Mechanisms and preventive measures of ALDH2 in ischemia-reperfusion injury: Ferroptosis as a novel target (Review)

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Abstract. Ischemia-reperfusion injury (IRI) refers to tissue or organ damage that occurs following a period of inadequate blood supply (ischemia) followed by restoration of blood flow (reperfusion) within a short time frame. This phenomenon is prevalent in clinical conditions such as cardiovascular and cerebrovascular disease, organ transplantation and stroke. Despite its frequency, effective therapeutic strategies to mitigate IRI remain elusive in clinical practice, underscoring the need for a deeper understanding of its molecular mechanisms. Aldehyde dehydrogenase 2 (ALDH2), a key enzyme in alcohol metabolism, serves a role in alleviating oxidative stress and cell damage during IRI by modulating oxidative stress, decreasing apoptosis and inhibiting inflammatory responses. ALDH2 exerts protective effects by detoxifying reactive aldehydes, thereby preventing lipid peroxidation and maintaining cellular homeostasis. Furthermore, ferroptosis, a regulated form of cell death driven by iron accumulation and subsequent lipid peroxidation, is a key process in IRI. However, the precise role of ALDH2 in modulating ferroptosis during IRI remains incompletely understood. Although there is an interaction between ALDH2 activity and ferroptosis, the underlying mechanisms have yet to be clarified. The present review examines the role of ALDH2 and ferroptosis in IRI and the potential regulatory influence of ALDH2 on ferroptosis mechanisms, as well as potential targeting of ALDH2 and ferroptosis for IRI treatment and prevention. By elucidating the complex interplay between ALDH2 and ferroptosis, the present review aims to provide new insights for the development of innovative therapeutic strategies to mitigate ischemic tissue damage and improve clinical outcomes.

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Contents

1. Introduction

Ischemia-reperfusion injury (IRI) is a clinical phenomenon encountered in conditions such as myocardial infarction, stroke, organ transplantation and surgical intervention. In these contexts, tissues or organs undergo ischemia due to compromised blood supply, followed by irreversible damage following reperfusion (1). The pathophysiology of IRI typically unfolds in several key stages: i) During ischemia, tissue is deprived of oxygen, leading to hypoxia and the accumulation of metabolites; this results in a notable decline in intracellular ATP levels, impairing cellular function and culminating in cell death; ii) in the reperfusion phase, restoration of blood flow re-establishes oxygenation but the sudden influx of oxygen may initiate a cascade of detrimental reactions, including oxidative stress and release of inflammatory mediators. These responses exacerbate cell injury, intensifying tissue necrosis and functional deterioration (2). Studies on the role of aldehyde dehydrogenase (ALDH)2 in IRI are summarized in Table I (3-25).

The role of ALDH2 in mitigating IRI has garnered increasing attention (1,26). ALDH2 is one of the 19 members of the ALDH family in humans, predominantly expressed in the liver, where it primarily resides in mitochondria as a tetramer (26). A key function of ALDH2 is metabolism of both exogenous and endogenous aldehydes. The gene encoding ALDH2 has allelic variants that affect its enzymatic activity. ALDH2 1*2 refers to a genotype where one allele carries the normal *1 variant (which encodes for the functional enzyme)

and the other carries the *2 variant (which causes decreased enzyme activity). ALDH2 2*2 refers to a genotype where both alleles of the ALDH2 gene carry the variant, which is associated with a reduced or absent enzyme activity. Upon alcohol consumption, hepatic metabolism generates acetaldehyde via pathways including alcohol dehydrogenase, microsomal ethanol oxidizing system and cytochrome P450 2E1 (27). Acetaldehyde, a toxic byproduct, is released into circulation, triggering harmful reactions. ALDH2 mitigates this by catalyzing removal of two hydrogen atoms from acetaldehyde, converting it into non-toxic acetic acid, which is subsequently metabolized into carbon dioxide and water (26,28). In addition to detoxifying exogenous aldehydes, ALDH2 serves a key role in eliminating endogenous aldehydes generated during oxidative stress, including 4-hydroxy-2-nonenal (4-HNE), malondialdehyde (MDA) and acrolein (29,30). ALDH2 also protects cellular integrity by preserving mitochondrial membrane function, inhibiting toxic intracellular pathways and decreasing tissue damage. The role of ALDH2 has surpassed its association with cardiovascular diseases, diabetes and neurodegenerative disorders, highlighting its importance as a key defender against IRI in multiple organs, including the heart, brain, intestine and kidneys (31).

Ferroptosis is a more recently identified form of regulated cell death (RCD), characterized by intracellular iron accumulation and subsequent oxidative stress, which induces both apoptosis and necrosis (32). IRI triggers release and accumulation of intracellular iron, amplifying cellular damage through oxidative stress and promoting inflammatory responses (32). While the mechanisms of ferroptosis in IRI are complex, its key role in the injury cascade has been well-established (32,33). As such, targeting ferroptosis regulation has emerged as a promising strategy for mitigating IRI (33).

