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Review



## Ferroptosis: An emerging strategy for managing epithelial ovarian cancer

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**Abbreviations:** 4-HNE, 4-hydroxynonenal; 4EBP, Eukaryotic translation initiation factor 4E; ACSL3, Acyl-CoA synthetase long chain family member 3; ACSL4, Acyl-CoA synthetase long chain family member 4; AIF, Apoptosis-inducing-factor; ALOX15, 15-lipoxygenase; AMPK, Adenosine monophosphate-activated protein kinase; APGS, Alkylglycerone phosphate synthase; ApoER2, Apolipoprotein E receptor 2; ATP, Adenosine triphosphate; BCS, Bathocuproinedisulfonic; BH<sub>2</sub>, Oxidized BH<sub>4</sub> dihydrobiopterin; BH<sub>4</sub>, Tetrahydrobiopterin; BI-1356, Linagliptin; BSO, Buthionine sulfoximine; C107, Residue cysteine 107; C148, Residue cysteine 148; Ca<sup>2+</sup>, Ion calcium II; CD44, Homing-cell adhesion molecule; CoQ<sub>10</sub>, Ubiquinone; COX17, Cytochrome C oxidase cooper chaperone; Cu<sup>2+</sup>, Ion copper II; D-PUFAs, Polyunsaturated fatty acids; DHA, Dihydroateminin; DHO, Dihydroorotate; DHODH, Dihydroorotate dehydrogenase; DMT1, Divalent metal transporter 1; DPC, Dermal papilla; DPP4, Dipeptidyl peptidase-4; EGFR, Epidermal growth factor receptor; EOC, Epithelial ovarian cancer; ER, Endoplasmic reticulum; EVs, Extracellular vesicles; FBXL5, F-box and leucine-rich repeat protein 5; Fe-S, Iron-sulfur; Fe<sup>2+</sup>, Ion iron II; Fe<sup>3+</sup>, Ion iron III; FMN, Flavin mononucleotide; FPN/FPN1, Ferroportin; FSP1, Ferroptosis suppressor protein 1; FTH, Ferritin heavy chain; FTL, Ferritin light chain; GALNT14, Polypeptide N-acetylgalactosaminyltransferase; GCH1, GTP cyclohydrolase 1; GPX4, Glutathione peroxidase 4; GPXs, Glutathione Peroxidases; GS, Glutathione; GSH, Reduced glutathione; GSSG, Oxidized glutathione; GTP, Guanosine triphosphate; H2Bub1, H2B monoubiquitination at lysine 120; H<sub>2</sub>O<sub>2</sub>, Hydrogen peroxide; HERC2, HECT and RLD domain containing E3 ubiquitin protein ligase 2; HERPUD1, Homocysteine inducible ER protein with ubiquitin like domain 1; HIF-1α, Hypoxia inducible factor 1 subunit alpha; HMGB1, High-mobility group protein B1; HMOX1, Heme oxygenase 1; HUVECs, Human umbilical vein endothelial cells; IKE, Imidazole ketone erastin; IMCA, 2-imino-6-methoxy-2H-chromene-3-carbothioamide; IONP-GA/PAA, Iron oxide nanoparticles coated with gallic acid and polyacrylic acid; IRP1/2, Iron regulatory protein 1/2; ITPR, Inositol 1,4,5-trisphosphate receptor; LAF-237, Vildagliptin; LOX, Lipoxygenases; LPCAT, Lysophosphatidylcholine acyltransferase; LRP8, Low density lipoprotein receptor-related protein 8; MDA, Malondialdehyde; MS4A15, Membrane Spanning 4-Domains A15; mTOR, Mammalian/mechanistic target of rapamycin; mTORC1, Mammalian/mechanistic target of rapamycin complex 1; mTORC2, Mammalian/mechanistic target of rapamycin complex 2; MUFAs, Monounsaturated fatty acids; N/A, Not available data; NADH, Nicotinamide adenine dinucleotide hydrogen; NADP<sup>+</sup>, Nicotinamide Adenine Dinucleotide Phosphate; NADPH, Nicotinamide Adenine Dinucleotide Phosphate Hydrogen; NCOA4/NCO4, Nuclear receptor coactivator 4; NDGA, Nordihydroguaiaretic acid; NDH-2, NADH:quinone oxidoreductase type II; NEAT1, Nuclear enriched transcript 1; Nedd4, Neural precursor cell-expressed developmentally downregulated gene 4; NF2, Neurofibromin 2; NPs, Nanoparticles; NRF2, Nuclear factor erythroid 2-related factor 2; oxPLs, Oxidized phospholipids; p53, Tumor protein P53; PDAC, Pancreatic ductal adenocarcinoma; Prdx I/II, Peroxiredoxins 1/2; PUFA-CoA, Coenzyme-A-activated polyunsaturated fatty acids; PUFA-ePLs, Polyunsaturated ether phospholipids; PUFA-GP, PUFA-glycerophospholipids; PUFA-OH, Non-toxic lipid alcohols; PUFA-OOH, Fatty acid to undergo peroxidation reactions; PUFAs/ PUFA, Polyunsaturated fatty acids; PUFA-PL, PUFA-containing phospholipid; Rag, Recombinant activating gene; RAS, Rat sarcoma virus; RNA, Ribonucleic acid; ROS, Reactive oxygen species; RSL, RAS-selective lethal; RSL3, 1S,3R-RAS-selective lethal 3; RTA, Radical trapping antioxidant; SCD1, Stearoyl-CoA desaturase 1; SEPP1, SEC-rich protein selenoprotein P; SLC30, Soluble carrier family 30 member 1; SLC39, Soluble carrier family 39 member 8; SLC7A11, Solute carrier family 7 member 11; SYR 322, Alogliptin; TAX1BP1, Tax1 binding protein 1; TFEB, Transcription factor EB; TFRC, Transferrin receptor 1; TRF, Transferrin; UMP, Uridine monophosphate; UV, Ultraviolet; VAMP8, Vesicle associated membrane protein 8; VDACC2/3, Voltage-dependent anion channel 2/3; VDACCs, Voltage dependent anionic channel; VK/VE, Vitamin K/ Vitamin E; VKH/VEH, Reduced vitamin K/ reduced vitamin E; YAP, Yes-associated protein; ZEB1, Zinc finger E-box-binding homeobox1; ZIP1, Zinc uptake transporter 1; ZIP7, Zinc transporter member of the SLC39 family; Zn, Ion zinc II; ZnO, Zinc oxide; ZnT, Zinc transporter.

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## ABSTRACT

Ferroptosis is a regulated form of cell death characterised by iron-dependent lipid peroxidation, a process intricately linked to cellular redox homeostasis. This form of cell death is induced by the accumulation of intracellular iron and the subsequent generation of reactive oxygen species (ROS), which leads to lipid peroxidation and ultimately cell death. Ferroptosis is distinct from traditional forms of cell death, such as apoptosis, and holds significant therapeutic potential, particularly in cancers harboring rat sarcoma virus (RAS) mutations, such as epithelial ovarian cancer (EOC). EOC is notoriously resistant to conventional therapies and is associated with a poor prognosis. In this review, we examine recent progress in the understanding of ferroptosis, with a particular focus on its redox biology and the complex regulatory networks involved. We also propose a novel classification system for ferroptosis modulators, grouping them into six categories (I, II, III, IV, V and VI) based on their mechanisms of action and their roles in modulating cellular redox status. By refining these categories, we aim to provide deeper insights into the role of ferroptosis in cancer biology, especially in EOC, and to identify potential therapeutic avenues. We propose that further investigation of ferroptosis in the context of redox biology could reveal novel biomarkers and therapeutic targets, offering promising strategies to overcome resistance mechanisms and improve clinical outcomes for patients with EOC and other treatment-resistant cancers.

## 1. Ferroptosis

In 2012, Dixon *et al.* studied the mechanism of action of erastin and RSL3, compounds they named rat sarcoma virus (RAS)-selective lethal (RSL) for their ability to specifically kill RAS-mutated tumour cells (Table 1). The phenotype observed in cells treated with such drugs, characterised by increased intracellular levels of reactive oxygen species (ROS), different from apoptotic cells, which exhibited cytochrome C release, caspase activation or chromatin fragmentation. These authors proposed the term ferroptosis to describe this new phenotype observed when treating cancer cells with erastin and RSL3 [1].

Ferroptosis can be defined as a type of regulated non-apoptotic cell death triggered by an increase in intracellular iron and ROS levels, which leads to intracellular lipid peroxidation culminating in cell death [2]. It has been associated with multiple pathophysiological conditions, such as cancer, neurodegenerative diseases, and pulmonary fibrosis, among others. Therefore, the therapeutic potential of using modulators of this type of cell death is enormous [2,3].

A review of ferroptosis in the context of epithelial ovarian cancer (EOC) is of paramount importance due to its potential to uncover novel therapeutic strategies for this aggressive malignancy. EOC, known for its poor prognosis and resistance to conventional treatments, may exhibit heightened vulnerability to ferroptosis-induced therapies. This susceptibility arises from its altered iron homeostasis, which promotes oxidative stress, and elevated lipid peroxidation. These cells rely heavily on iron, which increases ROS production and triggers ferroptosis. Additionally, mutations in key pathways like glutathione peroxidase 4

Table 1

Cancer types and the frequency of mutated RAS genes. This table summarises the percentage of RAS gene mutations in various cancer types. The percentage of cancers with RAS mutations varies widely, from as high as 90%–93% in pancreatic ductal adenocarcinoma to less than 2% in triple negative breast cancer. Data references for each cancer type are provided in the last column.

Type	% frequency mutated RAS gene	References
Pancreatic ductal adenocarcinoma	90–93	[126,127]
Estrogen receptor (ER)-positive endometrial cancers	80–90	[128]
Ovarian cancer	66	[129]
Colorectal cancer	50–56	[130]
Skin melanoma	52	[131]
Urachal adenocarcinoma	33	[132]
Malignant melanoma of the female genital tract	32	[133]
Primary bladder adenocarcinoma	25	[132]
Non-small cell lung cancer	20–25	[134,135]
Papillary thyroid carcinoma	11	[136]
Triple negative breast cancer	< 2	[137]

(GPX4) make EOC cells more vulnerable to this form of cell death [4].

