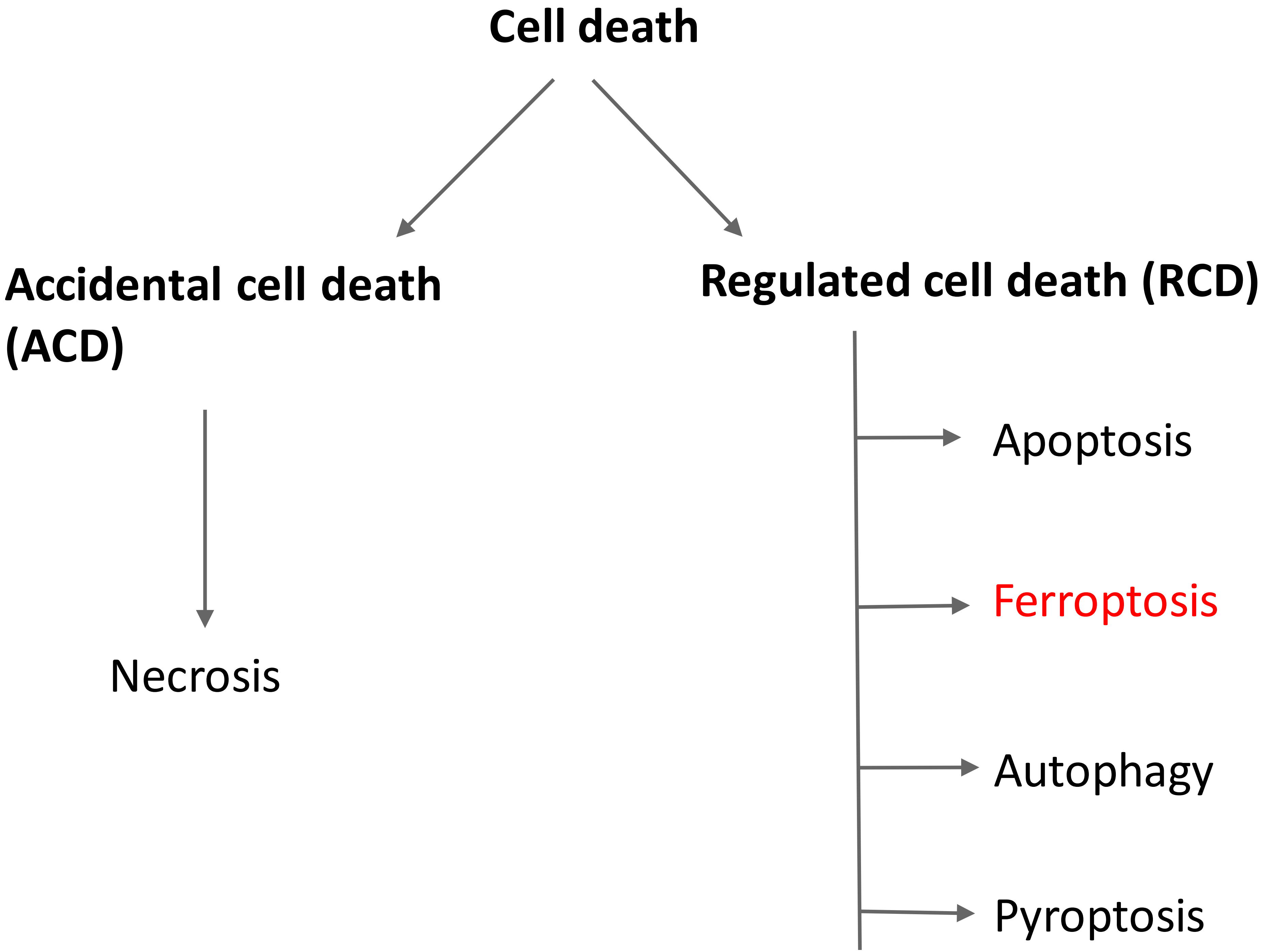
Ferroptosis

- Introduction
- Mechanism of ferroptosis
- Role of ferroptosis in diseases
- Inhibitors of ferroptosis
- Differences between apoptosis, necrosis and ferroptosis.
- Summary

Introduction

- **Cell death** : is the event of biological ceasing to carry out its functions. This may be the result of the nature process of old cell dying and being replaced by new ones ,as in programmed cell death ,or may result from factors such as diseases, localized injury ,or the death of the organism .


Cell death
Accidental cell death (ACD)
Necrosis
Regulated cell death (RCD)
Apoptosis
Ferroptosis
Autophagy
Pyroptosis

Differences between apoptosis , necrosis and ferroptosis

Apoptosis	Necrosis
Apoptosis is the programmed cell death	Necrosis is the premature cell death
A naturally occurring physiological process	A pathological process caused by external agents like toxins
Occurs through shrinking of cytoplasm followed by the condensation of the nucleus	Occurs through swelling of cytoplasm along with mitochondria followed by cell lysis
It is a caspace dependent pathway	It is a caspace independent pathway

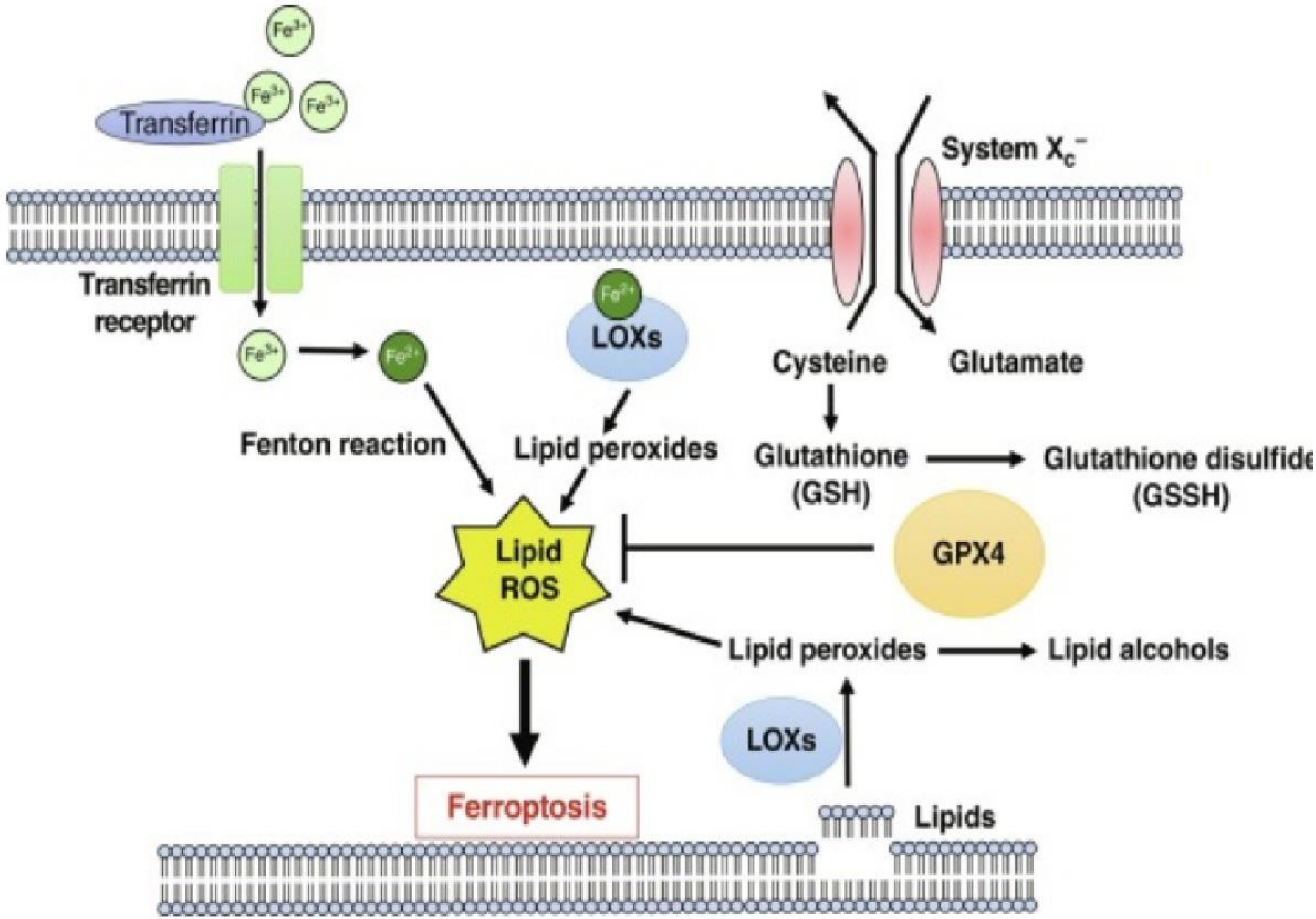
Ferroptosis
Iron dependent
Features of necrosis
It is a caspase-independent pathway

- Ferroptosis is a recently discovered ,its a form of programmed cell death distinct form apoptosis, necrosis and autophagy.
- Greek "Ferro"means iron and "ptosis"denotes falling.
- It is characterized by the accumulation of iron and inducing Reactive oxygen species (ROS) in turn it induce lipid peroxidation.