IRI is a multifaceted process that involves a range of cellular and molecular alterations. Despite application of certain therapeutic interventions in clinical practice, such as antioxidants (vitamin E, vitamin C and N-acetylcysteine), anti-inflammatory (corticosteroids, non-steroidal anti-inflammatory drugs), Calcium Channel Blockers (verapamil, dantrolene) effective treatment for IRI remains challenging. Thus, the identification of novel therapeutic targets and strategies is essential. Recent research underscores the importance of RCD pathways, particularly ferroptosis, in the pathogenesis of IRI (2,34). However, the mechanisms that regulate ferroptosis during IRI remain poorly understood. The present review aimed to summarize the roles of ALDH2 and ferroptosis in the context of IRI. ALDH2 has been proposed as a key regulator of ferroptosis. By detoxifying reactive aldehydes and preventing lipid peroxidation (LPO), ALDH2 may influence ferroptosis, thereby modulating severity of IRI (35,36). Additionally, ALDH2 regulates other forms of programmed cell death (20,37). The present aimed to review summarize these pathways to identify potential commonalities in ALDH2 regulation of ferroptosis and the mechanisms underlying cellular damage and inflammation to provide insight into their potential therapeutic applications. Through a comprehensive examination of ALDH2 and ferroptosis, the present review aims to provide a theoretical framework for development of innovative treatments and pharmacotherapies to improve clinical outcomes.

2. Mechanism of ALDH2 and ferroptosis in IRI

ALDH2 and reactive oxygen species (ROS) in IRI. ROS are highly reactive molecules, such as superoxide anion, hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH•), produced as byproducts of normal cell metabolism (38) (Fig. 1). However, excessive ROS accumulation can lead to oxidative stress and damage to proteins, lipids and DNA, which results in cellular injury and potentially cell death. ALDH2 functions as a potent scavenger of ROS (26). By degrading toxic aldehydes, ALDH2 decreases intracellular aldehyde levels, mitigating their harmful effects on cellular integrity (39). Aldehydes, with strong oxidative potential, bind and oxidize cellular macromolecules, including proteins and DNA, thereby inducing cell damage. Additionally, during the conversion of acetaldehyde to acetic acid, ALDH2 catalyzes the reduction of NAD^+ to NADH (40). NADH serves as a substrate for mitochondrial respiratory chain complex I, promoting oxidative phosphorylation and enhancing the efficiency of redox reactions, which limits ROS production. Furthermore, elevated ROS levels can influence ALDH2 activity and stability (41,42), establishing a feedback loop that modulates ALDH2 function.

In IRI, evidence highlights the role of ALDH2 in mitigating ROS production and protecting tissues and organs (18,20). In rat diabetic myocardial IRI and H9C2 cardiomyocyte hypoxia-reoxygenation models, Tan *et al* (18) observed that ALDH2 upregulation decreases mitochondrial ROS levels. This facilitates maintenance of mitochondrial dynamics, preserving the balance between fusion and fission and stabilizing mitochondrial morphology. Xu *et al* (20) revealed that ALDH2 activation promotes autophagy by increasing the phosphorylation of Beclin-1 at Ser90. This autophagy activation maintains cellular and tissue homeostasis by reducing ROS levels and clearing damaged organelles. These findings underscore the multifaceted protective mechanisms mediated by ALDH2 in IRI, from ROS reduction to preservation of mitochondrial dynamics and promotion of autophagy. These insights contribute to understanding of the complex interactions between ALDH2 and IRI, offering a foundation for development of targeted therapeutic interventions aimed at reducing tissue damage and improving clinical outcomes.

ALDH2 and toxic aldehydes in IRI. LPO is a key feature of IRI. Elevated ROS levels within cells directly target lipids, with unchecked oxidative stress disrupting the balance between ROS production and clearance, leading to accumulation of endogenous ROS (43). Of ROS species involved in LPO, hydroxyl and hydroperoxyl radicals are primary contributors. These radicals attack the carbon-carbon double bonds of polyunsaturated phospholipids in membranes, triggering a cascade of oxidation that compromises membrane integrity and impairs membrane functionality (44-46).

Membrane lipids, primarily composed of polar glycerophospholipids, are susceptible to oxidative damage. Cell membranes contain notable amounts of polyunsaturated lipids, which are vulnerable during IR, a phase in which mitochondria become the principal site of ROS generation (47). ROS interact with polyunsaturated phospholipids in mitochondrial membranes, forming lipid hydroperoxides. Secondary reactions produce >200 types of highly reactive lipid-derived

Table I. Role of ALDH2 in ischemia-reperfusion injury.

First author, year	Organ	Cells	Animal model	Mechanism	Downregulator	Upregulator	Function	(Refs.)
Zhang *et al*, 2018	Heart	H9c2	Mouse myocardial I/R injury	Activation of the PI3K/mTOR pathway	/	RIPostC	RIPostC exerts a cardioprotective role by inducing upregulation of ALDH2	(24)
Ma *et al*, 2021		/	Mouse hypertrophic preconditioning model	Activation of the AMPK pathway	/	TAC	TAC preconditioning enhances ALDH2 activity, promotes AMPK activation and improves mitochondrial energy metabolism	(12)
Tan *et al*, 2023		H9C2	Rat diabetic myocardial I/R	Inhibition of mitoPTP opening; activation of the PI3K/AKT/mTOR pathway	Daidzin		ALDH2 regulates dynamic balance of mitochondrial fusion and fission, maintains mitochondrial morphology stability and decreases mitochondrial ROS levels and apoptotic protein expression	(18)
Bai *et al*, 2023		Cardiomyocyte	/	Inhibition of the ERK/p38 signaling pathway	/	miR-330-5p	miR-330-5p mimic enhances ALDH2 activity, inhibits apoptosis and suppresses 4-HNE and MDA production in MIRI-induced cardiomyocytes	(3)
Gao *et al*, 2024		/	Mouse ALDH2 knockout myocardial I/R	Activation of ALDH2/SIRT3/ HIF1α signaling pathway	/	RIC	RIC increases ALDH2 protein levels (SIRT3/HIF1α) and inhibits autophagy	(6)
Sun *et al*, 2021		H9c2	Mouse myocardial I/R injury	Increased mitochondrial potential-mediated fusion	/	Alda-1	Alda-1 increases mitochondrial potential-mediated fusion, promotes oxygen consumption rate and enhances baseline mechanical function of cardiomyocytes	(17)
Yoval-Sanchez *et al*, 2020		/	Rat myocardial I/R	Protection of ALDH2 from inactivation by lipid aldehydes	Daidzin	Piperlonguminine	Protection of ALDH activity, decreased lipid aldehyde content, preservation of mitochondrial function and restoration of heart rate and blood pressure	(21)

Table I. Continued.