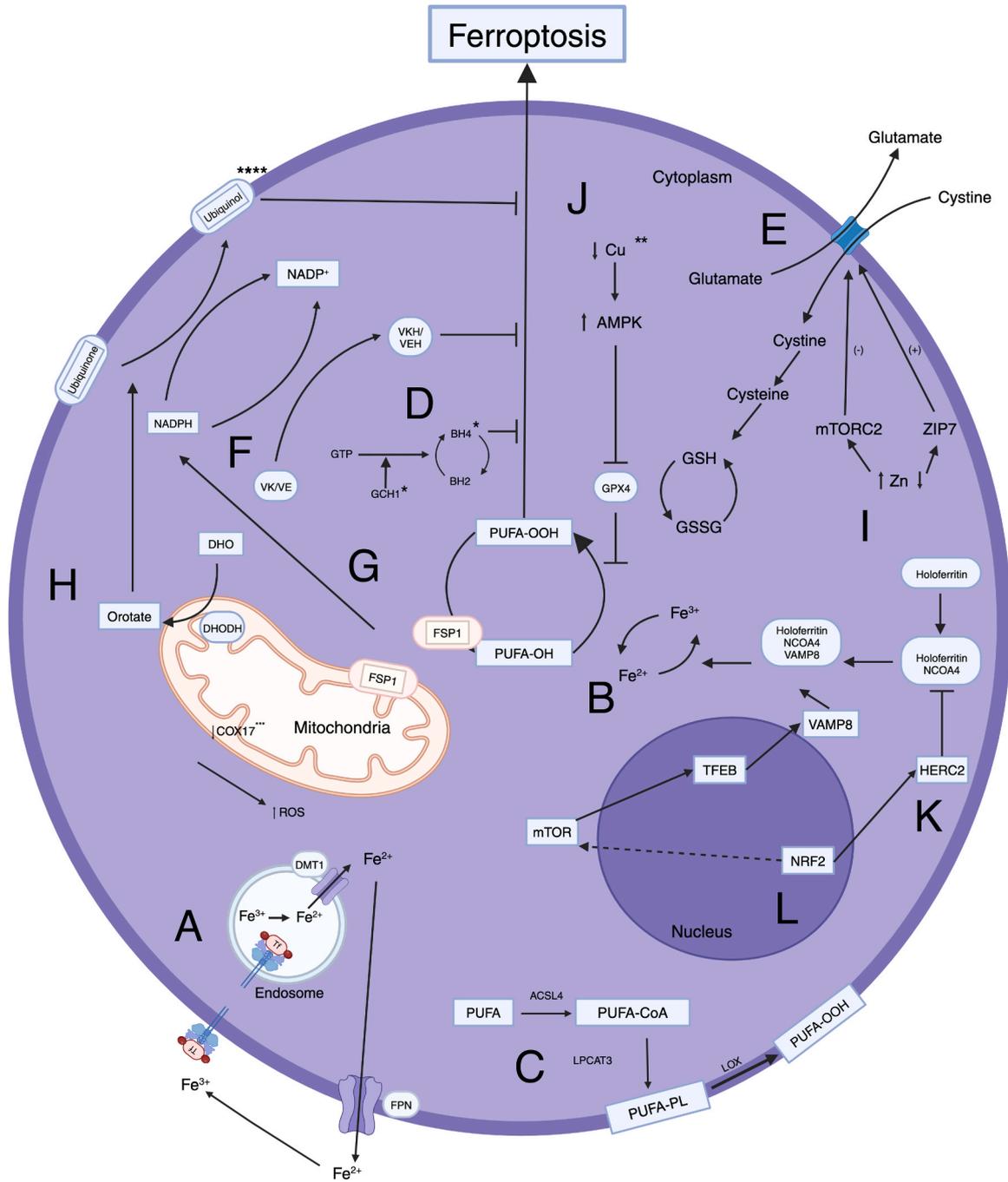
By comprehensively examining how ferroptosis can be triggered in EOC cells, such reviews can identify new molecular targets and biomarkers for treatment [5–8]. Additionally, they can elucidate the interplay between ferroptosis and other cell death pathways, offering a holistic understanding of tumour biology and resistance mechanisms. This knowledge is crucial for developing innovative treatments that aim to improve outcomes for EOC patients, ultimately leading to more effective and targeted cancer therapies.

## 1.1. Relevance of iron

Iron is enormously important for the proper functioning of the body. Within cells, it is normally found associated with complexes, such as heme (prosthetic group of many proteins), Fe-S clusters (co-factor of multiple enzymes) and bound to ferritin (iron storage protein). A small amount is found free in the labile iron pool inside the cell. It is usually present in the oxidation states, Fe<sup>2+</sup> or Fe<sup>3+</sup>, allowing it to act as a redox catalytic agent, accepting or donating electrons [9]. This property makes it a potentially toxic element that can react with ROS and cause peroxidation of different molecules, including lipids [10]. Therefore, in mammalian cells and under normal physiological conditions, iron homeostasis is finely regulated [9].

Iron is mainly obtained through diet, via a specific transporter found in the epithelial cells of the duodenum. Divalent metal transporter 1 (DMT1) allows iron to pass into the cytoplasm while ferroportin (FPN or FPN1) brings iron into the circulation (Fig. 1A). Once in circulation, transferrin, an iron-binding protein. Transports iron throughout the body [11]. Iron internalisation occurs through endocytosis process mediated by the transferrin receptor (a dimeric glycoprotein) whose extracellular domains have a high affinity for iron-bound transferrin [11]. Therefore, the ability of transferrin to induce ferroptosis is only present when it is bound to iron. Treatment with ribonucleic acid interference (RNAi) to decrease transferrin receptor RNA levels can significantly inhibit the development of this type of cell death [11]. Altering the cellular iron content can change the cell's susceptibility to ferroptosis. Thus, the increase in intracellular iron availability due to the degradation of ferritin, also called ferritinophagy, after treatment of cancer cells and fibroblasts with ferroptosis inducers, can promote ferroptosis [12,13].

Iron export is mediated by the plasma membrane-localised protein FPN 1 coupled to a ferroxidase, such as ceruloplasmin. Reduced FPN expression leads to increased sensitivity to ferroptosis [14]. Treatment of cancer cells with ferroptosis inducers can render them resistant by increasing the expression of the protein prominin-2, a pentaspanin that has been shown to promote the formation of multivesicular bodies and ferritin-loaded exosomes, removing iron from the cell and thus avoiding ferroptosis [15].



(caption on next page)

**Fig. 1.** Mechanisms of ferroptosis. The main pathways involved in the process: (A) Iron is absorbed in the duodenum through DMT1 and released into circulation via FPN1. Transferrin binds iron for transport, and iron is internalised by the transferrin receptor through endocytosis; (B) The non-enzymatic pathway generates reactive oxygen species (ROS) via the Fenton reaction, where free iron catalyses the conversion of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) into ROS; (C) The displacement of PUFAs from the plasma membrane by MUFAs, regulated by ACSL3, prevents lipid peroxidation, as MUFAs lack the double bonds required for peroxidation. Phospholipids with PUFAs are necessary for ferroptosis; (D) CGH/BH4 axis: This axis represents the relationship between BH4 and the control of oxidative stress, particularly in relation to cellular GSH levels, which are critical for maintaining redox homeostasis; (E) Cyst(e)ine/GSH/GPX4 axis: this axis highlights the importance of cysteine (or cystine) in glutathione synthesis, which in turn serves as a substrate for GPX4 in mitigating lipid peroxidation and preventing ferroptosis; (F) Vitamins (K and E): vitamin K plays a role in redox cycling, while vitamin E acts as a lipid-soluble antioxidant, both contributing to the protection against oxidative damage in cellular membranes; (G) NAD(P)H/FSP1/CoQ1 axis: this axis depicts the role of NAD(P)H-dependent FSP1 in reducing CoQ10, which helps in combating lipid peroxidation and protecting cells from ferroptosis.; (H) DHODH/CoQH2: DHODH generates reduced CoQH2 in the mitochondria, contributing to the prevention of oxidative stress and cell death through the reduction of lipid peroxides; (I and J) Metals (Zinc and Copper): zinc and copper are trace metals that play roles in antioxidant enzyme systems, such as copper's involvement in superoxide dismutase (SOD), which is important for neutralising superoxide radicals and (K and L) NRF2 pathway: is a key regulator of cellular antioxidant response, activating the transcription of various genes that protect against oxidative damage, including those involved in glutathione metabolism and NADPH regeneration. ACSL4 (acyl-CoA synthetase long chain family member 4); BH2 (oxidized BH4) (dihydrobiopterin); BH4 (tetrahydrobiopterin); COX17 (encoding cytochrome c oxidase copper chaperone); Cu (ion copper (II)); DHO (dihydroorotate); DHODH (dihydroorotate dehydrogenase); DMT1 (divalent metal transporter 1); Fe<sup>2+</sup> (ion iron (II)); Fe<sup>3+</sup> (ion iron (III)); FPN or FPN1 (ferroportin); FSP1 (ferroptosis suppressor protein 1); GCH1 (GTP cyclohydrolase 1); GPX4 (glutathione peroxidase 4); GSH (reduced glutathione); GSSG (oxidized glutathione); GTP (guanosine triphosphate); HERC2 (HECT and RLD domain containing E3 ubiquitin protein ligase 2); LOX (lipoxygenases); LPCAT3 (lysophosphatidylcholine acyltransferase); mTOR (mammalian/mechanistic target of rapamycin); mTORC2 (mammalian/mechanistic target of rapamycin complex 2); NADP<sup>+</sup> (nicotinamide adenine dinucleotide phosphate); NADPH (nicotinamide adenine dinucleotide phosphate hydrogen); NCO4 (nuclear receptor coactivator 4); NRF2 (nuclear factor erythroid 2-related factor 2); PUFA (polyunsaturated fatty acid); PUFA-CoA (coenzyme-A-activated polyunsaturated fatty acids); PUFA-OH (non-toxic lipid alcohols); PUFA-OOH (fatty acid to undergo peroxidation reactions); PUFA-PL (PUFA-containing phospholipids); ROS (reactive oxygen species); TFEB (transcription factor EB); TRF (transferrin); VAMP8 (vesicle associated membrane protein 8); VK/VE (vitamin K/ Vitamin E); VKH/VEH (reduced vitamin K/ reduced vitamin E); ZIP7 (zinc transporter member of the SLC39 family); Zn (ion zinc (II)). \*GCH1 is an enzyme that limits the synthesis of BH<sub>4</sub>; \* low levels of copper activate AMPK and inactivate GPX4; \* \*\*Copper depletion inactivates COX17, reducing ATP production and mitochondrial function, \* \*\* orotate uses coenzyme Q<sub>10</sub>/ubiquinone which is reduced to ubiquinol.

## 1.2. Relevance of fatty acids

Fatty acids, a structurally diverse and essential class of hydrophobic molecules, play a pivotal role in initiating ferroptosis. Their ubiquitous presence and functional importance make them key contributors to the lipid peroxidation processes that drive ferroptosis in various cellular contexts [16]. Mammalian cells obtain polyunsaturated fatty acids (PUFAs) by conversion of dietary essential fatty acids through the action of desaturase and elongase enzymes [2]. In the context of ferroptosis, lipid peroxidation takes place mainly on esterified PUFAs but not on free PUFAs. The presence of carbon-hydrogen bonds in the methylene groups flanking the double bonds in PUFAs makes this type of fatty acid particularly susceptible to undergo peroxidation reactions. Therefore, increasing the number of carbon-carbon double bonds in PUFAs brings about an increase in the rate and susceptibility of the fatty acid to undergo peroxidation reactions (PUFA-OOH) [17].