- The term ferroptosis was coined in 2012 by Brent Stockwell and Scott Dixon

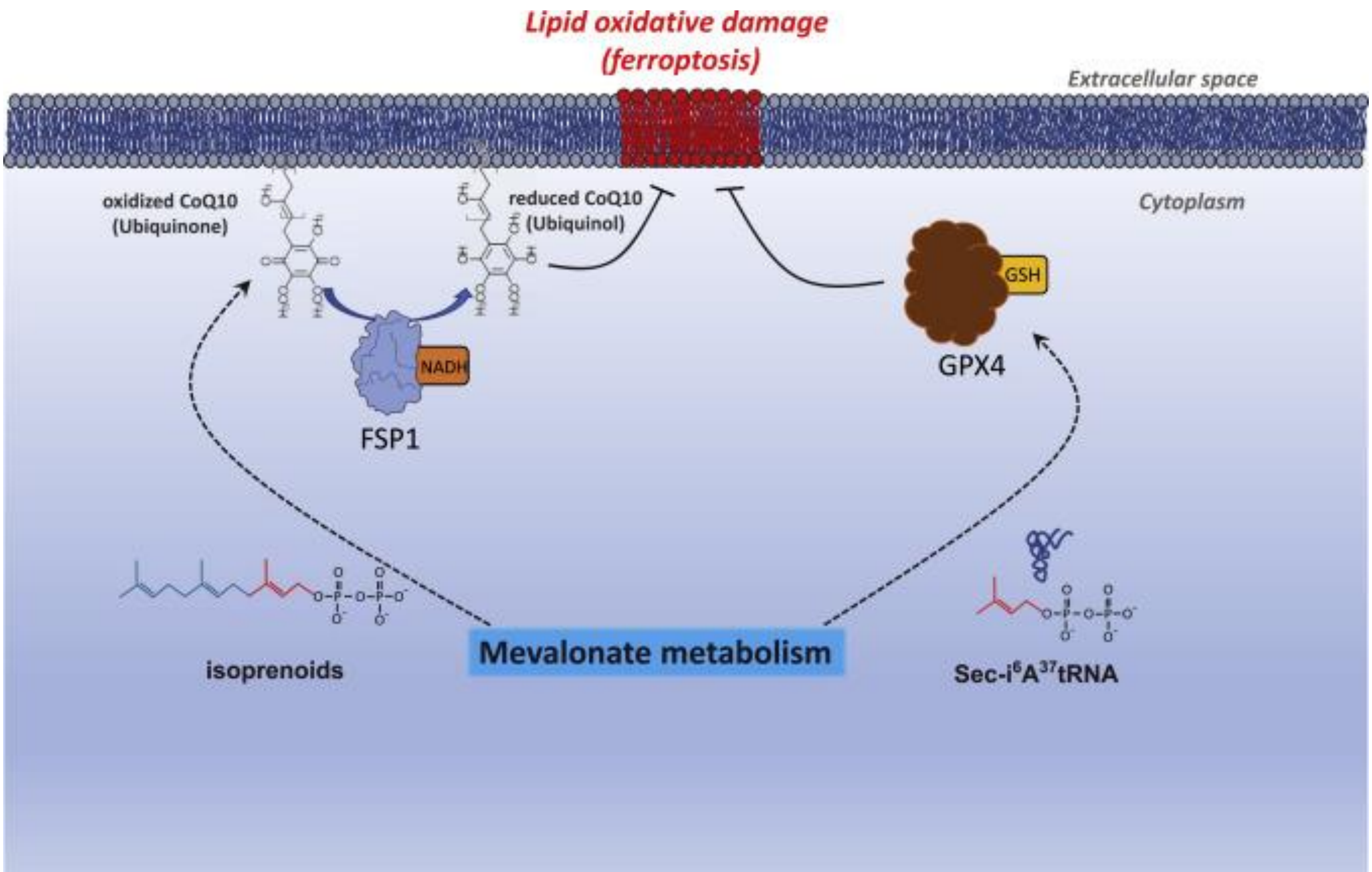
Brent Stockwell

Mechanism of ferroptosis



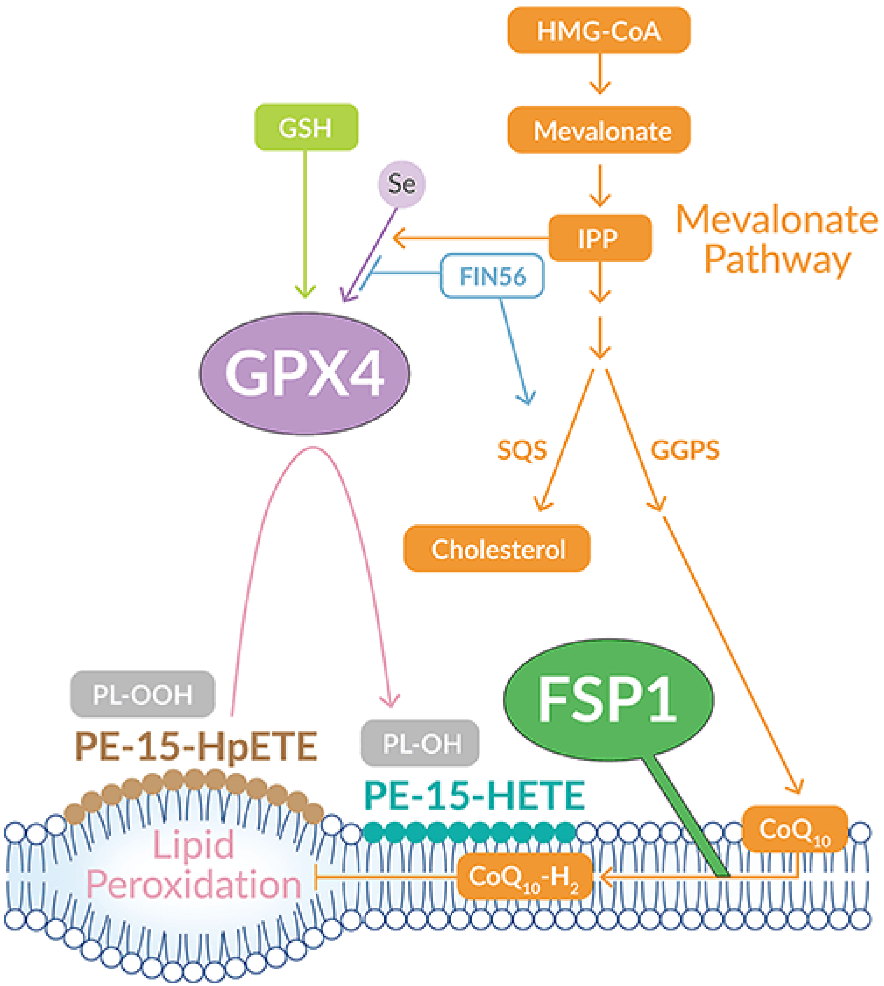
- Uncleared lipid hydroperoxides triggers the formation of lipid reactive oxygen species (ROS) that induces ferroptosis. Ferroptosis can therefore result from decreased levels of GSH or from reduced activity or the inhibition of system Xc− or GPX4.
- Also necessary for the induction of ferroptosis is disruption in iron homeostasis. Ferric iron (Fe^{3+}), imported through the transferrin receptor following binding with transferrin, is reduced to ferrous iron (Fe^{2+}). Accumulation of Fe^{2+} not only produces lipid ROS through the Fenton reaction but also can catalyze lipid peroxidation by combining with cytosolic LOXs, which then leads to the production of lipid ROS and ferroptosis.
- System Xc− imports cystine, which is reduced to cysteine within the cell, and used in biosynthesis of glutathione (GSH), a necessary substrate of glutathione peroxidase (GPX4).
- Toxic lipid hydroperoxides, derived from membrane lipids through the action of lipoxygenases (LOXs), are converted by GPX4 to their corresponding nontoxic alcohols, thus protecting the cell.

Protection from ferroptosis: The FSP1/CoQ10 branches



Santoro, *Cell Metabolism*, 2020

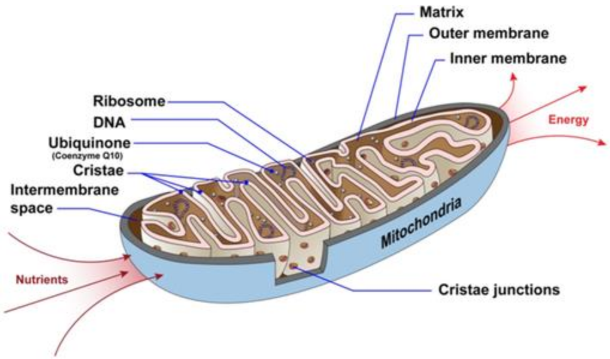
The FSP1/CoQ10 branch



San

Mitochondrial vs non-mitochondrial CoQ10 pools

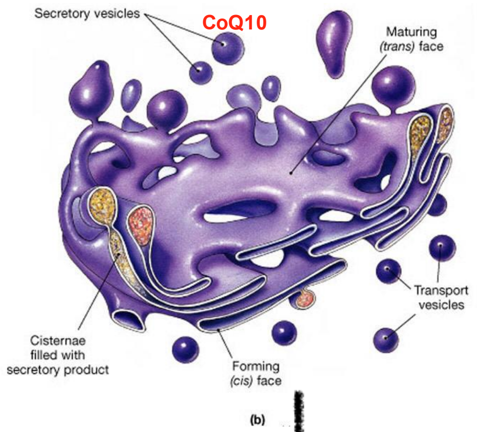
Mitochondria



COQ2

Mito-CoQ10 (energy)

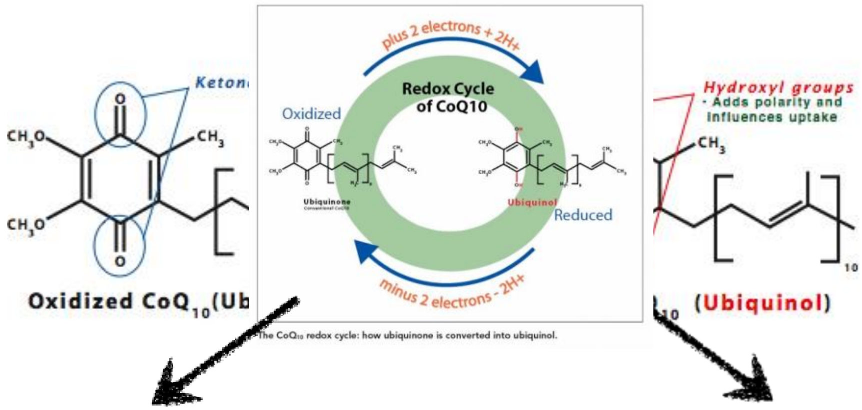
Golgi membrane



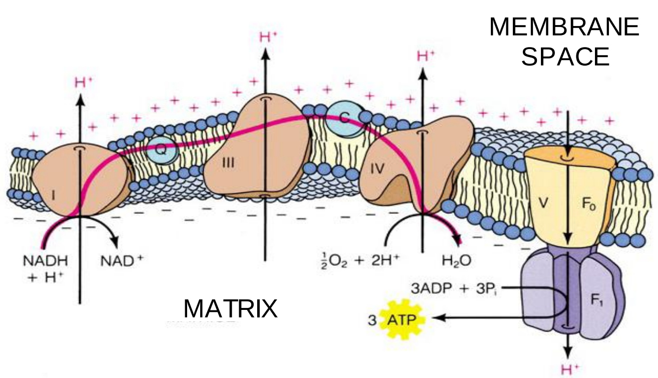
UBIAD1

Golgi-CoQ10 (AOX)