First author, year	Organ	Cells	Animal model	Mechanism	Downregulator	Upregulator	Function	(Refs.)
Pan *et al*, 2021		CEC	Mouse ALDH2 2*2 E487K knock-in	Alleviation of 4-HNE-mediated CEC injury	/	Alda-1	Decreased myocardial infarct size and dysfunction and coronary perfusion pressure during cardiac IRI by increasing CEC population and promoting coronary arteriole opening	(13)
Papatheodorou *et al*, 2021		/	Isolated rat heart I/R	Transcriptional upregulation of ALDH2	Cyanamide	PPARβ/δ	PPARβ/δ upregulates PGC-1α and IDH2 and enhances citrate synthase activity and mitochondrial function and energy production	(14)
Kang *et al*, 2020		Neonatal rat ventricular primary cardiomyocyte	/	Altered expression of MMP14 and TIMP4	Daidzin	Alda-1	Activation of ALDH2 prevents fibrosis, apoptosis and necroptosis	(7)
Zhang *et al*, 2020		H9c2	/	Suppression of Drp1 and AMPK phosphorylation	/	Alda-1	Inhibition of increased mitochondrial fission and fusion following OGD/R	(23)
Lin *et al*, 2022	Brain	PC12	Rat cerebral IRI	Increased ALDH2 expression/ enhancing ALDH2 activity	/	Alda-1	Alleviation of neuronal injury induced by hypoxia/reoxygenation	(10)
Qu *et al*, 2023		HT22/mouse cortical neurons	/	Promoter region hypermethylation of ALDH2	/	/	Attenuation of OGD/R-induced apoptosis, pyroptosis, ferroptosis and autophagy to promote cell viability	(15)
Diao *et al*, 2022		/	Swine CA/CPR	Inhibition of NLRP3 inflammasome activation and pyroptosis	/	Alda-1	Post-resuscitation cardiac and neurological dysfunction notably improve, accompanied by considerably decreased cardiac and cerebral injury	(5)
Lin *et al*, 2020	Kidney	/	Rabbit autologous kidney transplantation	Activation of the AKT-mTOR pathway	Cyanamide	Alda-1	Inhibition of 4-HNE in HMP, thereby protecting donated kidney following cardiac death	(9)

Table I. Continued.

First author, year	Organ	Cells	Animal model	Mechanism	Downregulator	Upregulator	Function	(Refs.)
Chen *et al*, 2023		HK-2	Mouse ALDH2-/- kidney IRI	Activation of the IκBα/NF-κB pathway	CYA	Alda-1	ALDH2 deficiency promotes IκBα/NF-κB p65 phosphorylation, leading to increased inflammatory factors	(4)
Xu *et al*, 2004		Primary murine renal tubular epithelial	Mouse AKI	Activation of the Beclin-1 pathway	/	Alda-1	ALDH2 activation enhances phosphorylation of Beclin-1 at Ser90 within its Bcl-2 binding domain; removal of ROS via Beclin-1-induced autophagy underlies renoprotection mediated by ALDH2	(20)
Yu *et al*, 2022		/	Swine CA/CPR	Inhibition of apoptosis and ferroptosis	/	Alda-1	Alleviation of post-resuscitation renal and intestinal injury	(22)
Sidramagowda Patil *et al*, 2020	Lung	/	Mouse Alzet pump	Activation of the AKT-mTOR pathway	/	Alda-1	Attenuation of hyperoxia-induced acute lung injury	(16)
Wu, 2022		/	Swine CA/CPR	Restoration of ALDH2 activity	/	Alda-1	Inhibition of apoptosis and ferroptosis and alleviation of lung injury following CA/CPR	(19)
Li *et al*, 2018	Liver	Primary hepatocytes	Mouse hepatic 70% ischemia	Activation of the AMPK pathway	/	Alda-1	Clearance of reactive aldehydes and enhancement of autophagy	(8)
Liu *et al*, 2020		/	Rat hepatic IRI	Activation of the AKT-mTOR and AMPK pathway	Daidzin	Alda-1	Upregulation of autophagy-related 7 and Rab7 increases microtubule-associated protein 1 light chain 3αII/I ratio while inhibiting p62 expression	(11)
Zhou *et al*, 2023	Skin	/	Rat McFarlane flap	Downregulation of PINK1/Parkin signaling	/	Alda-1	Enhancement of random skin flap viability by inhibition of PINK1/Parkin-dependent mitophagy; anti-inflammatory effects; promotion of angiogenesis	(25)

TAC, transverse aortic constriction; OGD/R, oxygen-glucose deprivation reperfusion; RIC, remote ischemic conditioning; CEC, coronary endothelial cell; HMP, hypothermic machine perfusion; PPARβ/δ, peroxisome proliferator activated receptor β/δ; CA/CPR, cardiac arrest/cardiopulmonary resuscitation.