Although the mechanism by which lipid peroxidation (a reaction that may or may not be catalysed by enzymes as explained below), due to ferroptosis, leads to cell death is not yet known, different hypotheses have been proposed [18–20]. The maintenance of the structure and geometry of the cell membrane is essential for it to keep its properties and functions, and lipid peroxidation causes changes in the lipid composition of this structure, greatly affecting its characteristics. The increase in the amount of lipid peroxides could be related to the disruption of local lipid domains, as well as changes affecting the features or functions of membrane-embedded proteins. A study using a molecular dynamics approach assessing the biophysical consequences of lipid peroxidation indicated that an increase in lipid peroxides in the membrane causes a change in membrane shape and curvature that makes it easier for oxidants to gain access, accelerating the process [18]. On the contrary, it appears that the rise in oxidised lipids correlates with an escalation in the membrane's water permeability. This phenomenon may extend to other polar substances, causing an imbalance among various cellular components and, ultimately, culminating in cell death [19]. The utilisation of substantial osmoprotectants can shield ferroptotic cells from dying, endorsing the notion that lipid peroxidation-induced modifications to the plasma membrane result in the creation of pores within the membrane [20].

In the enzymatic pathway, specific enzymes catalyse the production of bioactive lipid peroxides, which play a crucial role in regulating cell signalling. These lipid peroxides form a complex group of molecules that

influence cellular responses and contribute to key processes, such as ferroptosis, by driving oxidative damage within the cell [16,17]. The non-enzymatic pathway occurs via the Fenton reaction, which involves a series of reactions where free iron catalyses the generation of ROS from hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) (Fig. 1B) [16,17,21]. A recent study suggests that while auto-oxidation primarily triggers this process, a certain threshold of lipid peroxides must be reached. Moreover, it is crucial to recognise that reaching this threshold is also significant in the enzymatic pathway [22].

Several studies have shown the importance of enzymes such as acyl-CoA synthetase long chain family member 4 (ACSL4) in the development of ferroptosis. ACSL4 is responsible for the adenosine triphosphate (ATP)-dependent esterification of fatty acids, preferably long-chain PUFAs, to coenzyme A (CoA). These products can then be re-esterified into phospholipids by various lysophosphatidylcholine acyltransferase (LPCAT) enzymes, increasing their concentration in lipid membranes (Fig. 1C). Genetic loss or inhibition of the enzymes mentioned above causes a change in the lipid composition of membranes [23].

In 2019, Magtanong *et al.* discovered that the displacement of PUFAs from the plasma membrane by monounsaturated fatty acids (MUFAs) is another way for cells to prevent lipid peroxidation. This process is regulated by the enzyme acyl-CoA synthetase long chain family member 3 (ACSL3), which catalyses the esterification of MUFA with CoA [24]. MUFAs do not contain the double bonds, so they are not susceptible to the peroxidation process [25]. These studies support the idea that phospholipids containing PUFAs are a prerequisite for the execution of ferroptosis.

It has recently been described that ferroptotic cells are not only dying cells but can also exert paracrine effects by inducing ferroptosis in neighboring cells. In mouse embryonic cells, the propagation of the lipid peroxidation process was observed in a paracrine manner [26]. *In vitro* studies by Riegman *et al.*, suggest that this phenomenon propagates in a wave-like pattern, influenced by the method of ferroptosis induction. Their findings indicate that the induction of through direct inhibition of GPX4 does not transmit to adjacent cells. Conversely, cells subjected to inducers like erastin demonstrate their ability to propagate this phenomenon. Furthermore, it appears that lysis of the ferroptotic cells is not a prerequisite for the propagation of this phenomenon. Instead, these cells seem to disseminate ferroptosis to neighboring cells before succumbing to death [20]. Extracellular vesicles (EVs) could be a possible mechanism by which ferroptosis cells disseminate lethality to their

surroundings. A preliminary study using EOC cells showed that EVs from these cells, when treated with ferroptosis inducers such as erastin and RSL3, can induce ferroptosis in recipient cells [27].

### 1.3. Main regulatory pathways

Cells must possess mechanisms to be able to finely regulate ferroptosis and prevent it from being triggered at inappropriate times. Some of the cellular systems involved in controlling ferroptosis are shown below.

#### 1.3.1. GCH/BH<sub>4</sub> axis

New pathways for regulating cell entry into ferroptosis have recently been described. One of these regulatory mechanisms is the GTP cyclohydrolase/tetrahydrobiopterin (GCH1/BH<sub>4</sub>) axis (Fig. 1D). This pathway is involved in resistance to ROS generation. GCH1 is an enzyme that limits the synthesis of BH<sub>4</sub>, an important cofactor for aromatic amino acid monooxygenase and nitric oxide synthase families of enzymes [28].

GCH1 is a protein composed of 10 identical monomers grouped in dimers, giving rise to a highly conserved ringed structure like two pentamers facing each other. It is particularly well conserved at its C-terminal region end, which is related to its catalytic activity [28].

BH<sub>4</sub>, the other molecule involved in this pathway, is of particular interest due to its antioxidant capacity, either by inhibiting lipid peroxidation or by regulating the *de novo* synthesis of CoQ<sub>10</sub> (coenzyme Q<sub>10</sub>) [29]. BH<sub>4</sub> also prevents the formation of lipid peroxides by trapping free radicals, a function independent of its role as an enzyme cofactor [25]. The formation of BH<sub>4</sub> with its consequent free radical scavenging activity and participation in CoQ<sub>10</sub> synthesis is related, due to the ability of BH<sub>4</sub> to prevent depletion of phospholipids with two polyunsaturated fatty acyl tails [3,30,31]. However, this is a regulatory pathway that needs to be further characterised, as there are still many uncertainties about how it works.

#### 1.3.2. Cyst(e)ine/GSH/GPX4 axis

In the intricate regulatory network of cellular redox balance and cell death, the cysteine/glutathione (GSH)/GPX4 axis stands out as a pivotal system. GSH, a tripeptide with cysteine at its catalytic core, is integral to this axis. As a crucial cofactor for various enzymes, especially the glutathione peroxidases (GPXs), GSH plays a key role in defending cells against oxidative stress and ferroptosis. In its reduced form, GSH acts as an essential electron donor, enabling GPXs to convert H<sub>2</sub>O<sub>2</sub> and other organic peroxides into less harmful substances like water and alcohol. This process is vital for maintaining cellular redox balance and preventing lipid peroxidation, underscoring GSH's indispensable function in cellular defense and stability [3] (Fig. 1E).

Cysteine is required to synthesise GSH and can be obtained in two ways: from the diet via the reverse transsulfuration pathway or via a cystine/glutamate antiporter located in the cell membrane [3]. In the first case, cysteine is synthesised from methionine through a series of biochemical reactions [32,33].

In the second case, the cell utilises a cystine/glutamate antiporter (1:1 ratio) located in the cell membrane that is also named x<sub>c</sub> system. This transporter is a heterodimer composed of a light chain subunit called xCT, which is the substrate-specific part and is encoded by the solute carrier family 7-member 11 (SLC7A11) gene. Due to the oxidising conditions of the extracellular medium, extracellular cysteine is unstable and rapidly oxidises to cystine, the dimeric form. Thus, cystine is transported into the cells via the cystine/glutamate antiporter and, inside the cell it is rapidly converted to cysteine due to the high reducing conditions [16,34]. Inhibition of the antiporter with drugs such as erastin, or lack of cysteine can cause cells to become sensitive to ferroptosis, as GSH cannot be synthesised [35]. However, in ovarian cells, it has been described that prolonged treatment with the drug generates resistance to ferroptosis, as they are able to overcome the absence of cysteine by activating of the reverse transsulfuration pathway [35].

Voltage dependent anionic channels (VDACs) located in the outer mitochondrial membrane, are important in conferring sensitivity to cells for the development of ferroptosis. There are three isoforms of these channels, and together they make up the bulk of the outer mitochondrial membrane proteins. They control the flow of metabolites and substrates necessary for many processes, for example respiration, homeostasis, or apoptosis, and can alternate between an open or closed state. Treatment of cancer cells with drugs such as erastin, which directly binds to these channels, can keep them open altering the permeability of the outer mitochondrial membrane, causing an increase in mitochondrial metabolism with a consequent increase in ROS production and a decrease in glycolysis [36,37].

Treatment of cancer cells with erastin can induce resistance to ferroptosis by a different pathway than described above. Erastin stimulates the expression of neural precursor cell-expressed developmentally downregulated gene 4 (Nedd4), a ubiquitin ligase that leads to the degradation of voltage-dependent anion channel 2/3 (VDAC2/3). This increases the resistance of cancer cells to erastin treatment [38].

Conditions that alter the levels or activity of GPX4 will have an immediate impact on cell survival, as GPX4 catalyses the reduction of lipid peroxides. Thus, inhibition of GPX4 with drugs such as RSL3 or by genetic techniques confers sensitivity to ferroptosis in different cell lines [39].

The conventional model of GPX4 regulation envisaged only the cysteine/glutamate antiporter as the sole regulator of GPX4 activity. However, GSH depletion was observed to induce much milder ferroptosis cell death than the absence of cysteine or ferroptosis inhibitors acting on the antiporter, such as erastin [40]. A recent study by Zhang *et al.* shows that cysteine is not only able to promote GSH synthesis but also GPX4 protein synthesis through the Rag-mTORC1-4EBP signalling pathway. Proteomic analyses revealed that, following a decrease in cysteine levels, GPX4 protein levels decrease, which could not be attributed to a decrease in messenger RNA (mRNA) levels, increased proteasome activity or autophagy, but to a reduction in GPX4 protein synthesis. They also demonstrated that SLC7A11 deletion, erastin treatment, or the absence of cysteine promotes ferroptosis following treatment with ferroptosis inducers such as RSL3, due to changes in GPX4 protein levels. This is because the lack of cysteine reduces the localisation of mammalian/mechanistic target of rapamycin (mTOR) in lysosomes, an essential prerequisite for its amino acid-induced activation. These data suggest that mammalian target of rapamycin complex 1 (mTORC1) can induce resistance to ferroptosis at least in part by increasing GPX4 synthesis [41].

Additionally, it has been described that mTOR and GPX4 can reciprocally regulate each other. Treatment with RSL3 (GPX4 inhibitor) or knockdown of GPX4 is able to decrease the phosphorylation level of mTOR, suggesting the existence of a possible positive feedback between GPX4 and mTOR [35].