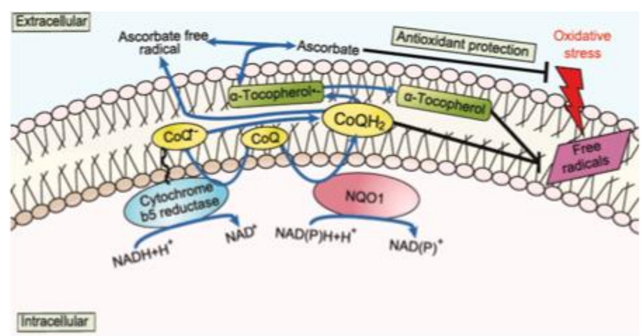
CoQ10 and its function

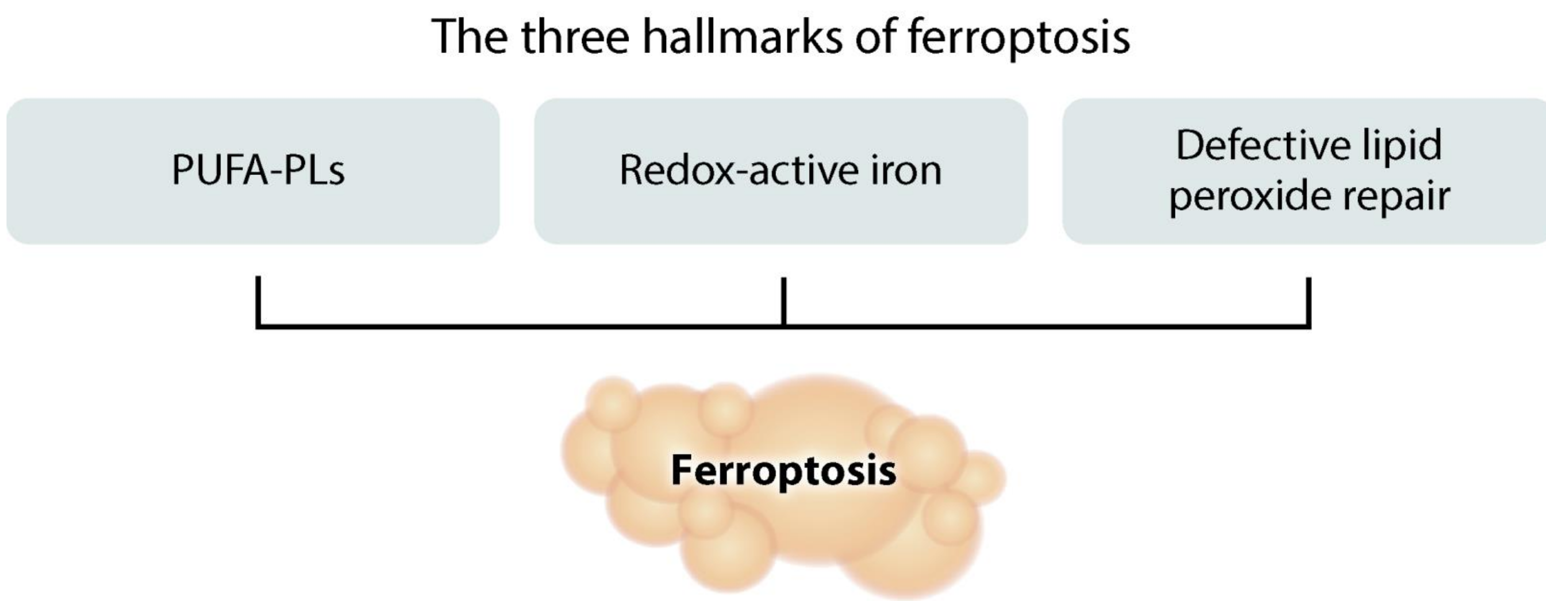


ELECTRON TRANSPORT (MITOCHONDRIA)
redox component of the mitochondrial ETC

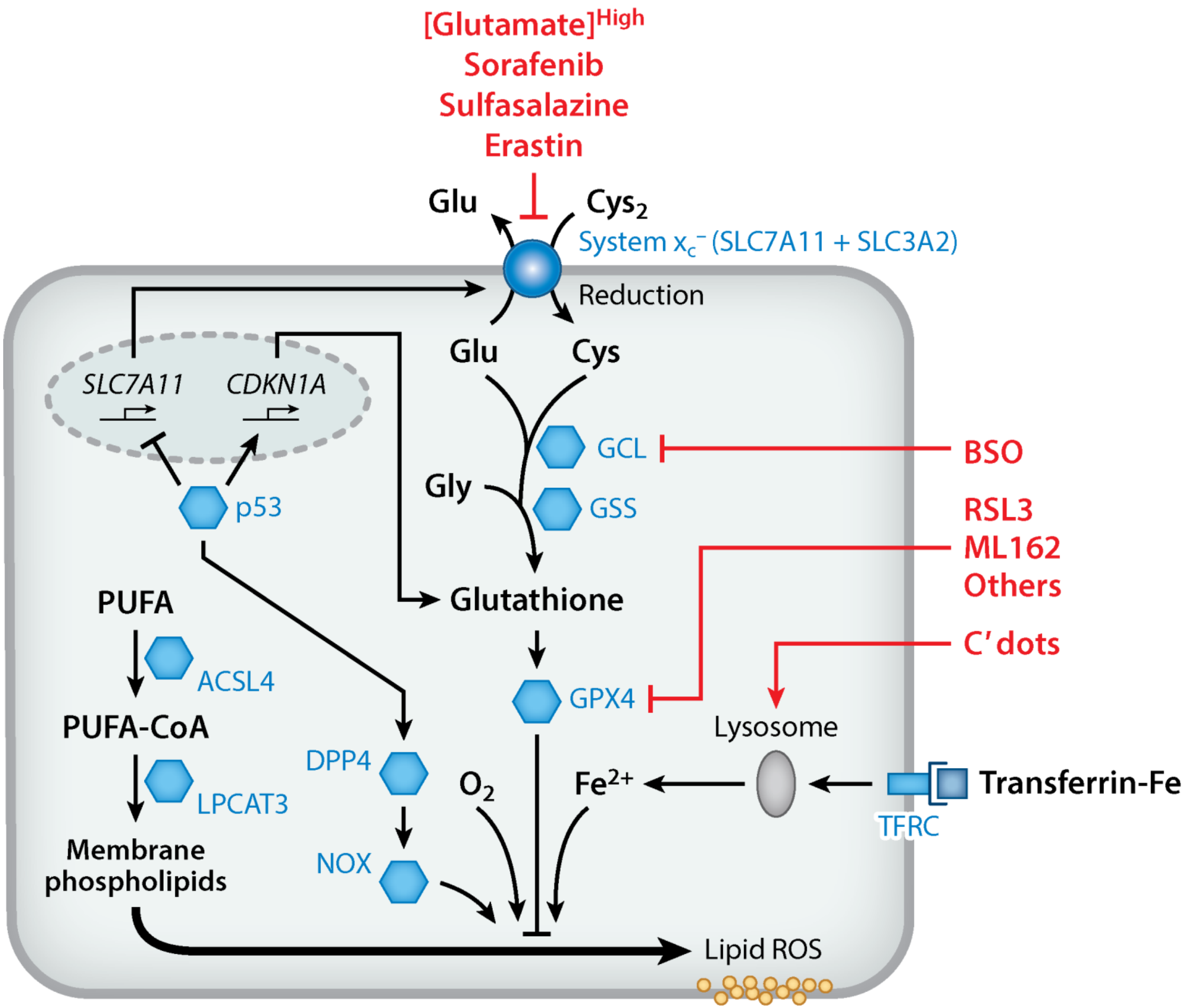


ANTIOXIDANT (CELLULAR MEMBRANE)
ROS scavenger at plasma membrane





Dixon SJ, Stockwell BR. 2019.
Annu. Rev. Cancer Biol. 3:35–54



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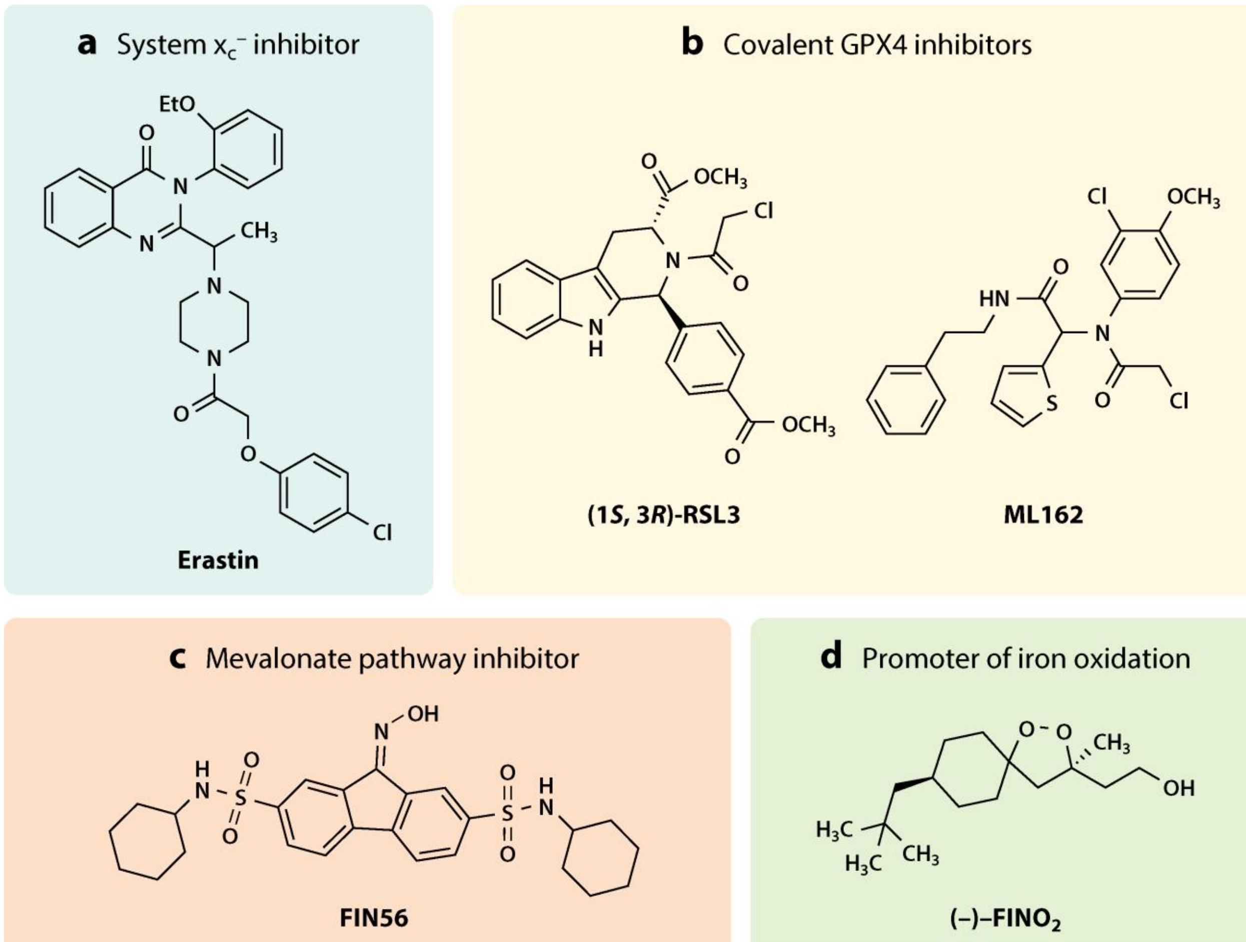