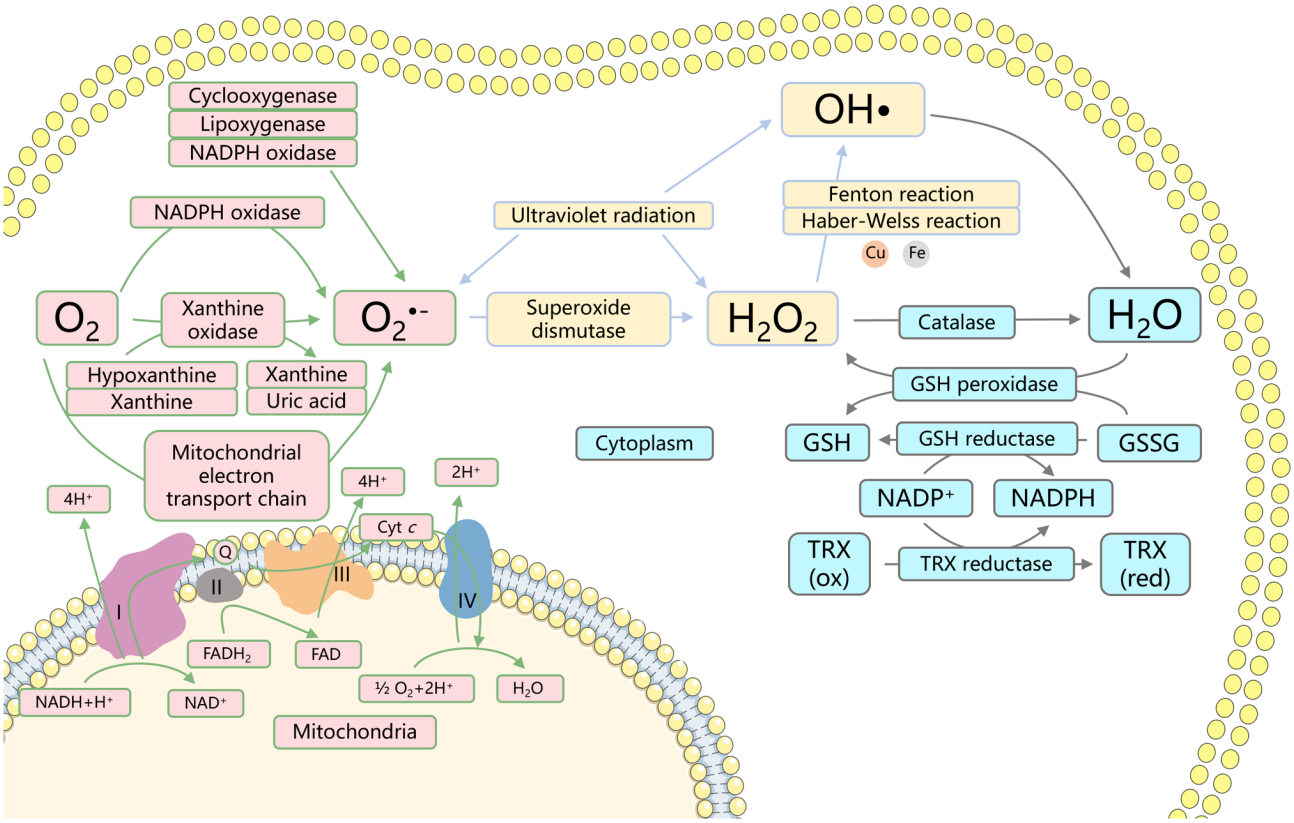

Figure 1. Production and clearance of intracellular reactive oxygen species in cells. In mitochondria, oxygen acts as the final electron acceptor in the electron transport chain, where it is reduced to superoxide anion ($O_2^{\bullet-}$). The NADPH oxidase enzyme complex on the cell membrane generates $O_2^{\bullet-}$. Xanthine oxidase catalyzes the oxidation of hypoxanthine to xanthine and then the conversion of xanthine to uric acid, which generating O_2^- as a byproduct. SOD catalyzes the conversion of O_2^- to H_2O_2. Catalase breaks down H_2O_2 into water and oxygen. Glutathione Peroxidase uses red GSH) to reduce H_2O_2 into water. TRX) Reductase helps regenerate red from ox) TRX using NADPH as an electron donor. GSH, glutathione; GSSG, glutathione disulfide; TRX, thioredoxin; ox, oxidized; red, reduced; NAD, nicotinamide adenine dinucleotide; FAD, flavin adenine dinucleotide; Cyt *c*, cytochrome *C*. Figure created using Adobe Illustrator 2021 and PowerPoint 2021.

aldehydes (LDAs), such as 4-HNE, MDA, 4-oxononenal, acrolein, crotonaldehyde and methylglyoxal (47). These LDAs not only serve as ROS byproducts but also further stimulate ROS production in mitochondria, intensifying tissue damage through a positive feedback loop. Consequently, excess aldehydes and ROS diffuse from mitochondria to other cell compartments, precipitating protein dysfunction, DNA damage and gene mutations, contributing to a range of diseases, including cardiovascular conditions, cancer, diabetes, osteoporosis and neurodegenerative disorder (48).

As markers of oxidative stress, 4-HNE and MDA are among the most potent reactive aldehydes (49). ALDH2 serves a key role in their detoxification by metabolizing MDA to malonic acid or acetaldehyde and converting 4-HNE to 4-hydroxy-2-nonenic acid. By reducing the accumulation of these toxic aldehydes, ALDH2 contributes to mitigating oxidative stress (49).