#### 1.3.3. Vitamins (K and E)

Vitamins play a crucial role in regulating ferroptosis, with notable examples being vitamins E and K. When discussing vitamin E, it is essential to highlight its most biologically active form,  $\alpha$ -tocopherol. This lipophilic antioxidant has been documented to effectively prevent cell death in fibroblasts cultured in a cysteine-free medium [42] (Fig. 1F). Furthermore, a link has been established between ferroptosis suppressor protein 1 (FSP1), which acts as a tocopherol reductase at the expense of nicotinamide adenine dinucleotide phosphate (hydrogen) (NADP(H)), as well as BH<sub>4</sub>, showing how different regulatory pathways are also related [43,44].

Continuing with vitamin K (phylloquinone (K1), menaquinone (K2), and menophthone (K3)), it is again a potent lipophilic antioxidant, reduced by FSP1, which also acts by trapping free radicals and preventing the propagation and formation of lipid peroxides. Thus, vitamin K is suggested to be the oldest anti-ferroptotic quinone, which was evolutionarily replaced by a more potent version such as ubiquinone

(CoQ<sub>10</sub>), which is also reduced by FSP1 [43,45].

#### 1.3.4. NAD(P)H/FSP1/CoQ<sub>10</sub> axis

Besides the aforementioned axis, recent genome-wide studies have unravelled other ferroptosis-protective systems independent of GPX4 [3].

Although the anti-ferroptotic potential of FSP1 has only recently been discovered [23,46], a protein with previously unknown nicotinamide adenine dinucleotide hydrogen (NADH) oxidase activity was described in 2001 that, together with GPX4 prevented "apoptosis" in Burkitt's lymphoma cells induced by culturing them at low densities [47].

FSP1 belongs to the NADH:quinone oxidoreductase type II (NDH-2) family. Due to its structural homology with the apoptosis-inducing factor (AIF) protein, it was first proposed that FSP1 may have a pro-apoptotic function [2]. As a member of the NDH-2 family, it employs NADH to reduce CoQ<sub>10</sub> and is mostly localised in lipid droplets and at the plasma membrane, acting as a system to remove lipid peroxides [23, 48]. At the N-terminal end, it contains a myristoylation motif that facilitates translocation to the membrane, where it is able to neutralise ROS, prevents lipid peroxidation and consequently the development of ferroptosis [23]. It performs its activity with CoQ<sub>10</sub> also known as ubiquinone. FSP1 catalyses the reduction of ubiquinone to ubiquinol which acts as a radical trapping antioxidant (RTA). In this way it can prevent ferroptosis from taking place, indicating that FSP1 acts in parallel to the pathway discussed above (Fig. 1G).

A link has also been established between FSP1 and vitamin E, highlighting its importance in the regulation of ferroptosis [43,49].

#### 1.3.5. DHODH/CoQH<sub>2</sub>

The enzyme dihydroorotate dehydrogenase (DHODH) is located on the outer surface of the inner mitochondrial membrane, and it is essential in the *de novo* pyrimidine synthesis pathway, enabling the generation of uridine monophosphate (UMP) (Fig. 1H). By using flavin mononucleotide (FMN) as a prosthetic group, it removes two electrons from dihydroorotate converting it to orotate. As an electron acceptor, it uses coenzyme Q<sub>10</sub>/ubiquinone, which is reduced to ubiquinol, an RTA [50]. DHODH inhibition reduces the CoQ/CoQH<sub>2</sub> ratio and supplementation with mitoQ and mitoQH<sub>2</sub> provides limited protection against the development of RSL3- or ML162-induced ferroptosis. Thus, it seems that DHODH would inhibit ferroptosis by reducing CoQ to CoQH<sub>2</sub> in mitochondria [51].

Recently, Mao *et al.* found that DHODH acts in parallel with GPX4 to protect against ferroptosis triggering. As overexpression or deletion of FSP1 does not affect the generation of lipid peroxides in DHODH KO cells, which affects RSL3-induced ferroptosis, suggesting that DHODH acts in parallel with the mitochondrial form of GPX4, but not with the cytosolic form or FSP1, to suppress lipid peroxidation at the mitochondrial level [52].

#### 1.3.6. Metals (Zinc and Copper)

Besides iron, it has been observed that other transition metals such, as zinc or copper could regulate ferroptosis [53–57]. Zinc is essential for all life forms, as it plays a role in cell proliferation, metabolism, and signalling, due to its catalytic and structural functions. Since it is toxic at high concentrations, levels and distribution are tightly regulated by the zinc transporter / Soluble carrier family 30 member 1 (ZnT/SLC30) and zinc uptake transporter 1/ Soluble carrier family 39 member 8 (ZIP/SLC39) family of transporters. The family is responsible for lowering intracellular zinc levels by transporting zinc from the cytoplasm either to the interior of different organelles or to the extracellular space. The ZIP family of transporters are responsible for increasing intracellular zinc levels [58] (Fig. 1I).

Emerging evidence suggests that ZIP7, a zinc transporter from the SLC39 family, plays a pivotal role in regulating ferroptosis in cancer cells. In particular, the knockdown (KD) or chemical inhibition of ZIP7 in MDA-MB-231 breast cancer cells, either treated with erastin or

deprived of cystine, has been shown to confer resistance to ferroptosis. This highlights the importance of zinc homeostasis in the ferroptotic pathway and positions ZIP7 as a potential target for therapeutic strategies aimed at overcoming ferroptosis resistance in cancer treatment.

Its inhibition induces the expression of genes associated with the response to unfolded proteins or endoplasmic reticulum (ER) stress. Among these genes is homocysteine inducible ER protein with ubiquitin-like domain 1 (HERPUD1) which is involved in the translocation of proteins from the ER to the 26S subunit of the proteasome for proteolysis [59]. While the specific mechanism by which this protein confers resistance to the development of ferroptosis is unknown, it has been shown to protect cells from H<sub>2</sub>O<sub>2</sub>-induced cell death by regulating the flow of calcium into the mitochondria via the inositol 1,4,5-trisphosphate receptor (ITPR) [60].

Likewise, the KD of ZIP7 increases the expression of the SLC7A11 gene, increasing the amount of cystine and, consequently, GSH production by GPX4 ferroptosis inhibition [59].

In A549, an adenocarcinoma human alveolar basal epithelial cell line, it was observed that supra-physiological levels of zinc do not affect the abundance of the x<sub>c</sub> system but do affect its activity. High concentrations of zinc lead to mTORC2-mediated phosphorylation of the antiporter at serine 26, inhibiting its activity and thus affecting either glutamate biosynthesis or GPX4 directly [57].

Subsequent studies evaluating the effect of zinc oxide nanoparticles (ZnO NPs), frequently used as food additives and for ultraviolet (UV) absorption in sunscreens, showed a depletion of GSH and GPX4 in human umbilical vein endothelial cells (HUVECs) treated with ZnO NPs, as well as an increase in ROS and MDA levels. Furthermore, qRT-PCR expression analysis revealed the upregulation of ACSL4 and 15-lipoxygenase (ALOX15) genes, both of which promote ferroptosis development. The expression of the VDAC2 and VDAC3 genes is also affected, specifically, they are overregulated after treatment with ZnO NPs, all of which affect redox homeostasis. Iron homeostasis is affected by treatment with these nanoparticles, in particular the expression of proteins associated with iron uptake increases, leading to an increase in iron levels [54].

Copper is an essential trace element for human physiology and its altered metabolism is associated with the pathogenesis of various diseases. Intracellular accumulation of copper has been associated with a new mode of cell death called cuproptosis. In pancreatic ductal adenocarcinoma (PDAC) cells treated with a low dose of erastin, the addition of copper (Cu<sup>2+</sup>) to the cell medium has been shown to amplify cell death and lipid peroxidation (Fig. 1J). After copper treatment, GPX4 depletion at the protein level is observed to be amplified, however, GPX4 mRNA levels are not affected. These authors found that the addition of copper after erastin treatment induces oligomerisation of GPX4 via binding of the metal to the C107 and C148 cysteine residues of GPX4.

This oligomer is subsequently degraded through autophagy, mediated by Tax1 binding protein 1 (TAX1BP1) autophagy receptor [32].

Another study highlights the connection between metabolism and ferroptosis, which is mediated by the activation of adenosine monophosphate-activated protein kinase (AMPK), a crucial sensor of the cell's energy level. Once activated, AMPK re-programmes cell metabolism by promoting or inhibiting catabolic and anabolic processes, respectively. In the absence of copper, cytochrome c oxidase is unable to assemble properly, the electron transport chain is disrupted, leading to a decrease in mitochondrial ATP production and activation of AMPK and accumulation of ROS. Treatment of dermal papilla (DPC) cells with bathocuproinedisulfonic (BCS) (removes copper), reduces cytochrome C oxidase copper chaperone (COX17) mRNA levels (transports copper to complex 4) suggesting that the concentration of copper in mitochondria is reduced. Copper depletion does not affect the protein levels of cytochrome c, but it does impact the oxidation of cytochrome c, which is reduced, and ATP production, suggesting that COX17 is inactivated. It also increases ROS generation and decreases mitochondrial membrane

potential. Additionally, it enhances the levels of phosphorylated AMPK at threonine 172 and reduces the protein levels of GPX4. Overproduction of ROS due to COX17 leads to increased ferroptosis. Copper depletion leads to mitochondrial dysfunction, inducing ATP depletion and finally AMPK activation [56].

### 1.3.7. NRF2 pathway

One of the most recent discoveries is the regulation by nuclear factor erythroid 2-related factor 2 (NRF2), which seems to play a very important role [61].

The transcriptional factor NRF2 is responsible for activating the HECT and RLD domains that contain E3 ubiquitin protein ligase (HERC2) and vesicle-associated membrane protein 8 (VAMP8) genes, involved in ferritin synthesis and degradation, respectively. HERC2 is an E3 ubiquitin ligase that associates with nuclear receptor coactivator (NCOA4) and F-box and leucine-rich repeat protein 5 (FBXL5), leading to their degradation (Fig. 1K). On one side, NCOA4 associates ferritin with  $\text{Fe}^{3+}$  and transports it to autophagosomes, allowing  $\text{Fe}^{3+}$  to be reduced to  $\text{Fe}^{2+}$ . On the other side, FBXL5 is responsible for the ubiquitination of iron regulatory protein 1/2 (IRP1/2), which inhibits ferritin heavy chain (FTH) and ferritin light chain (FTL), preventing ferritin synthesis [62].

In addition, NRF2 is also involved in the activation of the gene for the synthesis of VAMP8, a protein related to the correct fusion of autophagosomes and lysosomes for the degradation of ferritin with  $\text{Fe}^{3+}$  so that it can be reduced to  $\text{Fe}^{2+}$  [62] (Fig. 1L).

NRF2 plays a critical role in regulating ferritin metabolism and iron homeostasis (storage and degradation) through the activation of HERC2 and VAMP8. This ensures proper iron recycling within cells, supporting essential functions. Understanding this pathway could provide valuable insights into ferroptosis-related diseases and potential therapeutic approaches.