Dixon SJ, Stockwell BR. 2019.
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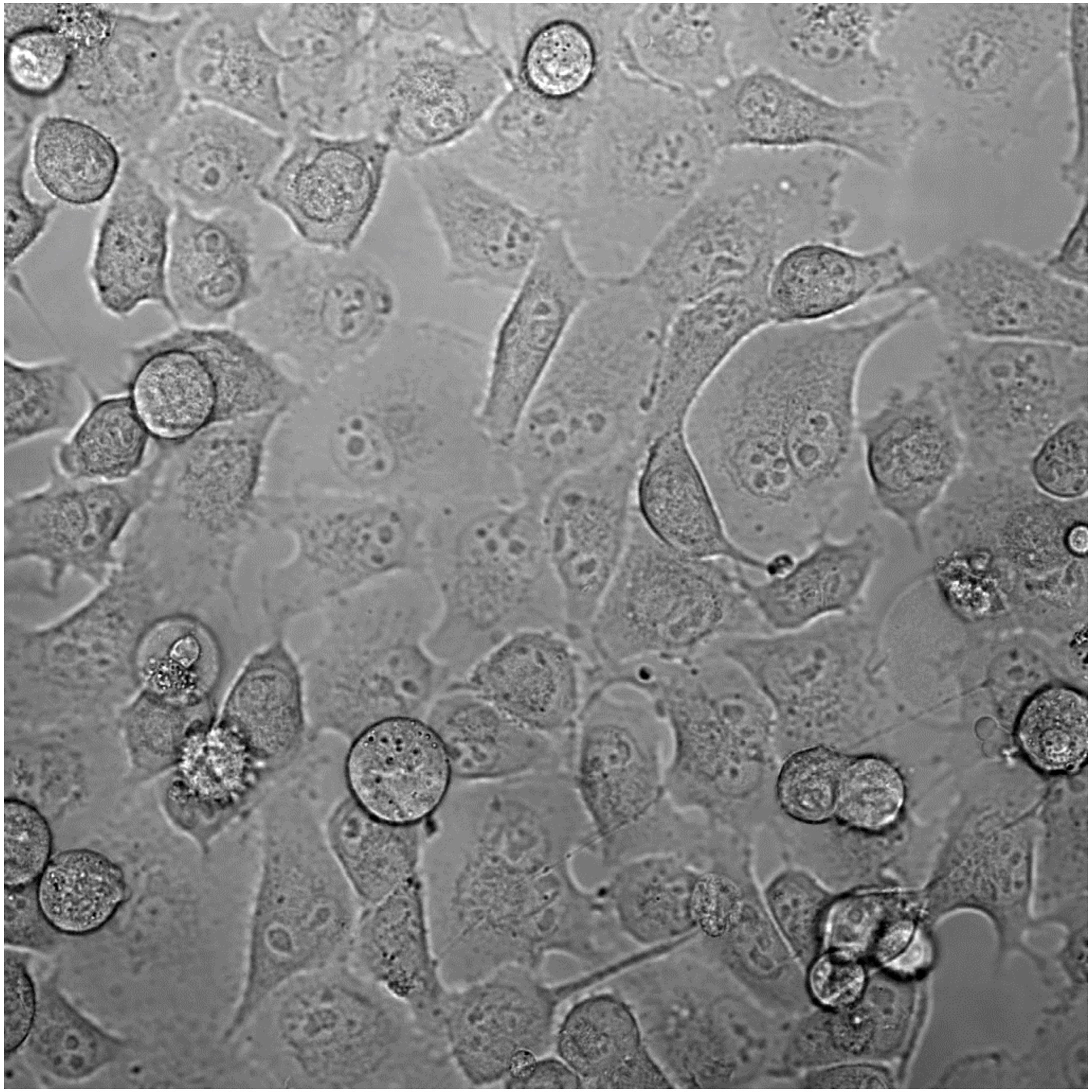
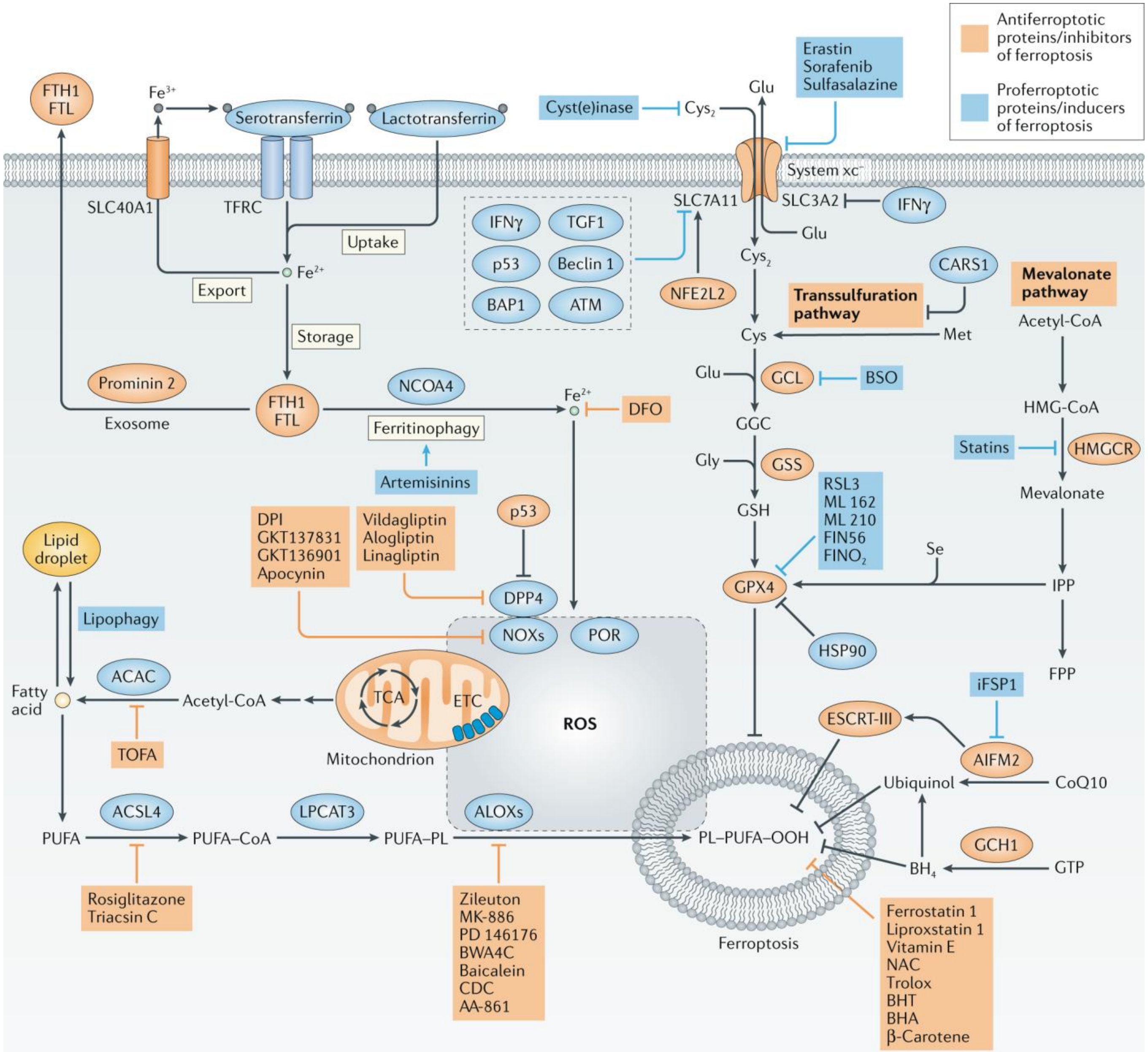
Table 1. Main ferroptosis activators and inhibitors.

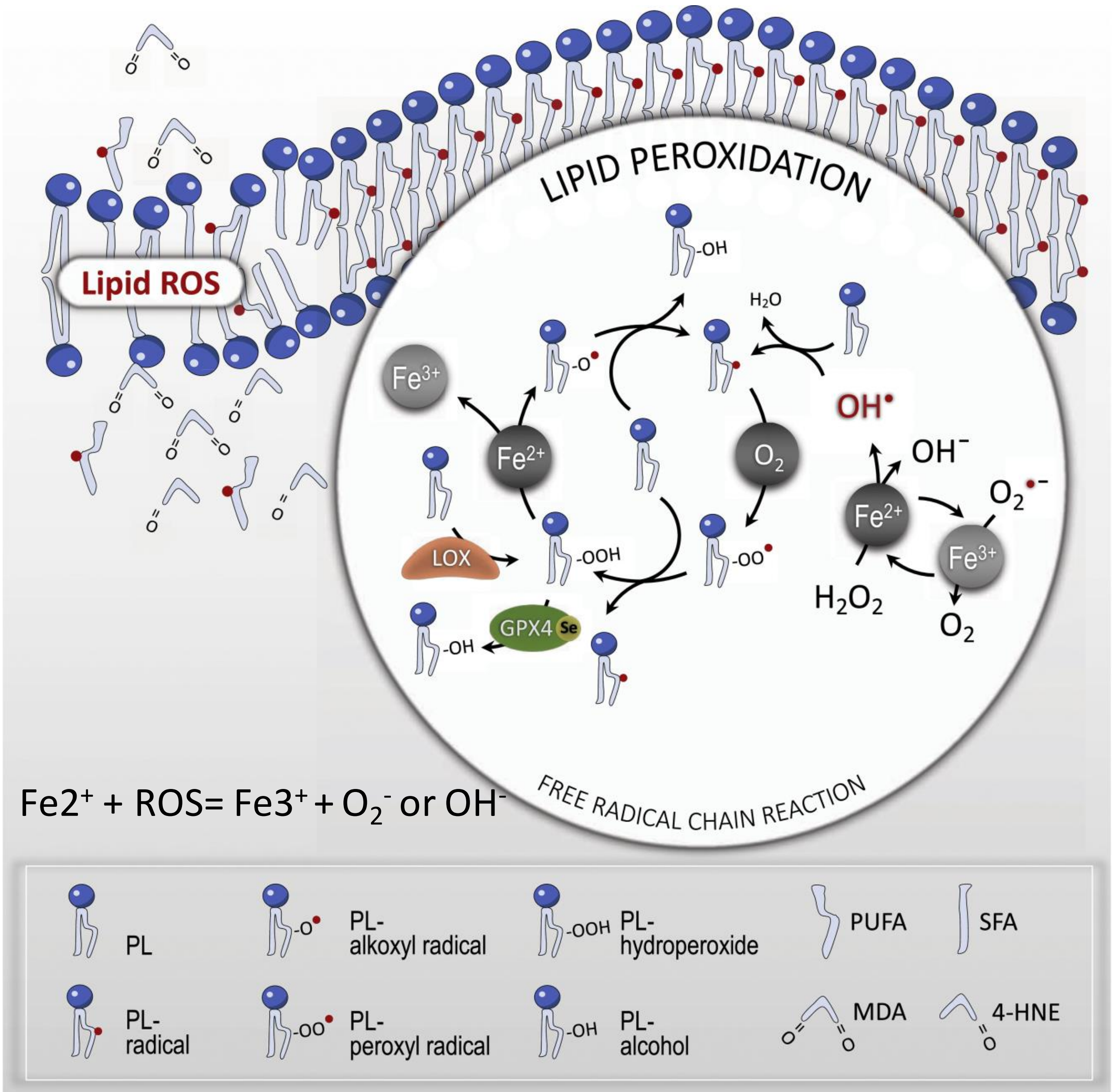
	Target	Example	Function	References
Ferroptosis activators	Autophagy	Loperamide, pimozide, STF-62247, BAY 87-2243, zalcitabine	Induces autophagy	[43,123,124]
	CoQ10	FIN56, iFSP1	Inhibits CoQ10 production	[47,125]
	GPX4	RSL3, ML162, ML210, DPIs, FIN56, $FINO_2$	Inhibits GPX4 activity or promotes GPX4 degradation	[126–128]
	glutathione (GSH)	Buthioninesulfoximine, CH004, cyst(e)inase	Inhibits GSH production	[128]
	System xc^-	Erastin, sulfasalazine, sorafenib, imidazole ketone erastin, erastin2, glutamate	Inhibits GSH production	[3,17]
Ferroptosis inhibitors	ACSL4	Rosiglitazone, triacsin C	Inhibits PUFA production	[61,62]
	ALOX	Zileuton, MK886, PD146176, BWA4C, baicalein, cinnamyl-3,4-dihydroxya-cyanocinnamate, AA-861, LOXBlock-1	Inhibits lipid peroxidation	[9,129,130]
	Iron	Deferoxamine (DFO), 2,2-bipyridyl, ciclopirox olamine (CPX), deferiprone, pioglitazone	Inhibits iron toxicity	[3,36,126]
	Lipid ROS	Ferrostatins (e.g., ferrostatin-1, SRS11-92, SRS12-45, SRS13-35, SRS13-37, and SRS16-86), liproxstatins (e.g., liproxstatin-1)	Inhibits lipid ROS	[3,9]
	Autophagy	Ammonium chloride, bafilomycin A_1, chloroquine, wortmannin, 3-methyladenine, cryptotanshinone, S3I-201, CA-074Me, NH_4Cl, pepstatin A, E64	Inhibits autophagy	[83,84,131,132]
	NOX	Diphenyleneiodonium chloride (DPI), GKT137831, GKT136901, apocynin	Inhibits membrane-associated ROS production	[3]