4-HNE. As aforementioned, 4-HNE results from LPO, with ω-6 polyunsaturated fatty acids (PUFAs) such as linoleic, γ-linolenic and arachidonic acid (AA) serving as precursors under oxidative stress mediated by ROS (50) (Fig. 2). 4-HNE primarily targets reduction-associated signaling molecules and upstream regulatory proteins, including thioredoxin (an intracellular ROS scavenger) and glutathione (GSH) (51). Additionally, 4-HNE affects protein post-translational modifications and gene expression: It upregulates the expression of transcription factors such as NF-κB and activating protein-1, which regulate genes involved in cell proliferation and differentiation (52). Moreover, 4-HNE activates transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which transactivates antioxidant response elements and enhances the expression of genes that are key for cell antioxidant defense and modulation of oxidative stress. Notable genes regulated by Nrf2 include hemeoxygenase-1 (HO-1), ALDH, glutathione S-transferase, multidrug resistance protein, aldo-keto reductase, nicotinamide adenine dinucleotide phosphate: quinone oxidoreductase (NQO1) and glutamate-cysteine ligase (53).

4-HNE is implicated in a range of oxidative stress-associated diseases, including neurodegenerative disorders, macular degeneration, cardiovascular disease, atherosclerosis, metabolic syndrome and cancer. In these pathological conditions, 4-HNE transcends its role as an oxidative stress marker to become a key pathogenic factor (54). Accumulation of 4-HNE has been detected in various types of tissue during IRI such as heart, brain and intestine. ALDH2 has a key role in neutralizing 4-HNE; loss of ALDH2 function exacerbates myocardial cell ferroptosis induced by iron overload, whereas ALDH2 activation mitigates ferroptosis (35). Furthermore, compounds such as isorhapontigenin have shown efficacy in decreasing

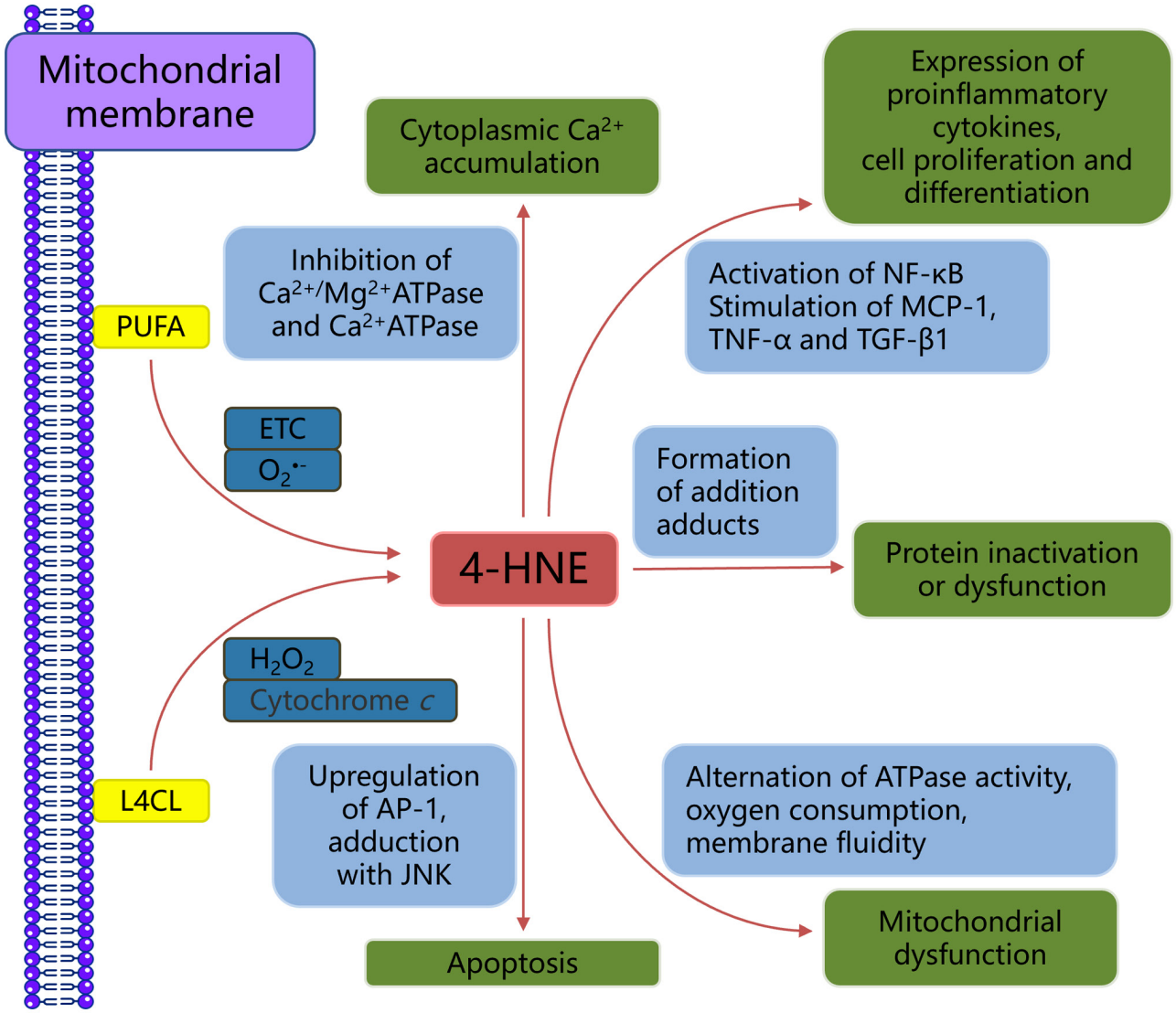

Figure 2. Generation of 4-HNE in mitochondria and its physiological and cytotoxic effects. ROS generated from electron transport chain, represented by $O_2^{\bullet-}$, initiate the oxidation by attacking the double bonds in PUFA), ultimately leading to the formation of 4-HNE. Hydrogen peroxide interacts with the double bonds of L4CL, initiating lipid peroxidation, which can further decompose to produce 4-HNE. Elevated H_2O_2 and lipid peroxides allow cytochrome *c* to leak from the mitochondria into the cytosol. The release of cytochrome *c* itself increases oxidative stress and contributes to 4-HNE production. PUFA, polyunsaturated fatty acids; ETC, electron transport chain; L4CL, tetralinoleoyl cardiolipinMCP-1, monocyte chemoattractant protein-1; AP-1, activator protein-1; 4-HNE, 4-hydroxy-2-nonenal. Figure created using Adobe Illustrator 2021 and PowerPoint 2021.

