 [96].	[96]
8e	An RSL3-based PROTAC that recruits VHL E3 ligase	Induces GPx4 degradation by recruiting VHL E3 ligase via PROTAC technology [101].	Effectively degrades GPx4 and inhibits the growth of drug-resistant tumors [101].	[101]
N6F11	The first cell type-specific degrader	Indirectly induces GPx4 degradation by activating tumor-specific protein TRIM25 [68,102].	Induces ferroptosis specifically in tumor cells without affecting immune cells; enhances the efficacy of immune checkpoint inhibitors [68,102].	[68,102]

5 Conclusions

This review systematically elucidates the structure and function of GPx4, focusing on its central position in the regulation of ferroptosis and its involvement in the molecular mechanisms underlying the development of a variety of diseases. As a specialized glutathione peroxidase containing selenocysteine substituting cysteine, GPx4 plays an irreplaceable role in maintaining cell membrane integrity and protecting cells from oxidative damage by specifically reducing phospholipid hydroperoxides. This unique antioxidant function makes it a key molecular switch linking oxidative stress to cell fate determination. Notably, GPx4 plays a protective role against normal tissues in the physiological state, whereas it exhibits pro-survival properties in the tumor microenvironment, and this seemingly contradictory dual function has brought new ideas for cancer therapy. In recent years, breakthroughs have been made in targeted intervention strategies against GPx4, from early covalent inhibitors such as RSL3, to the emerging PROTAC degradation technology, to the combined application of multiple therapeutic modalities. These innovative studies have not only deepened our understanding of the function of GPx4, but also provided practical solutions to overcome the resistance of tumor therapy. What is even more exciting is that the regulatory network of GPx4 is not only in the field of cancer, but also in neuroprotection in neurodegenerative diseases, myocardial protection in cardiovascular diseases, inflammation regulation in autoimmune diseases, and maintenance of lipid homeostasis in metabolic diseases, etc. These discoveries have demonstrated that GPx4 has a wide range of applications. These findings demonstrate the centrality of GPx4 as a "guardian of oxidative stress" in human health and disease.

Although significant progress has been made in therapeutic strategies targeting GPx4, many challenges remain in clinical translation. Future research should focus on drug design to develop novel inhibitors with higher targeting and lower toxicity; on therapeutic strategies to explore optimal combinations of GPx4 inhibitors with existing therapeutic tools, and ultimately to translate the laboratory results into clinical therapeutic solutions through solid translational medicine research. As these research directions continue to deepen, GPx4-targeted therapies will bring breakthroughs in the treatment of a variety of diseases, which will not only provide new treatment options for cancer patients, but also is expected to open up new avenues in the fields of neuroprotection and cardiovascular disease prevention, and to promote the development of individualized medicine to a higher level. Advances in this field will continue to enrich our understanding of oxidative stress and cell fate determination, and make significant contributions to the cause of human health.

Author contributions

CW: Writing – original draft, Writing – review & editing. YZ: Writing – review & editing. JW: Writing – review & editing. LM: Writing – review & editing.

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Conflict of interest

Authors declare no conflict of interest.

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