Signaling and metabolic pathways in ferroptosis

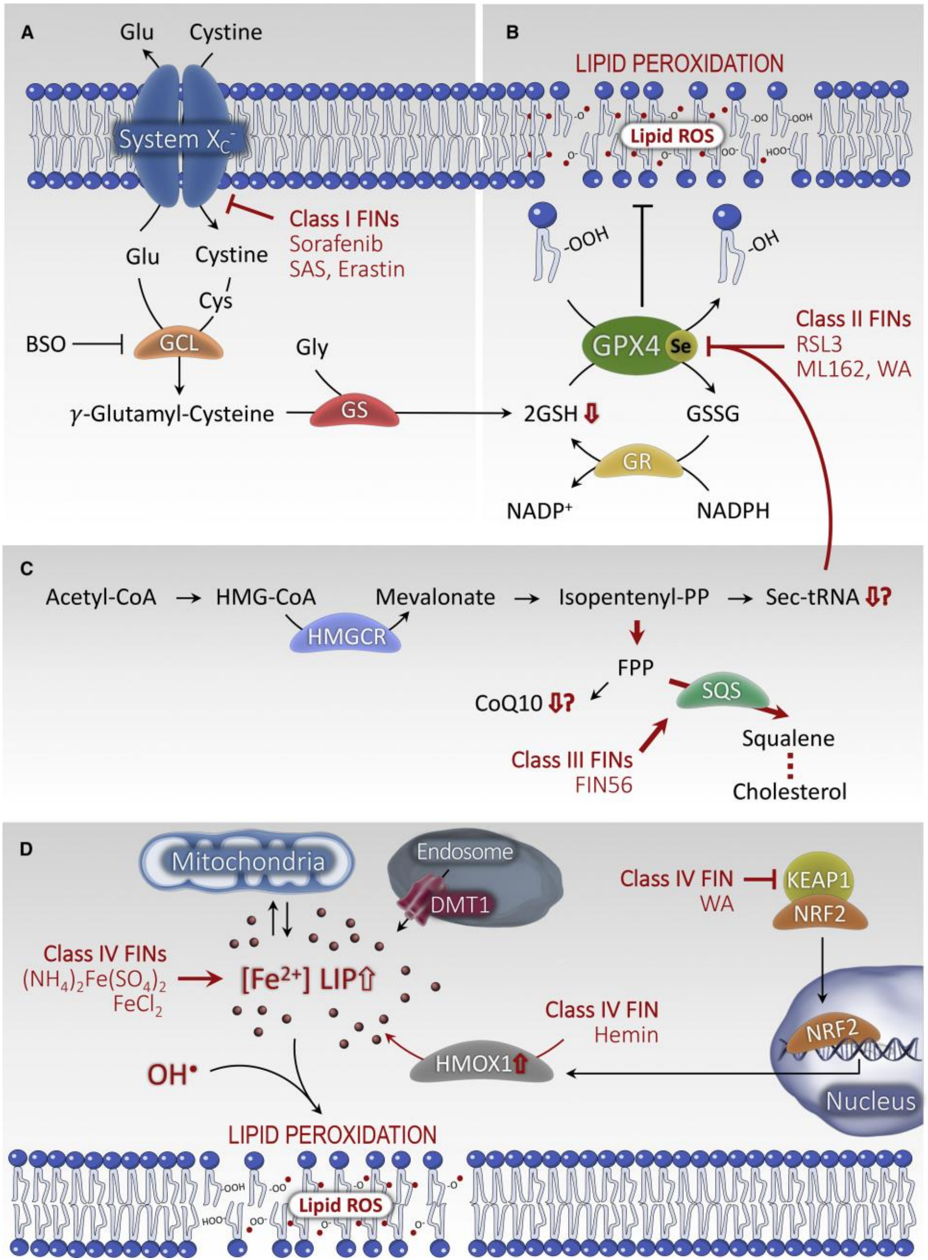


Lipid Peroxidation Process and Toxicity

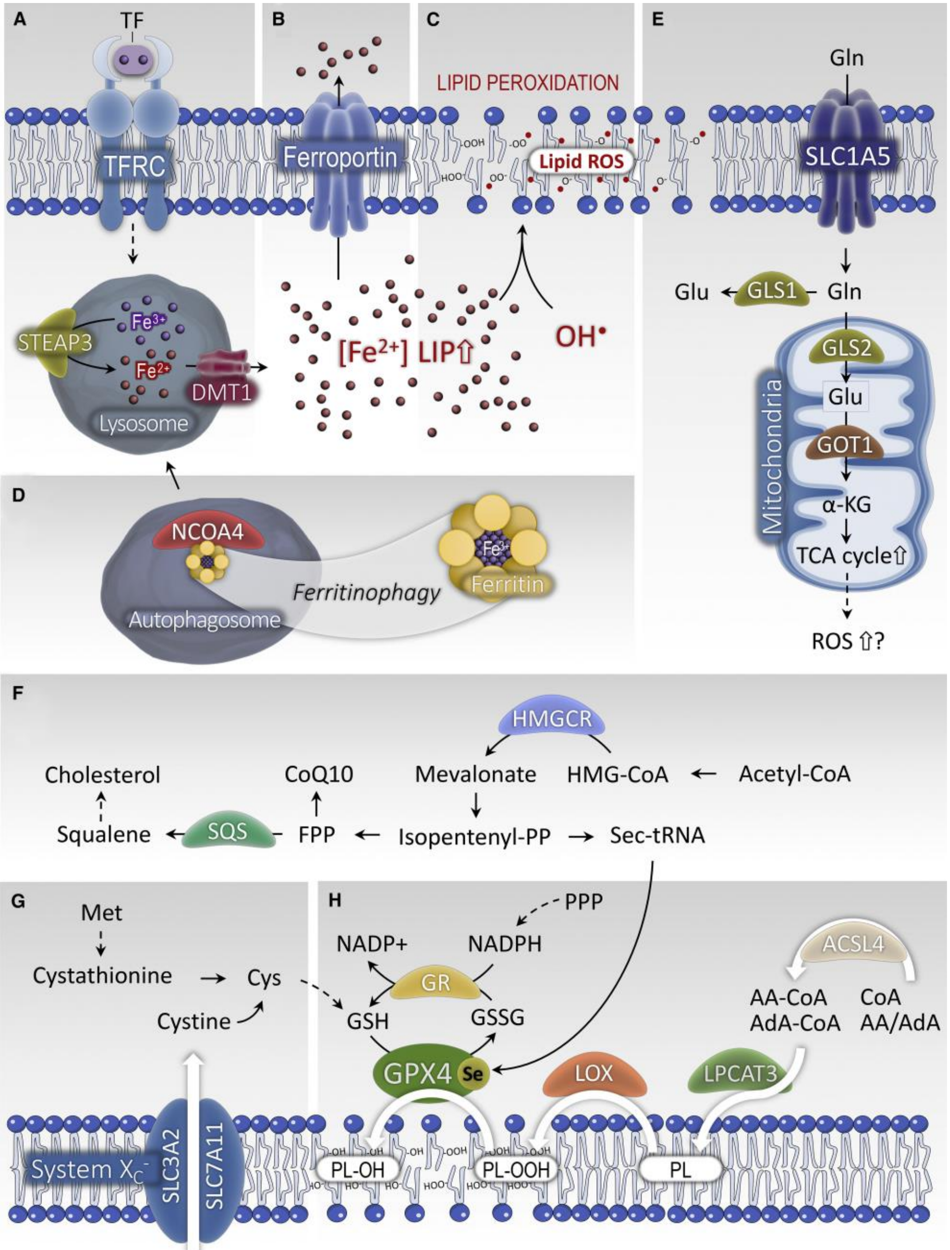


$Fe2^{+} + ROS = Fe3^{+} + O_2^{-}$ or OH^{-}

Mechanism of Ferroptosis Induction



Overview of Ferroptosis Modulation



Role of ferroptosis in Diseases

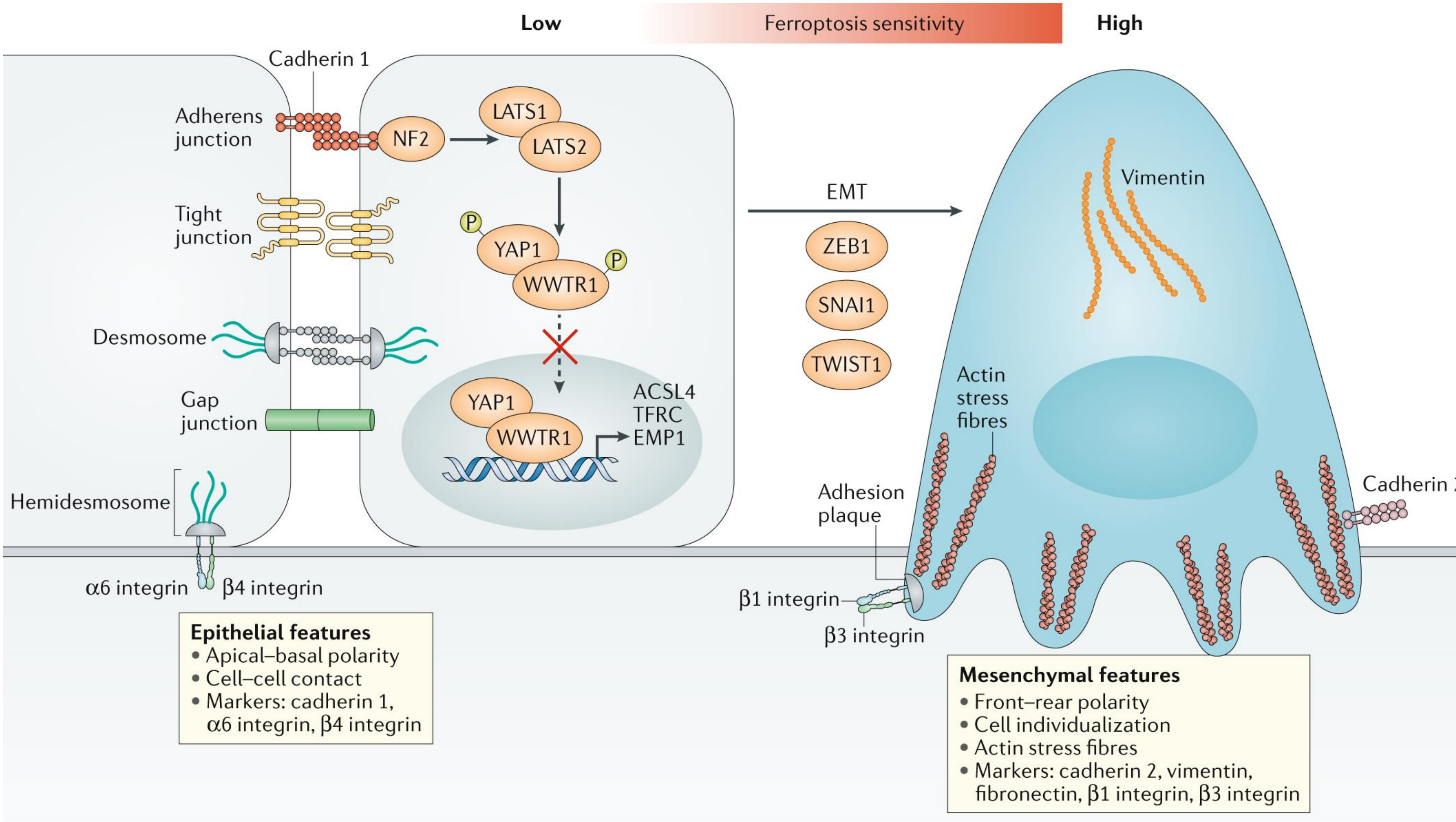
- **Neurodegenerative diseases :**Neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, are known to be associated with dysregulation of iron homeostasis and excessive ROS in the brain.