## 2. Pharmacological modulators of ferroptosis

Since ferroptosis was discovered in 2012 and its potential as a possible therapy for different types of cancer was established, researchers have been actively searching for different modulators to develop effective treatments.

Historically, four different classes have been established [63], both in the case of inducers (Table 2) and inhibitors (Table 3). On one hand, inducers are classified based on whether they: I) inhibit the  $\text{X}_c$  system, II) inhibit GPX4, III) deplete GPX4 or  $\text{CoQ}_{10}$  (decrease GSH levels), and IV) induce lipid peroxidation. On the other hand, ferroptosis inhibitors are categorised into the following classes: I) iron chelators, II) lipophilic antioxidants, III) polyunsaturated fatty acids (D-PUFAs), and IV) lipooxygenases (LOX) inhibitors.

Consequently, we propose a new classification of ferroptosis modulators based on their phenotypical effect: 1) inducers of ferroptosis with the common feature of diminishing cell viability and 2) inhibitors of ferroptosis that lead to elevated cell viability levels. Our proposition is grounded on accumulated knowledge and aims to adapt to recent discoveries in the field, as well as facilitate the understanding of rather convoluted previous classification systems (Table 2 and Table 3).

### 2.1. Ferroptosis inducers

Nonetheless, several problems exist with this classification, and many compounds are omitted, such as statins or buthionine sulfoximine (BSO). This is partly because the classification has not kept pace with new findings about this type of cell death. Many regulatory pathways have emerged, and the lack of detailed understanding about how different modulators work adds to the complexity. In numerous cases, the specific target of the drug is not known, but its effects on the cell are observed.

Considering the newly discovered regulatory pathways, we suggest

the inclusion of the two new categories in the classification (Table 2 and Fig. 2).

**Class I** encompasses compounds that specifically target and inhibit the  $\text{X}_c$  system (e.g., sulfasalazine, vorinostat, erastin or imidazole ketone erastin (IKE)) [1,64–67]. This action leads to a decrease in glutathione (GSH) levels, resulting in elevated  $\text{Fe}^{2+}$  and ROS levels, sometimes accompanied by increased MDA levels. Some compounds in this category, such as 2-imino-6-methoxy-2H-chromene-3-carbothioamide (IMCA), achieve this effect by down-regulating SLC7A11 expression [35], while others, like sorafenib [68], decrease hypoxia inducible factor 1 subunit alpha (HIF-1 $\alpha$ ), subsequently reducing SLC7A11 expression. Additionally, lidocaine reduces SLC7A11 expression through miR-382–5p [69] (Table 2 and Fig. 2).

In **Class II**, we include compounds capable of directly (e.g., RSL3, dihydroartemisinin (DHA), ML162 or ML210) [27,70–75] or indirectly (e.g., bufotalin, statins, FIN56, or ketamine) [16,41,76–80] inhibiting GPX4 (e.g.,  $\beta$ -elemene combined with cetuximab, and altretamine), often accompanied by decreased GSH levels and elevated  $\text{Fe}^{2+}$ , MDA, and ROS levels [76,81,82]. Some of these compounds in this category, such as curcumin analogs, dihydroorotate dehydrogenase (DMOCPTL), and palladium pyridone complex, induce the ubiquitination and degradation of GPX4 [83] (Table 2 and Fig. 2).

**Class III** consists of compounds that alter GSH levels by acting through various mechanisms such as inhibiting peroxiredoxins 1/2 (Prdx I/II) (e.g., Ent-kaurane diterpenoids) [84], GSH synthesis (e.g., BSO) [85], affecting the glutathione metabolism (e.g., Solasonine) [86] or depleting GSH and inhibiting GPX (e.g., acetaminophen) [87]. These compounds, like previous classes, reduce GSH levels while increasing ROS,  $\text{Fe}^{2+}$ , and occasionally MDA levels (Table 2 and Fig. 2).

**Class IV** comprises ferroptosis inducers that primarily trigger lipid peroxidation, elevating ROS, and MDA levels, and have varying impacts on  $\text{Fe}^{2+}$  and GSH. Mechanisms include direct mitochondrial complex I inhibition (e.g., BAY 87–2243) [88], indirect GPX4 inhibition coupled with iron oxidation (e.g., FINO2) [17], and interference with anti-ferroptotic complex formation (e.g., Gemcitabine) [89]. Additionally, bromelain modulates ASL4 levels [90], and ferumoxytol acts as a catalytic reactor in an oxidant environment such as that of a cancer cell [91] (Table 2 and Fig. 2).

**Class V** comprises compounds that alter iron homeostasis, resulting in increased  $\text{Fe}^{2+}$  and ROS levels, with certain instances also affecting MDA and GSH levels. Mechanisms of action within this class vary, including modulation of transferrin endocytosis (e.g., artemisin) [92], induction of ferritinophagy (e.g., JQ1, MMRI62, sorafenib combined with artesunate) [93–96], alteration of ferroportin and transferrin expression (e.g., siramesine combined with lapatinib) [97], or iron accumulation and ferritin degradation in lysosomes (e.g., ironmycin) [94]. Iron oxide nanoparticles coated with gallic acid and polyacrylic acid (IONP-GA/PAA) activate heme oxygenase 1 (HMOX1), which is an intracellular source of iron, increasing the labile  $\text{Fe}^{2+}$  [98] (Table 2 and Fig. 2).

Finally, **Class VI** includes compounds inhibiting the NRF2 pathway (e.g., withaferin A, trigonelline combined with artesunate) [89,95,99], a key antioxidant defense mechanism in cells, exhibiting characteristics akin to Class V compounds. Temozolomide inhibits the NRF2 pathway by upregulating expression levels of DMT1 [83].

### 2.2. Ferroptosis inhibitors

On the other hand, six different classes of ferroptosis inhibitors are proposed, all of which share a common goal of increasing cell viability (Table 3 and Fig. 3).

**Class I** groups together different substances that interfere with the maintenance of iron homeostasis, thereby decreasing intracellular iron levels and preventing the Fenton reaction from occurring and triggering ROS levels. Examples in this category are deferoxamine, cyclopyroxolamine or deferiprone [100–102] (Table 3 and Fig. 3).

**Table 2**

Mechanisms and effects of various compounds as inducers of ferroptosis in different cell models. Drug: the name of the drug or compound being studied. Model: the type of cells or animal models used in the study; Cell phenotype: indicates changes in cell phenotype (↑ for increase, ↓ for decrease, N/A for not available); Fe<sup>2+</sup>: effects on iron levels; MDA/4HNE: levels of malondialdehyde (MDA) or 4-hydroxynonenal (4HNE), markers of lipid peroxidation; ROS: levels of reactive oxygen species; GSH: levels of glutathione, an antioxidant; Cell viability: The viability or survival of cells after treatment. Classes of Inducers: Class I: Inhibition of system X<sub>c</sub>: compounds that inhibit the cystine/glutamate antiporter, affecting cellular redox balance; Class II: GPX4 inhibition, compounds that inhibit Glutathione Peroxidase 4, leading to increased lipid peroxidation; Class III: alteration of GSH levels, compounds that alter levels of glutathione, an important cellular antioxidant; Class IV: induction of lipid peroxidation, compounds that induce lipid peroxidation directly; Class V: alter iron homeostasis, compounds that disrupt iron metabolism, contributing to ferroptosis; Class VI: NRF2 pathway inhibition, compounds that inhibit the NRF2 pathway, which regulates the expression of antioxidant proteins. Interpretation of Symbols: ↑: Increase in the parameter; ↓: Decrease in the parameter. N/A: not available data.

Inducers							References	
Class I: Inhibition of system X <sub>c</sub>								
Drug	Model	Cell phenotype						
		Fe <sup>2+</sup>	MDA/4HNE	ROS	GSH	Cell viability		
2-imino-6-methoxy-2H-chromene-3-carbothioamide	Colorectal cancer	↑	N/A	↑	↓	↓	[35]	
Erastin	RAS-mutant tumor cells	↑	N/A	↑	↓	↓	[1]	
Imidazole ketone Erastin (IKE)	Collagen-induced arthritis fibroblasts and mouse lymphoma model	↑	N/A	↑	↓	↓	[66,67]	
Lanperisone	Kras-mutant tumor cells	↑	N/A	↑	↓	↓	[138]	
Sorafenib	Liver fibrosis	↑	↑	↑	↓	↓	[68]	
Lidocaine	Ovarian and breast cancer	↑	N/A	↑	N/A	↓	[69]	
Sulfasalazine	Paclitaxel-resistant tumor cells	N/A	N/A	N/A	↓	↓	[64]	
Vorinostat	Lung cancer	↑	N/A	↑	↓	↓	[65]	
Class II: GPX4 inhibition								
RSL3	RAS-mutant tumor cells		↑	↑	↑	↓	↓	[27,70,71]
Bufotalin	Non-small cell lung cancer		↑	↑	↑	↓	↓	[76]
Curcumin analogs	Glioblastoma		N/A	N/A	↑	↓	↓	[83]
								[139]
Dihydroateminin (DHA)	Glioblastoma		N/A	N/A	↑	↓	↓	[72]
DMOCPTL	Triple-negative breast cancer		↑	N/A	↑	N/A	↓	[140]
DPI compounds	Vascular smooth muscle cells		N/A	N/A	N/A	N/A	↓	[141]
ML162	COS-7 cancer cells, tongue squamous cancer cells and breast cancer cells		N/A	↑	N/A	↓	↓	[73-75]
ML210	Ovarian cancer cells		N/A	↑	↑	↓	↓	[73,124]
Palladium pyrrithione complex (PdPT)	NCI-H1299 and A549 cell line		N/A	N/A	N/A	N/A	↓	[142]
Statins	High-mesenchymal state cancer cells and breast cancer cells		N/A	↑	↑	N/A	↓	[16,73,143]
β-elemene + cetuximab	Colorectal cancer		↑	↑	↑	↓	↓	[81]
Altretamine	U-2932 cell line		↑	N/A	↑	N/A	N/A	[82]
FIN56	Bladder cancer cells and glioblastoma cell lines (LN229 and U118)		↑	↑	↑	↓	↓	[41,78,79]
CIL 56	Hematological cancer cell lines		N/A	N/A	N/A	↓	↓	[144]
Ketamine	Liver cancer		↑	↑	↑	↓	↓	[80]

Class III: Alteration of GSH levels

(continued on next page)

Table 2 (continued)