oxidative damage in brain IRI through the PKCε/Nrf2/HO-1 pathway, markedly lowering ROS generation and 4-HNE and 8-hydroxydeoxyguanosine levels (55). Similar protective effects have been observed in intestinal IRI, where administration of corilagin, an IRI protectant, reduces 4-HNE levels and ferroptosis (56). 4-HNE can react with various cellular components, forming adducts that contribute to tissue damage. Numerous studies have revealed the protective role of ALDH2 in IRI by effectively removing 4-HNE (18,57). Transgenic mice with impaired ALDH2 2*2 activity show elevated 4-HNE and GSH levels, along with decreased resistance to acute oxidative stress induced by IR (57). Additionally, recent evidence has highlighted the ability of ALDH2 to improve cardiac hemodynamic parameters and reduce myocardial injury by lowering 4-HNE levels and inhibiting mitochondrial permeability transition pore opening (18). In liver IRI, supplementation of ALDH2 activator Alda-1 reduces 4-HNE accumulation, reverses mitochondrial damage and decreases hepatocyte apoptosis (11). These findings underscore the key role of ALDH2 in mitigating harmful effects of 4-HNE accumulation in IRI in various tissues and organs.

MDA. PUFAs, including AA and docosahexaenoic acid, serve as precursors for MDA generation. PUFAs with ≥2 methylene-interrupted double bonds are susceptible to oxidative degradation, resulting in MDA production (58) (Fig. 3). Thiobarbituric acid (TBA) assay, initially developed by food chemists to assess the rancidity of Ω-3 and -6 fatty acids, is commonly used for the colorimetric or fluorometric determination of MDA and MDA-like substances (59). However, TBA reacting substances test lacks specificity. Treatment of biological samples with TBA may generate complexes with similar colors to the TBA-MDA complex, potentially confounding quantification of MDA. Furthermore, MDA or

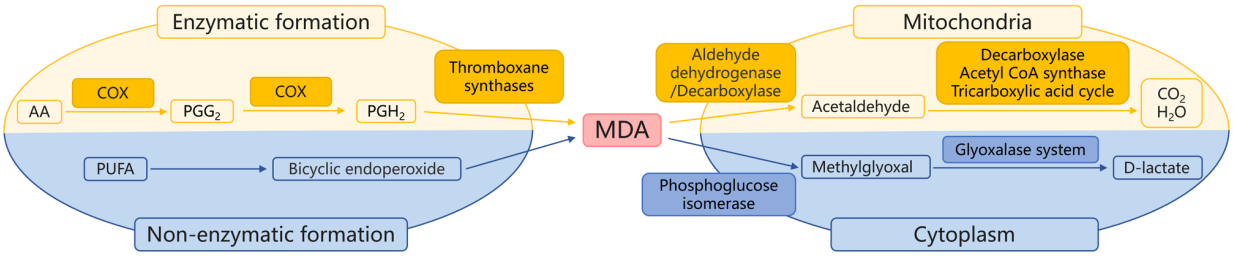

Figure 3. Formation and metabolism of MDA. MDA can be generated via enzymatic and non-enzymatic formation pathways: The oxidation of PUFA form a highly reactive intermediate bicyclic endoperoxide, and subsequent decomposition produces MDA. Furthermore, COX catalyze the conversion of AA to PGG_2) and catalyzes prostaglandin H2(PGH_2), MDA is formed by human platelet thromboxane synthetase from PGH_2. MDA is degraded to H_2O and CO_2 by tricarboxylic acid cycle in mitochondria under the action of aldehyde dehydrogenase and decarboxylase. MDA can also be degraded to D-lactate in the cytoplasm. AA, arachidonic acid; PGG2, prostaglandin G2; PGH_2, prostaglandin H_2; PUFA, polyunsaturated fatty acid; COX, cyclooxygenase; CoA, coenzyme A; MDA, malondialdehyde. Figure created using Adobe Illustrator 2021 and PowerPoint 2021.

MDA-like substances are derived from various precursors produced during LPO, including oxidized lipids, 2-alkenals and 2,4-alkadienals (58).

While MDA is the primary aldehyde generated during LPO, production of 4-HNE constitutes only 10% of MDA (60). Despite this, the role of MDA as a signaling molecule and gene expression regulator remains is understudied compared with 4-HNE. MDA, however, has gained attention as a biomarker in various types of disease, including cancer, cardiovascular diseases and neurodegenerative disorders, with its levels in blood, urine and exhaled breath condensate used for disease detection (61,62). MDA-modified low-density lipoprotein (LDL) particles serve a key role in atherosclerosis pathogenesis (63). These modified LDL particles are efficiently recognized and internalized by vascular wall macrophages by scavenger receptors, leading to accumulation in lipid vesicles. The subsequent engulfment of MDA-modified LDLs by macrophages results in foam cell formation, initiating lipid deposition in the vascular wall, which represents early atherosclerotic lesions (63). Moreover, MDA conjugates with autologous biomolecules to generate neo-self epitopes, which interact with the innate immune system. Effects of various MDA epitopes are mediated via protein kinase C pathways, including PI3K, Src kinase, phospholipase C/inositol trisphosphate (IP3), Erk 1/2, spleen tyrosine kinase and NF-κB (64). These findings underscore the multifaceted role of MDA in disease pathogenesis and immune modulation, positioning it as a potential therapeutic target in various pathological conditions.