- **Alzheimer's disease :** It is one of the most common cause of dementia in aging individuals. It is characterized by progressive memory impairment and cognitive dysfunction

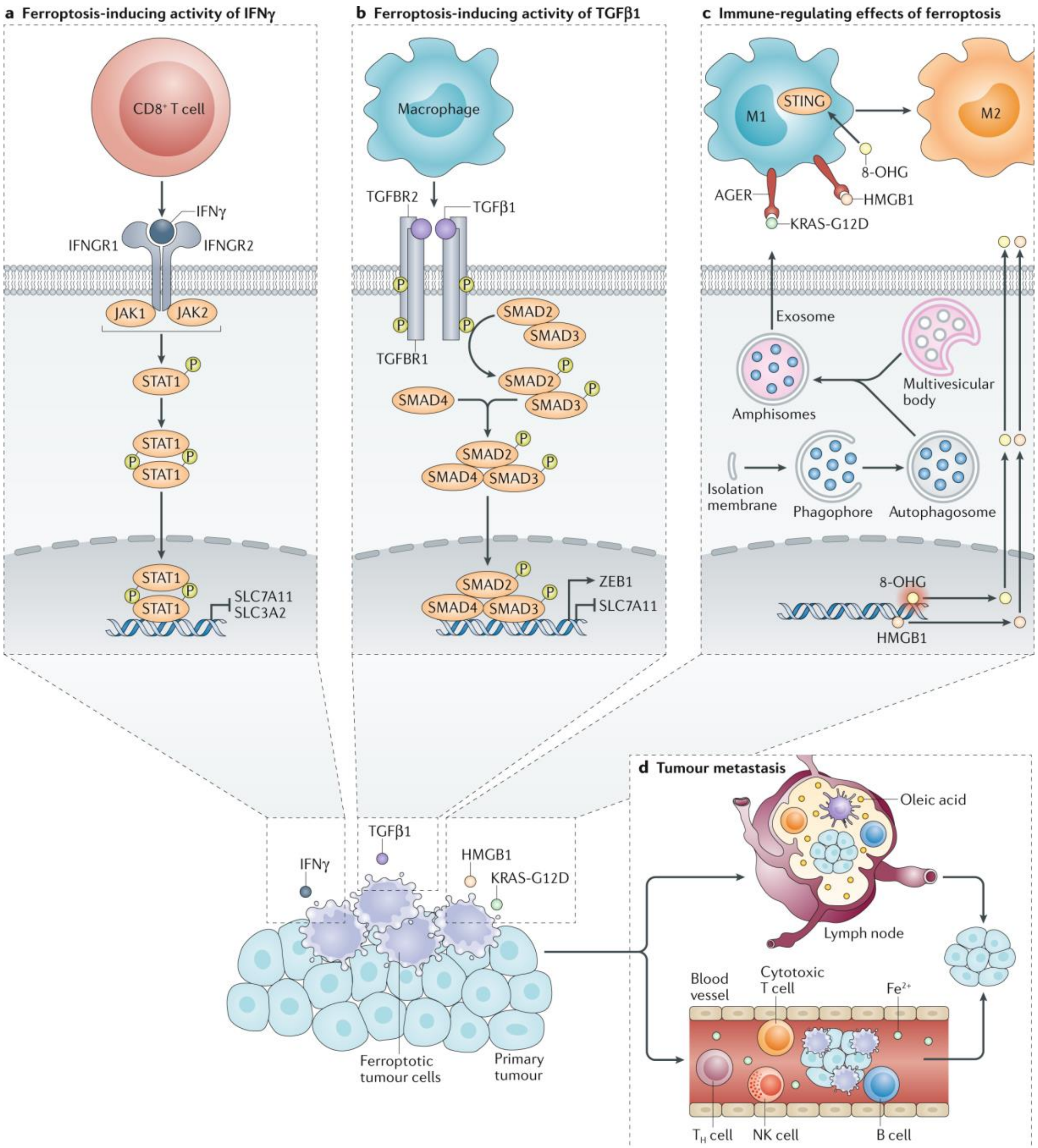
- **Parkinson's disease :** Parkinson's disease is the second most common neurodegenerative disease and it is characterized by the loss of dopaminergic neurons in the substantia nigra a eosinophilic inclusion bodies.

- **Other diseases:** Excessive accumulation of iron ions causes lipid peroxidation and tissue damage, leading to atherosclerosis and diabetes

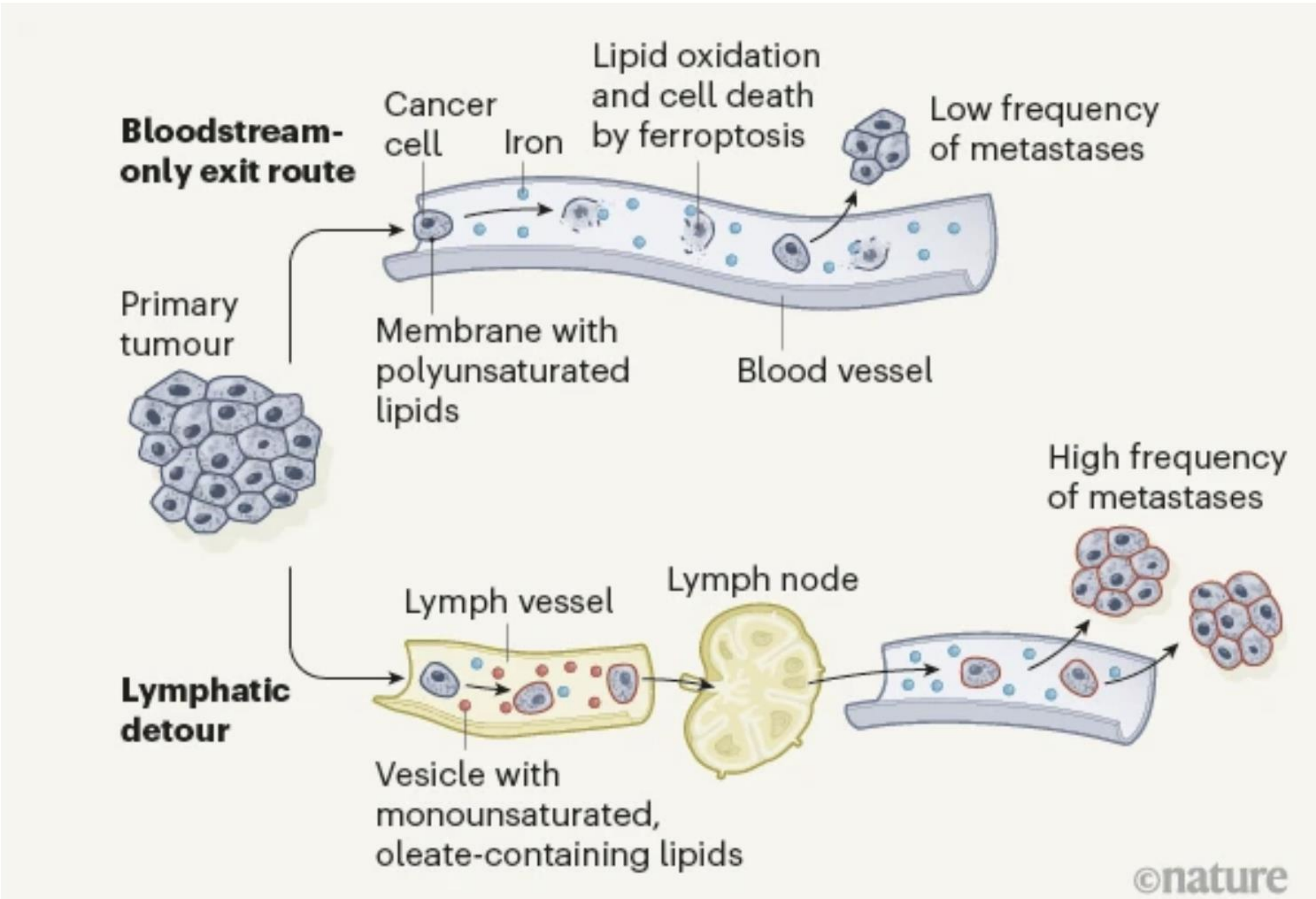
Cancer and ferroptosis



Role of ferroptosis in tumour immunity



Role of ferroptosis in melanoma spreading and metastasis



Inhibitors of ferroptosis

- **Ferrostatin-1:** Fer-1 inhibits erastin and RSL-3 induced ferroptosis in HT1080 cells, which specially inhibits lipid peroxidation. SRS11-92 & SRS 16-186 ferrostatins show significant enhancement cellular metabolism and damage prevention.

- **Liproxstatin -1:** Lip-1 can inhibits ferroptosis at low nano molar dose, but it does not interfere with other typical cell death patterns. Similarly, BHT, N-acetylcystein antioxidants, alpha-tocopherol etc, can block ferroptosis by inhibiting the lipid peroxidation pathway.

- Ferroptosis can also be inhibited by iron chelator such as **Deferoxamine (DFO)** Since they prevent the inhibition of lipid peroxidation by inhibiting iron fenton reaction.