Acetaminophen	Primary hepatocytes cells	↑	↑	↑	↓	↓	[87]
BSO	Retinal pigment epithelium	↑	↑	↑	↓	↓	[85]
							[145]
Ent-kaurane diterpenoids	Lung cancer	↑	N/A	↑	↓	↓	[84]
Solasonine	Hepatoma carcinoma cells	↑	N/A	↑	↓	↓	[86]
<b>Class IV: Induction of lipid peroxidation</b>							
BAY-87-2243	Melanoma cells	↑	↑	↑	↓	↓	[88]
Ferumoxytol	Leukemia cells	↑	↑	↑	N/A	↓	[91]
FINO2	Fibrosarcoma cells	↑	↑	↑	N/A	↓	[4]
Gemcitabine	Pancreatic cancer	N/A	↑	↑	N/A	↓	[89]
Bromelain	Kras mutant colorectal cancer cells	N/A	↑	↑	N/A	↓	[90]
<b>Class V: Alter iron homeostasis.</b>							
Artemisin	Different cancer cell lines		↑	N/A	↑	N/A	↓
							[92]
Artesunate + sorafenib	Hepatocellular carcinoma Head and neck cancer cells		↑	↑	↑	↓	↓
							[95,96]
IONP-GA/PAA	Glioblastoma, neuroblastoma and fibrosarcoma cells		↑	N/A	↑	N/A	↓
							[98]
MMRi62	Pancreatic ductal adenocarcinoma		N/A	↑	↑	N/A	↓
							[127]
JQ1	Breast cancer, lung squamous cell carcinoma		↑	↑	↑	N/A	↓
							[93]
Ironomycin	Cancer stem cells		↑	N/A	↑	↓	↓
							[94]
Siramesine + lapatinib	Breast cancer cells		↑	N/A	↑	N/A	↓
							[97]
<b>Class VI: NRF2 pathway inhibition</b>							
Withaferin A	Different neuroblastoma cell lines and hepatocellular carcinoma		↑	N/A	↑	N/A	↓
							[99]
Temozolomide	Glioblastoma		↑	↑	↑	↓	↓
							[83]
Trigonelline + artesunate	Cisplatin-resistant head and neck cancer cells		↑	↑	↑	↓	↓
							[95]

**Class II** is made up of those compounds that are characterised by being lipophilic antioxidants, i.e., they prevent the lipid peroxidation reaction from occurring. Within this class are vitamins (K and E) [43, 103], radical scavengers (e.g., Fer-1) [27,104] and other antioxidant compounds, such as U0126 [105] (Table 3 and Fig. 3).

**Class III** consists of D-PUFAs that prevent the initiation and propagation of lipid peroxidation (e.g., D4- arachidonic acid), thus preventing the triggering of the ferroptotic response [100–102] (Table 3 and Fig. 3).

**Class IV** is about inhibitors of proteins associated with lipid metabolism; these inhibitors act on proteins, such as LOX, which are involved in the formation of lipid peroxides. Within this class, we can find nordihydroguaiaretic acid (NDGA) [106], zileuton [107] or nuclear enriched transcript 1 (NEAT1) miR-522 [54,108] (Table 3 and Fig. 3).

**Class V** are epigenetic inhibitors, compounds that modify the regulation of genes by turning them on or off (e.g., baicalein, sulforaphane and BRD4770) [109–113] (Table 3 and Fig. 3).

In **Class VI** are inhibitors of dipeptidyl peptidase-4 (DPP4), which associates with tumour protein P53 (TP53), increasing the expression of the SLC7A11 gene, which is related to the inhibition of ferroptosis. Examples are linagliptin (BI-1356), alogliptin (SYR 322), or vildagliptin (LAF-237) [59] (Table 3 and Fig. 3).

### 3. Epithelial ovarian cancer (EOC)

EOC arises from a layer of cells lining the surface of the ovaries and fallopian tubes and accounts for approximately 90 % of primary ovarian tumours. Since in the early stages of the development of the disease the symptoms are non-specific, diagnosis is complex, and it is often misdiagnosed. All of this means that by the time the disease is correctly diagnosed it is in advanced stages, the prognosis is poor, and the survival rate is low. Thus, EOC is one of the most lethal gynaecologic cancers, with a 5-year survival rate after the diagnosis of only 46 % [114].

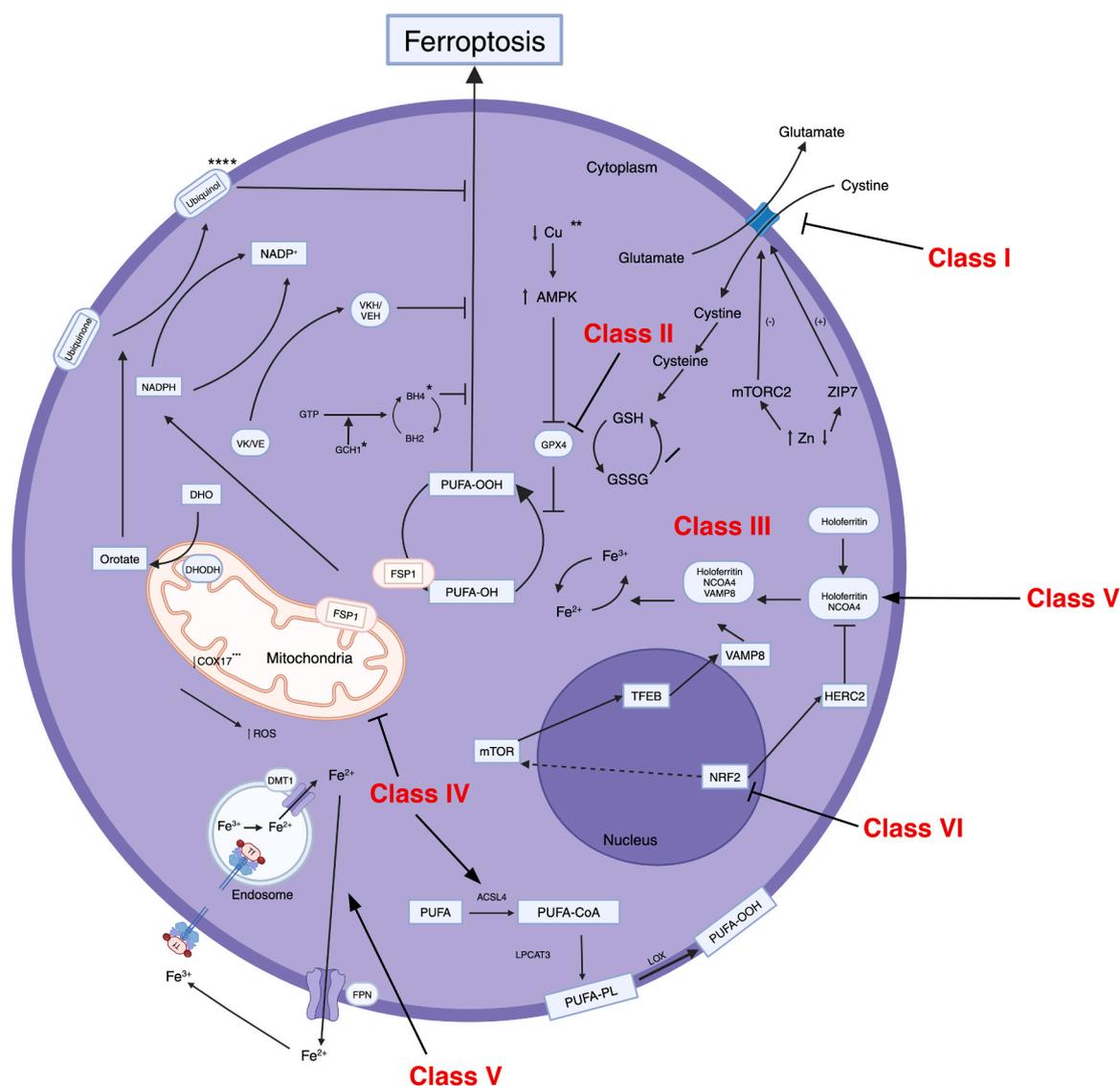
Several treatment options are available, with surgery being the cornerstone of treatment in both early and advanced stages. Surgery can be combined with pharmacological treatments such as chemotherapeutic agents, angiogenesis inhibitors, or poly-ADP ribose polymerase (PARP) inhibitors, particularly in advanced EOC, achieving remission in most cases initially [114,115]. However, many patients eventually relapse as they develop resistance to treatments that were initially effective for primary tumours. Consequently, the results obtained with these therapies remain unsatisfactory, with favourable outcomes achieved in only 10 %-25 % of patients. Therefore, it is crucial to improve early detection techniques, as well as to explore new alternatives for the treatment of resistant EOC cells, to enhance patient prognosis and

**Table 3**

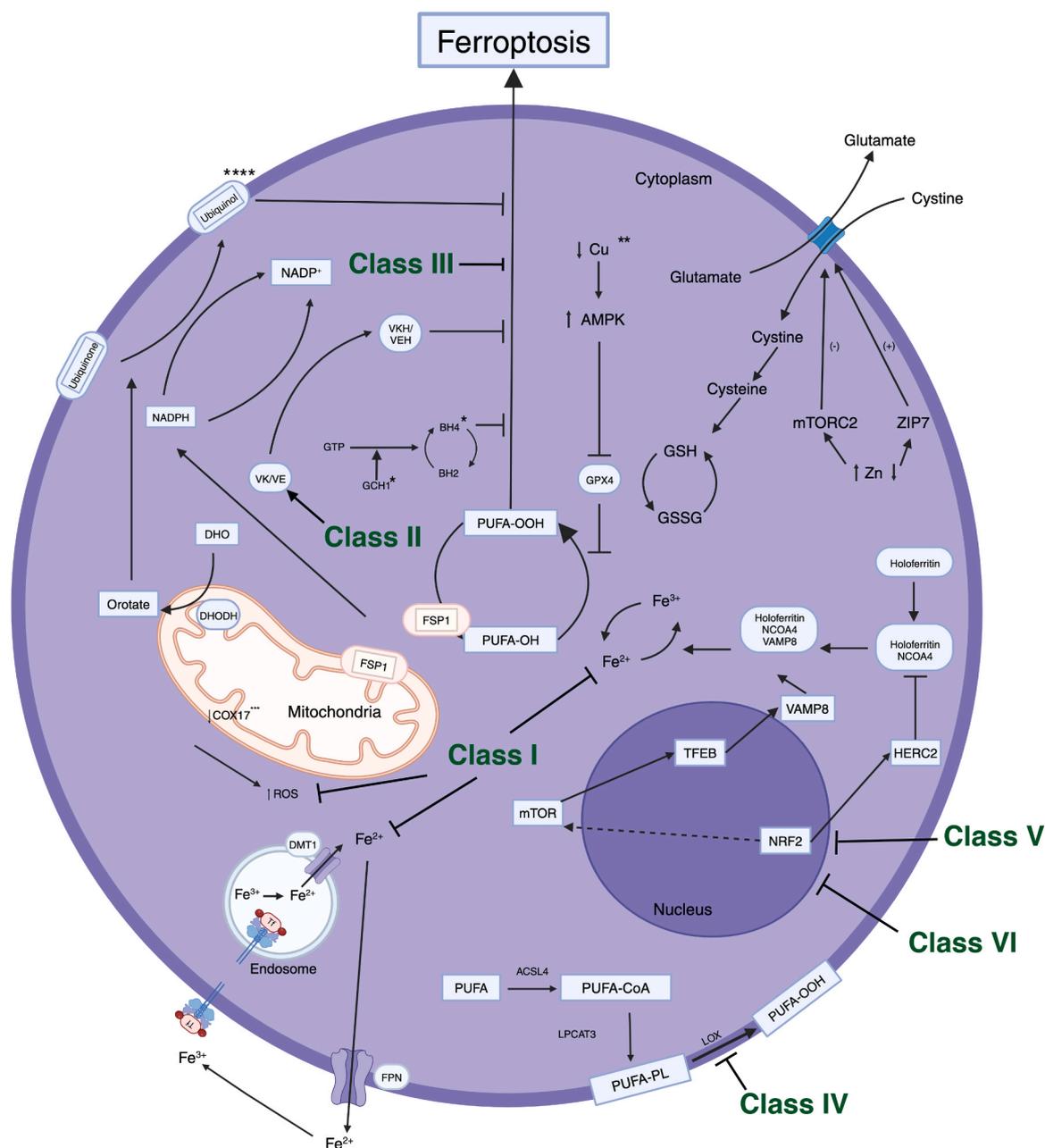
Mechanisms and effects of various compounds as inhibitors of ferroptosis in different cell models. Drug: the name of the drug or compound being studied. Model: the type of cells or animal models used in the study; Cell phenotype: indicates changes in cell phenotype (↑ for increase, ↓ for decrease, N/A for not available); Fe<sup>2+</sup>: effects on iron levels; MDA/4HNE: levels of malondialdehyde (MDA) or 4-hydroxynonenal (4HNE), markers of lipid peroxidation; ROS: levels of reactive oxygen species; GSH: levels of glutathione, an antioxidant; Cell viability: the viability or survival of cells after treatment. Classes of Inhibitors: Class I: agents that interfere with iron homeostasis, compounds that disrupt iron homeostasis to prevent ferroptosis; Class II: lipophilic antioxidants, compounds that are lipid-soluble antioxidants and can prevent lipid peroxidation; Class III: D-PUFAs, polyunsaturated fatty acids that can protect against lipid peroxidation; Class IV: inhibitors of lipid-associated metabolism proteins, compounds that inhibit proteins involved in lipid metabolism; Class V: Epigenetic inhibitors: Compounds that affect gene expression to prevent ferroptosis; Class VI: DPP4 inhibitors: Compounds that inhibit DPP4 to modulate ferroptosis. Interpretation of Symbols: ↑: Increase in the parameter; ↓: Decrease in the parameter. N/A: not available data.