MDA undergoes enzymatic metabolism, with the ALDH family in mitochondria serving a central role in its degradation. Initially, MDA is oxidized to acetaldehyde by ALDH, which is further oxidized to acetate. Acetate is then converted to carbon dioxide and water. Alternatively, MDA metabolism occurs via GSH-mediated pathways, where phosphoglucose isomerase uses GSH as a cofactor to convert MDA to methylglyoxal (MG) in the cytoplasm. MG is metabolized to D-lactate by the glyoxalase system enzymes (65) (Fig. 3). In the context of IRI, elevated oxidative stress in cells triggers considerable MDA production, contributing to tissue and organ dysfunction. Modulating up- and downstream molecular pathways to attenuate MDA production can markedly alleviate IRI severity (66,67). In cerebral IRI, reducing MDA production and inflammatory mediators alleviates brain tissue damage by inhibiting phosphorylation and nuclear translocation of NF-κB (66). Similarly, in the liver, the Nrf2/solute carrier family 7 member 11 (SLC7A11)-HO-1 axis regulates MDA production and inhibits ferroptosis (67). The role of MDA in cardiac IRI has been extensively studied, revealing that inhibiting ROS production and MDA levels and enhancing superoxide dismutase activity mitigates oxidative stress *in vitro* (5,68). These interventions also inhibit ferroptosis and reduce apoptotic protein levels (68). The cell MDA levels are associated with ALDH2 activity, with animal models of acute lung injury (69), cardiac reperfusion (5) and liver IR (11) demonstrating a negative regulatory association between ALDH2 activity and MDA levels.

4-HNE and MDA are among the most potent and extensively studied aldehydes in IRI (18,57,60,66,67). ALDH2 exhibits varying sensitivity to LPO-derived aldehydes, with the highest efficacy in oxidizing 4-HNE, acrolein and MDA (70). To the best of our knowledge, however, research on ALDH2 and toxic aldehydes predominantly focuses on the heart (5,18,35,68), with limited studies on other organs such as the brain, intestine, kidney and liver. Although the pathophysiological mechanisms of IRI are largely similar across different types of tissue, structural and functional differences in various organs result in distinct responses to oxidative stress. While several studies document decreased ALDH2 activity during oxidative stress (1,26,31), ALDH2 activity remains stable (71). Thus, investigating ALDH2 alterations in different tissues to enable the development of targeted therapeutic strategies is key. By exploring the differential responses of ALDH2 to oxidative stress in different types of tissues, valuable insights can be gained into tissue-specific vulnerability, leading to tailored interventions aimed at mitigating IRI. This underscores the need for continued research to unravel the complex interactions between ALDH2 and oxidative stress in diverse physiological contexts.

Mechanism of ferroptosis in IRI. Ferroptosis is a more recently identified iron-dependent form of RCD, characterized by excessive ROS accumulation and LPO (32). During IRI, ferroptosis predominantly occurs during the reperfusion phase rather than the ischemic phase (72), marked by GSH depletion and inactivation of GSH peroxidase 4 (GPX4) (32). Ferroptosis is the primary form of cell death during IR in various organs, including the brain, kidney and heart (73). The mechanisms