Inhibitors of ferroptosis

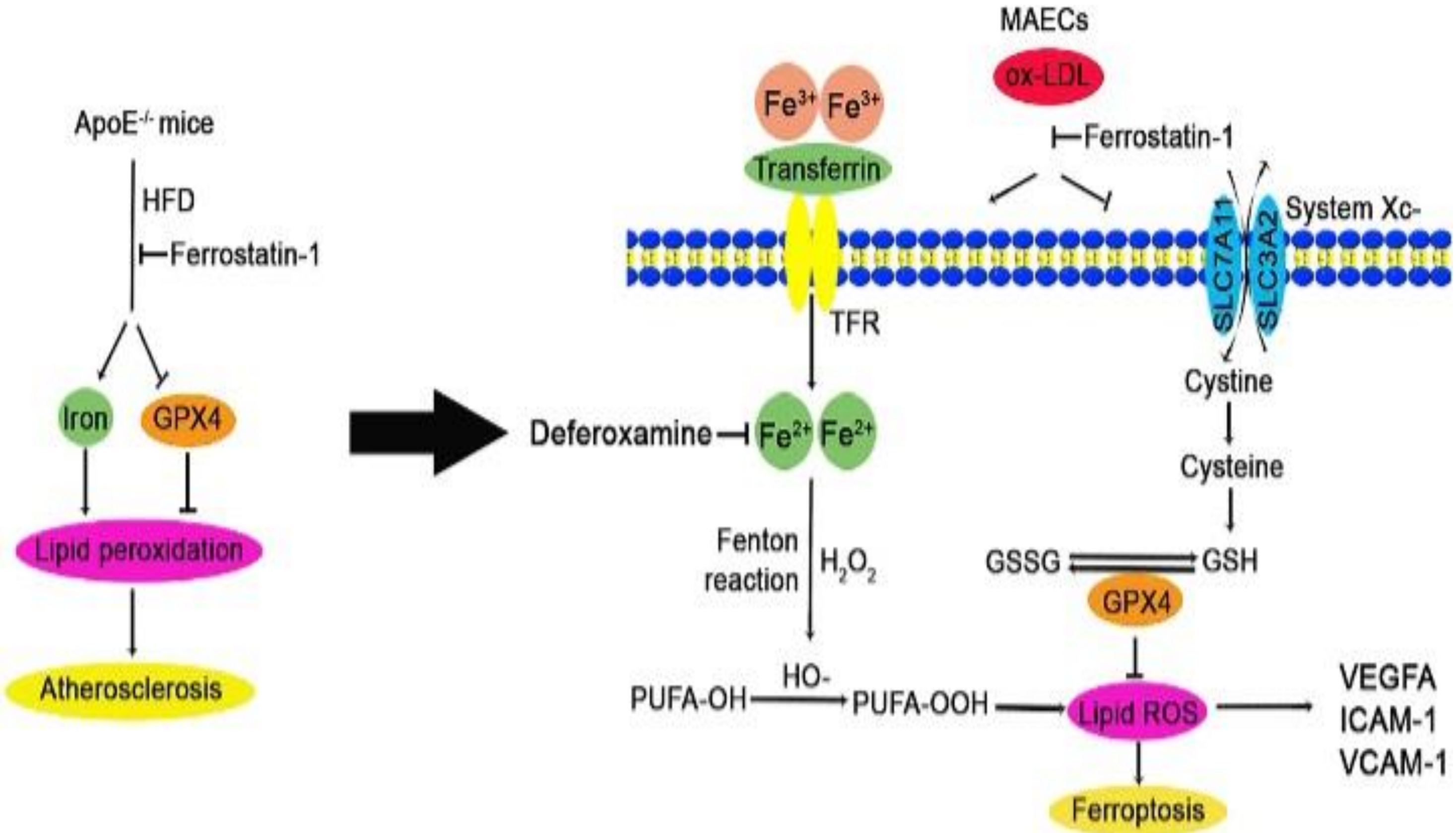


Table 1. Ferroptosis Stimuli

Mechanism	Target	Compound/Drug	Phenotype and Readout	References
GPX4 inactivation due to GSH depletion (class I FINs)	system X_C^-	erastin	lipid ROS[a] death inhibited by DFO, Fer1, and Trolox	Dixon et al., 2012; Dolma et al., 2003
		piperazine erastin	increase in PTGS2 mRNA regression HT1080 xenografts	Yang et al., 2014
		imidazole ketone erastin (IKE)	lipid ROS[a]	Larraufie et al., 2015; Yang et al., 2016
		sulfasalazine	death inhibited by DFO, Fer1, and Trolox	Dixon et al., 2012; Gout et al., 2001
		sorafenib	lipid ROS[a] death inhibited by DFO and Fer1	Louandre et al., 2013
		glutamate	inhibited by CPX and Fer1	Dixon et al., 2012
	glutamate-cysteine ligase	buthionine sulfoximine (BSO)	lipid ROS[a]	Griffith, 1982; Yang et al., 2014
	glutathione S-transferase	artesunate	lipid ROS[a] death inhibited by DFO, Fer1, and Trolox	Eling et al., 2015; Hamacher-Brady et al., 2011; Liswewski et al., 2014
	unknown	DPI2	death inhibited by DFO and α-Toc	Yang et al., 2014
	[Cys] depletion	cyst(e)inase	reduced GSH levels regression of MDA-MB-361, DU145 and PC3 xenografts	Cramer et al., 2017
	ND dehydrogenase	BAY 87-2243	lipid ROS[a] death inhibited by Fer1 and α-Toc	Basit et al., 2017; Schockel et al., 2015
GPX4 inactivation/ depletion (class II, III FINs)	GPX4	1*S*,3*R*-RSL3[b,c]	lipid ROS[a] death inhibited by DFO and Fer1 increase in PTGS2 mRNA HT1080 tumor regression	Dixon et al., 2012; Yang et al., 2014; Yang and Stockwell, 2008
		DPI7/ML162[b],DPI10/ ML210[b], DPI12-13[b], DPI17-19[b]	lipid ROS[a]	Weiwer et al., 2012; Yang et al., 2014
		altretamine[b]	lipid ROS[a]	Woo et al., 2015
		FIN56[b]	lipid ROS[a] death inhibited by DFO and α-Toc	Gaschler et al., 2018a; Shimada et al., 2016b
		withaferin A[c]	lipid ROS[a] in neuroblastoma cells death inhibited by DFO, Fer1 and α-Toc	Hassannia et al., 2018
	Squalene synthase	FIN56[b]	lipid ROS[a] death inhibited by DFO and α-Toc	Gaschler et al., 2018a; Shimada et al., 2016b
	HMG-CoA reductase	fluvastatin, lovastatin acid, simvastatin	lipid ROS[a]	Shimada et al., 2016b; Viswanathan et al., 2017

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Table 1. *Continued*

Mechanism	Target	Compound/Drug	Phenotype and Readout	References
Iron loading (class IV FINs)		hemoglobin	lipid ROS[a] death inhibited by Fer1 in organotypic hippocampal slice cultures	Li et al., 2017
		$FeCl_2$	death inhibited by Fer1 in organotypic hippocampal slice cultures	Li et al., 2017
		hemin	death inhibited by DFO and Fer1	Hassannia et al., 2018; Imoto et al., 2018; NaveenKumar et al., 2018
		$(NH_4)_2Fe(SO_4)_2$	death inhibited by Fer1	Hassannia et al., 2018
		non-thermal plasma	lipid ROS[a] death inhibited by DFO	Furuta et al., 2018; Shi et al., 2017
		salinomycin	lipid ROS[a] death inhibited by Fer1	Mai et al., 2017
		amino acid depletion + Cornell dots	lipid ROS[a] death inhibited by Fer1 and Trolox	Kim et al., 2016
		amino acid depletion, cystine deprivation + holo-transferrin	death inhibited by Fer1	Gao et al., 2015
	transferrin ↑ ferroportin-1 ↓	lapatinib + siramesine	death inhibited by DFO and Fer1	Ma et al., 2016
Iron oxidation (class IV FINs)		$FINO_2$	lipid ROS[a] death inhibited by Fer1	Gaschler et al., 2018a
Increase in LIP by HMOX1↑ (class IV FINs)	KEAP1 inactivation	withaferin A	lipid ROS[a] in neuroblastoma death inhibited by DFO, Fer1 and α-Toc	Hassannia et al., 2018
	IκBα	BAY 11-7085	death inhibited by Fer1, Lip1 and NAC	Chang et al., 2018
Unknown		lanperisone	death inhibited by DFO and Trolox	Shaw et al., 2011
		artemisinin derivatives	death inhibited by DFO and Fer1	Lin et al., 2016; Ooko et al., 2015
		CIL41, CIL56, CIL69, CIL70, CIL75, and CIL79	lipid ROS[a] for CIL56 death inhibited by DFO and α-Toc	Shimada et al., 2016b

α-Toc, α-tocopherol; CIL, caspase-3/7-independent lethal; CPX, ciclopirox olamine; DFO, deferoxamine; Fer1, ferrostatin-1; FIN, ferroptosis-inducing compound, GPX4, glutathione peroxidase 4; GSH, glutathione; HMOX1, heme oxygenase-1; IκBα, nuclear factor of κ light-chain polypeptide gene enhancer in B cell inhibitor α; KEAP1, kelch-like ECH-associated protein 1; LIP, labile iron pool; Lip1, liproxstatin-1; PTGS2, prostaglandin-endoperoxide synthase 2, ROS, reactive oxygen species; VDAC, voltage-dependent anion channel.

[a]Lipid ROS shown by C11-BODIPY staining.

[b]GPX4 inactivation shown using LC-MS-based GPX4 assay (PCOOH).

[c]Direct GPX4 binding shown through pull-down.

Table 2. Modulators of Ferroptosis

Gene	Protein	Function	Modulatory Effect	References
Iron Metabolism				
TFRC	transferrin receptor	cellular transferrin-iron uptake	knockdown suppresses erastin-induced ferroptosis	Yang and Stockwell, 2008
			knockdown suppresses ferroptosis induced by amino acid/cystine deprivation	Gao et al., 2015, 2016
PHKG2	phosphorylase kinase, γ2	activates glycogen phosphorylase to release glucose-1-phosphate from glycogen	iron regulatory function? knockdown suppresses erastin-induced ferroptosis	Yang et al., 2016
IREB2	iron response element-binding protein 2	RNA-binding protein that regulates iron levels in the cells by regulating the translation and stability of mRNAs that affect iron homeostasis upon iron depletion	knockdown suppresses ferroptosis induced by erastin or amino acid/cystine deprivation	Dixon et al., 2012; Gao et al., 2016
HSBP1	heat-shock 27-kDa protein 1	activated in heat stress response by heat-shock factor 1 (HSF1)	iron regulatory function? knockdown enhances erastin-induced ferroptosis *in vitro* and *in vivo*	Sun et al., 2015
HMOX1	heme oxygenase 1	catalyzes the degradation of heme to biliverdin, CO, and Fe^{2+}	inhibition or knockdown suppresses withaferin A-induced ferroptosis	Hassannia et al., 2018
			inhibition or knockout suppresses erastin-induced ferroptosis	Kwon et al., 2015
			inhibition or knockdown suppresses BAY-induced ferroptosis	Chang et al., 2018
CISD1/mitoNEET	CDGSH iron-sulfur domain 1	inhibits mitochondrial iron transport into the matrix	knockdown enhances erastin-induced ferroptosis	Yuan et al., 2016a
NCOA4	nuclear receptor coactivator 4	cargo receptor mediating ferritinophagy	knockdown suppresses ferroptosis induced by amino acid/cystine deprivation	Gao et al., 2016
			knockdown suppresses erastin-induced ferroptosis	Hou et al., 2016
ACO1	aconitase 1	iron-sulfur protein that converses citrate to isocitrate, controls iron inside cell	knockdown suppresses ferroptosis induced by amino acid/cystine deprivation	Gao et al., 2016
FTH1	ferritin heavy chain 1	subunit of major intracellular iron storage protein	expression level controls ferroptosis sensitivity	Yang and Stockwell, 2008
			knockdown enhances erastin- or sorafenib-induced ferroptosis in hepatocellular carcinoma	Sun et al., 2016
STEAP3	six-transmembrane epithelial antigen of prostate 3	metalloreductase converting Fe^{3+} to Fe^{2+}	upregulated in response to erastin in bone marrow stromal cells	Song et al., 2016
FANCD2	Fanconi anemia complementation group D2	nuclear protein involved in DNA damage repair	iron regulatory function? knockout enhances erastin-induced ferroptosis in bone marrow stromal cells	Song et al., 2016
NFS1	cysteine desulfurase	enzyme involved in synthesizing iron-sulfur clusters using sulfur from cysteine	knockdown activates the iron-starvation response promoting erastin-induced ferroptosis	Alvarez et al., 2017