Inhibitors										
Class I: Agents that interfere with iron homeostasis.										
Drug	Model	Cell phenotype					References			
		Fe <sup>2+</sup>	MDA/4HNE	ROS	GSH	Cell viability				
Deferoxamine	<i>In vivo</i> model of traumatic spinal cord injury	↓	N/A	↓	↑	↑	[100]			
Cyclopiroxolamine (CPX)	ADPKD and NHK epithelial cells	↓	N/A	↓	N/A	↑	[101]			
Deferiprone	<i>In vivo</i> model of Parkinson's disease	↓	↓	↓	↑	↑	[102]			
Prominin2	Breast cancer cells	↓	N/A	↓	N/A	↑	[15]			
2,2-bipyridyl	Iron chelator	↓	N/A	↓	N/A	↑	[1]			
Class II: Lipophilic antioxidants										
Vitamin E	Mouse striatal Q7 cells				↓	N/A	↓	↑	↑	[103]
Vitamin K	Pfa1, Fibrosarcoma (HT-1080), renal cell carcinoma (786-O), melanoma cells (A375 and B16F10), fibroblasts from embryonic rat heart (H9C2), fibroblasts from kidney (NRK49F), muscle cells (C2C12), hepatocellular carcinoma cells (HepG2), T lymphoblasts (Jurkat), fibroblasts from adipose tissue (L929) and embryonic kidney cells (HEK293T)				↓	↓	↓	N/A	↑	[43]
Butylated hydroxytoluene (BHT)					N/A	N/A	↓	N/A	↑	[141]
Fer-1	Embryonic kidney cells (HEK293T) and epithelial ovarian cancer cells (A2780 and SK-OV-3)				↓	↓	↓	↑	↑	[27, 104]
Lipoxstatin-1	Embryonic kidney cells (HEK293T)				N/A	N/A	↓	N/A	↑	[104]
XJB-5-131	Tubular epithelial cells				N/A	↓	↓	↑	↑	[146]
SRS 11-92	Fibrosarcoma (HT-1080)				N/A	N/A	↓	N/A	↑	[147]
Trolox	Fibrosarcoma (HT1080) and pancreatic carcinoma (Panc-1).				N/A	N/A	↓	N/A	↑	[109]
U0126	Cells from adrenal gland (PC-12)				N/A	N/A	↓	N/A	↑	[105]
Class III: D-PUFAs										
D4-arachidonic acid	Epithelial cells from kidney	N/A	N/A	↓	N/A			↑		[5,148]
D-10 docosahexaenoic acid	Retinal pigment epithelium	N/A	N/A	↓	N/A			↑		[141]
Class IV: Inhibitors of lipid-associated metabolism proteins										
PD146176	HT1080 (human fibrosarcoma) and Panc-1 (human pancreatic carcinoma) cells				N/A	N/A	N/A	N/A	↑	[104,109, 149]
Zileuton	Hippocampal HTT22 cells and acute lymphoblastic leukemia cells				N/A	N/A	↓	N/A	↑	[107]
Nordihydroguaiaretic acid (NDGA)	Acute lymphoblastic leukemia cells				N/A	N/A	↓	N/A	↑	[106]
Rosiglitazone (BRL49653)	Pfa1 cell type				N/A	N/A	N/A	N/A	↑	[23]
Triacsin C	Pfa1 cell type								↑	[150]
Nuclear enriched transcript 1 (NEAT1)	Non-small-cell lung cancer			↓	↓	N/A	N/A		↑	[108]
miR-522	Gastric cancer cell lines				N/A	N/A	↓	N/A	↑	[54]

Class V: Epigenetic inhibitors							
Baicalein	H9c2 rat myocardial cells Rat Pheochromocytoma PC12 Cells	↓	↓	↓	↑	↑	[109–111]
Sulforaphane	Neonatal mouse ventricular cardiac cells	↓	↓	N/A	↑	↑	[112]
BRD4770	Human aortic smooth muscle cells	N/A	↓	N/A	N/A	↑	[113]
Class VI: DPP4 inhibitor							
Linagliptin (BI–1356)	Erastin-induced ferroptosis in human colorectal cancer (CRC)	N/A	↓	N/A	N/A	↑	[59]
Alogliptin (SYR 322)	Erastin-induced ferroptosis in human colorectal cancer (CRC)	N/A	N/A	N/A	N/A	↑	[59]
Vildagliptin (LAF–237)	Erastin-induced ferroptosis in human colorectal cancer (CRC)	N/A	↓	N/A	N/A	↑	[59]



**Fig. 2.** Pharmacological manipulation to induce ferroptosis. Some pharmacological compounds have been described to induce ferroptosis in several models. They are classified in several classes (I, II, III, IV, V and VI). The Class I are Inhibitors of system X<sub>c</sub> (2-imino-6-methoxy-2H-chromene-3- carbothioamide, erastin, imidazole ketone erastin (IKE), lanperisone, sorafenib, lidocaine, sulfasalazine and vorinostat); Class II are specific inhibitors of GPX4 (RSL3, bufotalin, curcumin analogs, dihydroatemisisin (DHA), DMOCPYL, DPI compounds, ML162, ML210, palladium pyriithione complex (PdPT), statins, β-elmene+cetuximab, altretamine, FIN56, CIL 56 and ketamine); Class III are compounds that alter GSH levels (acetaminophen, BSO, ent-kaurane diterpenoids and solasoine); Class IV are inducers of lipid peroxidation (BAY-87–2243, ferumoxytol, FINO2, gemcitabine and bromelain); Class V are agents altering iron homeostasis (artemisin, artesunate+sorafenib, IONP-GA/PAA, MMRi62, JQ1, ironomycin, siramesine+lapatinib) alter iron homeostasis; Class VI, inhibitors of the NRF2 antioxidant pathway (withaferin A, tomozolomide and trigonelline+artesunate) inhibit the antioxidant NRF2 pathway.



**Fig. 3.** Pharmacological manipulation to prevent ferroptosis. Various pharmacological compounds have been identified to prevent ferroptosis and are categorised into six classes based on their mechanisms: Class I: agents involved in regulating iron homeostasis and reducing ROS production (e.g., deferoxamine, cyclopiroxolamine (CPX), deferiprone, prominin2, and 2,2-bipyridyl); Class II: lipophilic antioxidants (e.g., vitamin E, vitamin K, butylated hydroxytoluene (BHT), Fer-1, liproxstatin-1, XJB-5-131, SRS 11-92, Trolox, and U0126); Class III: D-PUFAs, which include D4-arachidonic acid and D-10 docosahexaenoic acid; Class IV: inhibitors of lipid metabolism (e.g., PD146176, zileuton, nordihydroguaiaretic acid (NDGA), rosiglitazone (BRL49653), triacsin C, nuclear enriched transcript 1 (NEAT1), and miR-522); Class V: epigenetic inhibitors (e.g., baicalein, sulforaphane, and BRD4770); Class VI: dipeptidyl peptidase-4 (DPP4) inhibitors (e.g., linagliptin (BI-1356), alogliptin (SYR 322), and vildagliptin (LAF-237)).

quality of life [114].

In recent years, new avenues for the treatment of this type of cancer have been studied, among these alternatives is the use of cell death modulators [112]. Cell death and proliferation are balanced during the life of multicellular organisms. In them, most cell deaths occur due to a normal physiological process that plays a key role in embryonic development and in adult tissues. The recent discovery of ferroptosis, has become a promising tool for cancer treatment and specifically, for the management of EOC using pharmacological modulators [116].

#### 4. Ferroptosis and cancer

Ferroptosis has been linked to cancer ever since the discovery of this novel cell death type, emerging from research efforts to find compounds that can treat the disease [1]. Several studies have revealed links between genes related to cancer development and different signaling pathways involved in the control of ferroptosis. In principle, it would seem logical to think that cancer cells have a greater tendency to undergo ferroptosis due to their higher metabolic activity and, therefore, a greater amount of ROS [2]. In addition, they have been described as having altered iron metabolism, specifically showing an increased amount of the transferrin receptor involved in iron import [30].