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Table 2. *Continued*

Gene	Protein	Function	Modulatory Effect	References
Lipid Metabolism				
ACSF2	acyl-CoA synthetase family member 2	regulation of mitochondrial fatty acid metabolism	knockdown suppresses erastin-induced ferroptosis	Dixon et al., 2012
CS	citrate synthase	regulation of mitochondrial fatty acid metabolism	knockdown suppresses erastin-induced ferroptosis	Dixon et al., 2012
LPCAT3	lysophosphatidylcholine acyltransferase 3	incorporation of acylated fatty acids into membranes by catalyzing the reacylation of lysophospholipids to phospholipids	identified in haploid cell genetic screen	Dixon et al., 2015
			knockdown suppresses RSL3-induced ferroptosis	Kagan et al., 2017
ACSL4	acyl-CoA synthetase long-chain family member 4	converts free fatty acids (preferentially AA) into fatty acyl-CoAs	identified in haploid cell genetic screen	Dixon et al., 2015
			knockdown suppresses erastin-induced ferroptosis	Yuan et al., 2016b
			inhibition or knockout suppresses RSL3-induced ferroptosis	Kagan et al., 2017
			inhibition or knockout suppresses erastin-, RSL3-, or GPX4-depletion-induced ferroptosis inhibition suppresses GPX4-depletion-induced damage *in vivo*	Doll et al., 2017
ACSL3	acyl-CoA synthetase long-chain family member 3	converts exogenous monounsaturated fatty acids (MUFAs) into fatty acyl-CoAs	required for MUFA-induced protection from erastin2-induced ferroptosis knockout attenuates MUFA-induced resistance to ferroptosis	Magtanong et al., 2018
ACACA	Acetyl-CoA carboxylase alpha	Converts acetyl-CoA to malonyl-CoA, the rate-limiting step in fatty acid synthesis	identified in haploid cell genetic screen	Dixon et al., 2015
			inhibition suppresses FIN56-, but not erastin- or RSL3-induced ferroptosis	Dixon et al., 2015; Shimada et al., 2016b
GPX4	glutathione peroxidase 4	lipid repair enzyme	inhibition or knockout induces ferroptosis	Yang et al., 2014
AKR1C	aldo-keto reductase family 1 member C1	regulate the detoxification of oxidative lipid breakdown products	upregulation confers protection against erastin-induced ferroptosis	Dixon et al., 2014
LOX	lipoxygenase-12/15	catalyzes the dioxygenation of polyunsaturated fatty acids in lipids	inhibition or knockout suppresses GPX4-depletion-induced ferroptosis	Seiler et al., 2008
	lipoxygenases		knockout protects against imidazole keto erastin (IKE)-, but not RSL3-induced ferroptosis inhibition protects against erastin-induced ferroptosis	Yang et al., 2016
PEBP1	phosphatidylethanolamine-binding protein 1	protein scaffold	controls substrate specificity of LOX15 knockdown suppresses RSL3-induced ferroptosis	Wenzel et al., 2017
ZEB1	zinc finger E-box-binding homeobox 1	EMT regulator and lipogenic factor	knockout suppresses GPX4-depletion-induced ferroptosis	Viswanathan et al., 2017

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Table 2. *Continued*

Gene	Protein	Function	Modulatory Effect	References
SQS/FDFT1	squalene synthase/farnesyl-diphosphate farnesyltransferase 1	responsible for synthesis of squalene and involved in cholesterol synthesis	knockdown or inhibition suppresses FIN-56-induced ferroptosis	Shimada et al., 2016b
			knockout or inhibition sensitizes SQLE-deficient anaplastic large cell lymphoma (ALCL) cells to ML162-induced ferroptosis	Garcia-Bermudez et al., 2019
SQLE	squalene monooxygenase	catalyzes the conversion of squalene to squalene-2,3-epoxide and involved in cholesterol synthesis	overexpression sensitizes SQLE-deficient ALCL cells to ML162-induced ferroptosis	Garcia-Bermudez et al., 2019
HMGCR	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase	synthesis of mevalonic acid	inhibition enhances FIN-56-induced ferroptosis	Shimada et al., 2016b
FADS2	fatty acid desaturase 2/acyl-CoA 6-desaturase	involved in biosynthesis of highly unsaturated fatty acids, desaturates palmitate to produce the monounsaturated fatty acid sapienate	knockdown decreases sapienate production and suppresses RSL3- induced lipid peroxidation in HUH7 liver cancer cells	Vriens et al., 2019
(Anti)oxidant Metabolism				
NRF2	nuclear factor erythroid 2-related factor 2	key regulator of anti-oxidant response including the expression of system X_C^-	inhibition or knockdown enhances erastin- or sorafenib-induced ferroptosis in hepatocellular carcinoma *in vitro* and *in vivo*	Sun et al., 2016
			knockdown enhances artesunate-induced ferroptosis in head and neck cancer *in vitro* and *in vivo*	Roh et al., 2017
			overexpression confers resistance to erastin- and RSL3-induced ferroptosis in glioma cells, while knockdown enhances ferroptosis	Fan et al., 2017
KEAP1	kelch-like ECH- associated protein 1	binds to and regulates NRF2 by keeping its levels at control	overexpression enhances erastin- and RSL3-induced ferroptosis in glioma cells, while knockdown confers resistance to ferroptosis	Fan et al., 2017
			knockdown confers resistance to artesunate-induced ferroptosis in head and neck cancer	Roh et al., 2017
HMOX1	heme oxygenase 1	catalyzes the degradation of heme to biliverdin, CO, and Fe^{2+}	knockout enhances erastin-induced ferroptosis in proximal tubular cells	Adedoyin et al., 2018
			knockout enhances erastin- and sorafenib-induced ferroptosis in hepatocellular carcinoma cells	Sun et al., 2016
NQO1	quinone oxidoreductase-1	reduces quinones to hydroquinones	knockdown enhances erastin- and sorafenib-induced ferroptosis in hepatocellular carcinoma cells	Sun et al., 2016
SLC7A11	solute carrier family 7 member 11	subunit of system X_c^- to import cystine in the cell	inhibition induces ferroptosis	Dixon et al., 2012

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Table 2. *Continued*

Gene	Protein	Function	Modulatory Effect	References
GCLC	glutamate-cysteine ligase catalytic subunit	enzyme involved in GSH synthesis	inhibition induces ferroptosis	Yang et al., 2014
CARS	cysteinyl-tRNA synthetase	protein translation	knockdown suppresses erastin-induced ferroptosis through compensatory activation of transsulfuration pathway [Cys]↑	Hayano et al., 2016
CBS	cystathionine-β-synthase	converts homocysteine to cystathionine	inhibition or knockdown resensitizes erastin-induced ferroptosis in CARS knockdown cells	Hayano et al., 2016
NOX	NADPH oxidase	superoxide-producing enzymes	inhibition suppresses erastin-induced ferroptosis in non-small cell lung cancer cells	Dixon et al., 2012
ABCC1/MRP1	multidrug-resistance protein 1	mediates GSH and chemotherapeutics efflux from cells	overexpression sensitizes to ferroptosis induced by erastin2 and cyst(e)inase, RSL3 and ML162	Cao et al., 2019
Energy Metabolism				
SLC1A5	solute carrier family 1 member 5	amino acid transporter feeding glutaminolysis	inhibition or knockdown suppresses ferroptosis induced by amino acid/cystine deprivation	Gao et al., 2015
GLS2	glutaminase 2	converts glutamine to glutamate	inhibition or knockdown suppresses ferroptosis induced by erastin or amino acid/cystine deprivation	Gao et al., 2015
GOT1	glutamic-oxaloacetic transaminase 1	involved in synthesis of α-ketoglutarate from glutamate	inhibition suppresses ferroptosis induced by erastin or amino acid/cystine deprivation	Gao et al., 2015
microRNA 137		targets and regulates SLC1A5 levels	overexpression suppresses SLC1A5 and confers resistance to erastin- and RSL3-induced ferroptosis, while inhibition sensitizes to ferroptosis	Luo et al., 2018
G6PD	glucose-6-phosphate dehydrogenase	involved in pentose phosphate pathway	knockdown suppresses erastin-induced ferroptosis in non-small cell lung cancer cells Calu-1	Dixon et al., 2012
			knockdown suppresses ferroptosis induced by amino acid/cystine deprivation	Gao et al., 2016
PGD	phosphoglycerate dehydrogenase	involved in pentose phosphate pathway	knockdown suppresses erastin-induced ferroptosis in non-small cell lung cancer cells Calu-1	Dixon et al., 2012

Table 3. Regulation of Ferroptosis by Cancer Metabolism

Gene	Protein	Function	Modulatory Effect	References
TP53	wild-type p53	tumor suppressor	knockout/knockdown increases cystine uptake and suppresses ferroptosis in osteosarcoma U2OS and breast cancer MCF7 cells	Jiang et al., 2015; Xie et al., 2017
			knockdown sensitizes colorectal cancer HCT116 and SW48 cell to ferroptosis	Xie et al., 2017
			stabilization with nutlin-3 in mouse embryonic fibroblasts, HT-1080 fibrosarcoma, renal cancer Caki-1, and osteosarcoma U2OS cells suppresses ferroptosis	Tarangelo et al., 2018
	mutated $p53^{3KR}$	triple acetylation-defective mutant (K117/161/162) that fails to induce cell-cycle arrest, senescence, and apoptosis	retains the ability to regulate SLC7A11 expression and induce ferroptosis	Jiang et al., 2015
	Mutated $p53^{S47}$	nonsynonymous single-nucleotide polymorphism at codon 47 in African-descent populations	impaired ferroptosis induction in $p53^{S47}$ knockin MEF cells	Jennis et al., 2016
			intact ferroptosis induction in E1A/Ras-transformed $p53^{S47}$ knockin cells	Basu et al., 2016
	mutated $p53^{4KR}$	quadruple acetylation-defective mutant (K98/117/161/162) that fails to induce cell-cycle arrest, senescence, and apoptosis	impaired ferroptosis induction and loss of tumor-suppressor activity	Wang et al., 2016
	mutated p53	missense mutations (R273H, R175H) that impair p53 sequence-specific binding to DNA	accumulated mutant-p53 protein sensitizes esophageal and lung cancer cells to ferroptosis	Liu et al., 2017
BAP1	BRCA1-associated protein 1	nuclear deubiquitinating epigenetically regulates gene expression	promotes ferroptosis by repression of SLC7A11 expression	Zhang et al., 2018
CDKN1A	cyclin-dependent kinase (CDK) inhibitor 1A (p21)	inhibits CDK causing cell-cycle arrest	overexpression confers resistance to erastin2-induced ferroptosis (by retarding GSH depletion?)	Tarangelo et al., 2018
SAT1	spermidine/spermine N1-acetyltransferase 1	acetylates spermidine and spermine	transcription target of p53 overexpression leads to ferroptosis upon ROS stress knockout suppresses p53-induced ferroptosis	Ou et al., 2016
SOCS1	suppressor of cytokine signaling 1	cytokine-induced negative regulators of cytokine signaling	regulates p53 expression and sensitizes cells to ferroptosis	Saint-Germain et al., 2017
TP63	ΔN tumor protein 63α	oncogene	orchestrates GSH metabolism overexpression confers resistance to erastin- or RSL3-induced ferroptosis, while knockdown enhances ferroptosis	Wang et al., 2017a
OTUB1	ovarian tumor (OTU) family member deubiquitinase	directly interacts with SLC7A11 and regulates SLC7A11 stability	suppresses ferroptosis by stabilizing SLC7A11 knockout sensitizes to erastin-induced ferroptosis	Liu et al., 2019

Take home message

- Ferroptosis is a recently discovered form of programmed cell death distinct form apoptosis, necrosis and autophagy.
- It has a GPX4 and FSP1 mechanisms of inhibition
- Excessive accumulation of iron ion causes lipid peroxidation and tissue damage leading to atherosclerosis and neurodegenerative diseases.
- Deferoxamine and ferrosatin-1 inhibits ferroptosis which does not allow to produce lipid peroxidation