It has been observed that many tumour suppressors promote ferroptosis, and tumour suppression may be conceived as an innate physiological function of this type of cell death. Among all tumor suppressors, p53 is one of the most studied (Table 2). On the one hand, p53 was found to be able to sensitise cells to undergo ferroptosis through transcriptional repression of SLC7A11, supporting the idea that through p53, ferroptosis contributes to the tumor suppressor role of p53 [117]. Recently, a type of epigenetic mark associated with histone H2B monoubiquitination at lysine 120 (H2Bub1), an epigenetic mark associated with transcriptional activation has been linked to the regulation of SLC7A11 and ferroptosis. Specifically, increasing SLC7A11 expression decreases sensitivity to ferroptosis. p53 acts as a negative regulator of H2Bub1 by interacting with and promoting nuclear translocation of ubiquitin carboxyl-terminal hydrolase 7 (USP7), a deubiquitinase that removes the epigenetic mark from the SLC7A11 regulatory region, decreasing SLC7A11 expression [118].

On one hand, other studies show that p53 acts to prevent the development of ferroptosis. Loss of p53 prevents nuclear accumulation of DPP4 in the nucleus by facilitating DPP4-dependent membrane lipid peroxidation, which ultimately leads to ferroptosis [59]. On the other hand, through p21, p53 can prevent the development of ferroptosis in the absence of cysteine, suggesting that it acts as a mechanism to prevent cancer cell proliferation [119]. Thus, p53 can regulate a large group of genes involved in different biological processes including ferroptosis, and its activity may be context dependent.

Activation of ferroptosis is one of the promising approaches for the treatment of cancer cells resistant to current treatments. For example, mesenchymal cancer cells, which are typically characterised by high zinc finger E-box-binding homeobox1 (ZEB1) expression, are highly sensitive to ferroptosis induced by GPX4 inhibition. It has been proposed that ZEB1 is a lipogenic factor that regulates lipid metabolism, establishing a relationship between its expression in these mesenchymal cells and vulnerability to lipid peroxidation [77]. Furthermore, the survival of drug-resistant cells is highly dependent on GPX4, making it an important target for treatment. GPX4 has been found to be required for relapse in a melanoma xenograft model [77]. Therefore, the ability of a given cancer cell to be resistant or sensitive to the development of ferroptosis will depend on its genetic background (Table 2). A more detailed discussion is warranted here, regarding Table 2, which provides the most recent and comprehensive data on various cancer types. While the following sections will focus on a subset of these malignancies, it is important to highlight that Table 2 includes extensive information on a wide range of cancers. For a complete overview of the latest advancements and classifications, readers are encouraged to consult Table 2, which provides an in-depth analysis across all major cancer types.

How cancer cells respond to different ferroptosis modulators is context-specific. Recently, a mechanism was discovered that explains why cancer cells resist GPX4 inhibition in a way that is FSP1-independent. These cells show increased levels of low-density lipoprotein receptor-related protein 8/ apolipoprotein E receptor 2 (LRP8/ApoER2), a protein that, among other things, binds and engulfs SEC-rich protein selenoprotein P (SEPP1) to maintain proper selenium levels in the cells. Loss of LRP8 makes cancer cells more sensitive to ferroptosis, induced both by GPX4 inhibitors and SLCA711. The drop in intracellular selenium levels disrupts GPX4 translation, likely due to early interruptions in translation caused by ribosome collisions, possibly due to limited amounts of SEC-charged tRNAs [56].

Cancer cells with mesenchymal or metastatic traits, along with various non-epithelial cell types, exhibit heightened sensitivity to ferroptosis. This heightened sensitivity is linked to Yes-associated protein (YAP)'s nuclear translocation and the expression of ferroptosis-related genes such as transferrin receptor 1 (TFRC) and ACSL4. Conversely, maintaining high levels of cell confluence serves as a protective mechanism against ferroptosis. The co-expression of E-cadherin and neurofibromin 2 (NF2) leads to YAP phosphorylation and subsequent degradation, preventing its translocation to the nucleus. This process

confers resistance to ferroptosis [30,120].

Ovarian cancer cells overexpressing stearoyl-CoA desaturase 1 (SCD1) show resistance to ferroptosis development, mimicking the effect of MUFA treatment. SCD1 inhibition triggers ferroptosis because it removes CoQ10, a protein used by FSP1 to protect against the development of ferroptosis [121]. For all these reasons, the study and description of ferroptosis is promising not only as a biological mechanism *per se* but may help to clarify therapeutic molecular targets for the treatment of this particular disease.

## 5. Ferroptosis and epithelial ovarian cancer

In particular, the use of ferroptosis modulators appears to be a promising strategy for treating EOC, owing to the specific characteristics observed in EOC cells. The latter were described as having low levels of ferroportin and high levels of transferrin, so that intracellular iron accumulation occurs. Increased intracellular iron promotes ovarian cancer cells' invasion and metastasis through induction of matrix metalloproteases and interleukin 6 [30].

It has been shown that elevated intracellular iron levels are closely associated with EOC. FPN was decreased, TFR1 and TF were increased, and iron levels were elevated in high-grade plasma EOC tissues compared with normal ovarian tissues [27,121,122]. Numerous studies have confirmed that elevated intracellular GSH levels and high expression of related metabolic enzymes are closely associated with drug resistance in EOC [121–124]. Chen *et al.* found that erastin induced ferroptosis and increased ROS levels, thereby enhancing the cytotoxic effects of cisplatin [83]. Erastin synergistically with cisplatin significantly inhibited EOC cell growth (Table 2). Polypeptide N-acetylgalactosaminyltransferase (GALNT14) promoted mTOR by modifying epidermal growth factor receptor (EGFR). The combination of mTOR inhibitor and cisplatin resulted in a cumulative effect on cell death [8].

It has been observed that ovarian carcinoma cells, susceptible to ferroptosis, can transition to a state of resistance by down-regulating polyunsaturated ether phospholipids (PUFA-ePLs), which serve as substrates for lipid peroxidation and induce ferroptosis. Interestingly, the resistance is not attributed to a decrease in peroxisome abundance, but rather to the downregulation of APGS alkylglycerone phosphate synthase (APGS) levels, an enzyme involved in the synthesis of lipid ether precursor and located in the peroxisome [39]. Additionally, alterations in Ca<sup>2+</sup> homeostasis in the ER have been identified as triggers for lipogenesis. The over-expression of membrane-spanning 4-Domains A15 (MS4A15), a tetraspanin found in the ER, facilitates the depletion of calcium stores in the endoplasmic reticulum. This calcium removal results in lipid remodelling, specifically a reduction in long-chain PUFA-glycerophospholipids (PUFA-GP) and an increase in short-chain MUFA-GP, providing resistance to these cells by acting as ROS sinks. Alongside lipid remodelling, this process induces a redistribution of lipid droplets, making them smaller and limiting oxidation [125].

One of the fundamental ways in which EVs promote metastasis involves their ability to mediate cell–cell interactions. For example, the cell-adhesion molecule CD44, which regulates the process of ovarian cancer metastasis in an organ-specific manner, was reported to be transferred to the peritoneal mesothelial cells from EOC cells via EVs to assist in their invasion. To be a potential therapeutic target, EVs can also be used as carriers for drugs and other forms of therapies. Jin *et al.* reported that EVs secreted by breast cancer or EOC contributed to the pharmacodynamics between nearby cells where they transferred drugs from one cell to another [123]. ROS act as crucial messenger molecules and play dual roles in cancer biology. On the one hand, high levels of ROS are frequently observed in cancer cells and are associated with cancer initiation and oncogenic transformation by transcriptional induction of proto-oncogenes. On the other hand, studies describe that depletion of the ROS scavenger GSH and the consequent increase in ROS levels protect against tumor initiation but not tumour progression. It is therefore likely that a delicate balance of ROS levels in tumours is

crucial. Several classes of potential immune modulators released from ferroptotic cells have been studied. The release of oxidised phospholipids (oxPLs), the lipid peroxidation by-product 4-hydroxynonenal (4-HNE), high-mobility group protein B1 (HMGB1), and ATP were reported as potential immune modulators released from ferroptotic cells [122].

## 6. Conclusion and outlook

Research into ferroptosis is still in its infancy, and new studies are gradually revealing more mechanisms involved in its regulation. Ferroptosis represents a promising avenue for the treatment of EOC due to its unique mechanism of inducing cell death via iron-dependent lipid peroxidation. This process is markedly different from apoptosis and offers a potential strategy to overcome resistance to conventional therapies. The therapeutic exploitation of ferroptosis in EOC has the potential to improve patient outcomes significantly.

Research into ferroptosis has highlighted its critical regulatory pathways, including the cyst(e)ine/GSH/GPX4 axis and the involvement of lipid metabolism enzymes such as ACSL4. By targeting these pathways, it is possible to selectively induce ferroptosis in cancer cells, which could lead to more effective treatments for EOC. Additionally, understanding the role of intracellular iron levels and ROS in ferroptosis can help identify new biomarkers and therapeutic targets.

Recent advancements have also underscored the importance of additional pathways, including the NAD(P)H/FSP1/CoQ<sub>10</sub> axis and the DHODH/CoQH<sub>2</sub> pathway, which are emerging as vital regulators of ferroptosis. Vitamins such as K and E play a protective role against ferroptosis, while metals like zinc and copper influence the NRF2 pathway, which is central to the cellular antioxidant response. These pathways offer new therapeutic opportunities to manipulate ferroptosis more precisely and effectively in EOC.

One of the key contributions of our works lies in the classification of ferroptosis inhibitors and inducers. By identifying specific compounds that either promote or inhibit ferroptosis, we can begin to better define their potential therapeutic roles.

Future research should focus on further elucidating the molecular mechanisms of ferroptosis and its regulation. This includes identifying new ferroptosis modulators and understanding their specific roles and targets within the cell. Moreover, clinical trials are necessary to evaluate the safety and efficacy of ferroptosis-inducing compounds in EOC patients. Exploring the use of EVs as drug carriers to induce ferroptosis selectively in cancer cells presents another promising direction for therapeutic innovation.

In conclusion, the therapeutic exploitation of ferroptosis in EOC holds significant promise, but its successful implementation will require continued research into the underlying molecular mechanisms, the development of novel compounds, and clinical validation through rigorous trials. By leveraging our understanding of ferroptosis inducers and inhibitors, we can take critical steps toward designing more effective and personalized treatment strategies for EOC patients.

## Ethical approval and consent to participate

Not applicable.

## CRediT authorship contribution statement

C. Alarcón-Veleiro and I. López-Calvo conducted research and drafted the manuscript. L. Berjawi, S. Lucio-Gallego, R. Mato-Basalo, M. Quindos-Varela, R. Lesta-Mellid, I. Santamarina-Caínzos, S. Varela-Rodríguez, M. Fraga, M. Quintela, A. Vizoso-Vázquez and M.C. Arufe helped in the process of revised drafting manuscript and figure and tables construction. J. Fafián-Labora contributed to conceptual framework, supervised, and conducted the study, drafted, and revised the manuscript. All authors read the final manuscript and approved.

## Consent for publication

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Data availability

Data will be made available on request.

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