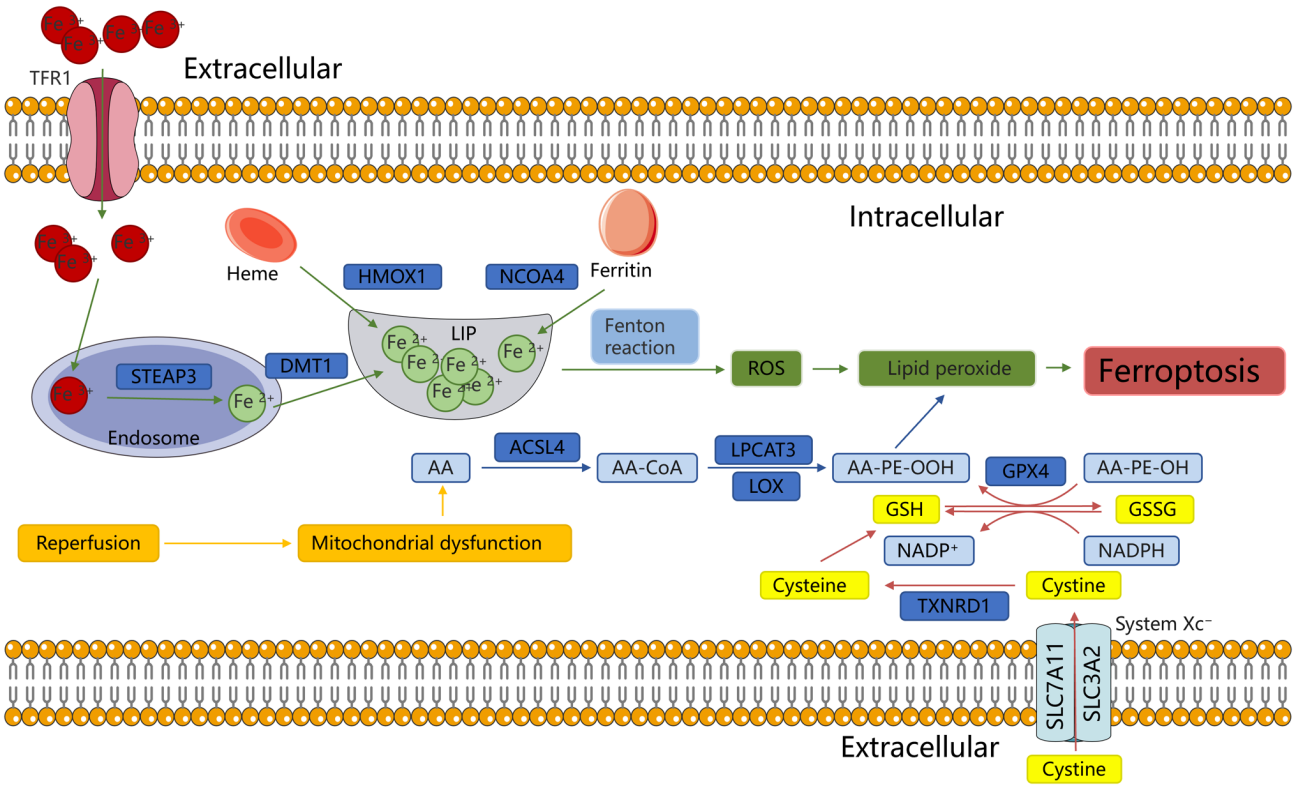

Figure 4. Mechanism of ferroptosis in ischemia-reperfusion injury. TFR1) on the cell membrane transports iron ions (Fe^{3+}) into the cell. Subsequently, Fe^{3+} was reduced to Fe^{2+} by STEAP3). Finally, Fe^{2+} is released from the endosome into the labile iron pool (LIP) in the cytoplasm under the mediation of DMT1. In the Fenton reaction, Fe^{2+} reacts with H_2O_2 to generate ROS, triggering lipid peroxidation and leading to cell death. Additionally, mitochondrial dysfunction caused by reperfusion produces AA-PE-OOH, further exacerbating lipid peroxidation. AA-PE-OOH can be reduced to AA-PE-OH by glutathione TFR1, transferrin receptor 1; STEAP3, six-transmembrane epithelial antigen of the prostate 3; DMT1, divalent metal-ion transporter 1; LIP, labile iron pool; HMOX1, heme oxygenase 1; NCOA4, nuclear receptor coactivator 4; AA, arachidonic acid; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; LOX, lipoxygenase; TXNRD1, thioredoxin reductase 1; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; GSSG, oxidized GSH. AA-PE-OOH, arachidonic acid-phosphatidylethanolamine-hydroperoxide; System Xc^-, cystine/glutamate antiporter. Figure created using Adobe Illustrator 2021 and PowerPoint 2021.

underlying ferroptosis involve numerous interconnected pathways, including lipid, iron and amino acid metabolism (74) (Fig. 4).

Lipid metabolism serves a key role in ferroptosis during IRI. LPO is initiated by the oxidation of PUFAs, particularly AA-containing phosphatidylethanolamine (AA-PE) (75). ROS generated by the Fenton reaction contribute to LPO (76). PUFAs exhibit a high affinity for ROS, such as OH• and H_2O_2, which remove hydrogen atoms from PUFAs, generating lipid ROS. These lipid radicals are further oxidized to lipid peroxide radicals (LOO^-) or AA-OOH-PE (77). When the reduction system fails to neutralize excess of LOO•, ferroptosis is triggered (78,79). In mice, ischemia induces arachidonic acid 15-lipoxygenase to oxidize AA-PE into oxidized phosphatidylethanolamines, which, following reperfusion, initiate LPO and promote ferroptosis (72). Lipoxygenases (LOXs) catalyze generation of ROS (34) and oxidation of AA-PE to AA-OOH-PE (80); while LOXs are considered to be iron-dependent enzymes (81), another study has reported iron-oxidizing phospholipids independent of LOXs (82). In IRI, expression of LOX increases with extended reperfusion, reaching a peak at 5 h post-reperfusion (83). The accumulation of toxic aldehydes, such as 4-HNE and MDA, also serve a key role in ferroptosis (35). Biomarkers such as MDA levels, the glutathione disulfide (GSSG) ratio and Fe^{2+} and ROS levels are used to assess ferroptosis in cells (84,85). Additionally, 4-HNE impedes the accumulation of ALDH1 family member B1 by activating eukaryotic initiation factor 4E and induces ferroptosis by activating NADPH oxidase 1 (86).

Iron serves a dual role in ferroptosis: It promotes ROS accumulation via the Fenton reaction and serves as a key element in enzymes such as LOXs. The Fenton reaction accelerates production of OH•; excessive OH• exacerbates LPO, yielding 4-HNE and activating cyclooxygenase 2 (COX2). COX2, a pro-inflammatory enzyme, triggers cellular inflammation and may be released into the extracellular space by vesicles (87,88). Furthermore, 4-HNE induces mitochondrial dysfunction by binding to mitochondrial proteins, leading to electron leakage and increased ROS production. This activates NRF2-mediated antioxidant responses (88).

Iron overload serves a key role in ferroptosis through several mechanisms. i) HO-1 catalyzes release of Fe^{2+} from hemoglobin, contributing to iron overload (89); ii) nuclear receptor coactivator 4 (NCOA4) mediates ferritin degradation by autophagy (ferritinophagy), releasing free iron (90) iii) transferrin receptor protein 1 (TFR1) induces ferroptosis during IRI, with p53 promoting TFR1 upregulation through deubiquitination of ubiquitin-specific protease 7 (91). Both ferritinophagy and TFR1 are considered key regulators of iron accumulation (92). This iron is released into the labile

iron pool in the cytoplasm. During IR, ferritinophagy induces intracellular iron overload, leading to ferroptosis. Targeting ferritinophagy with inhibitors notably decreases organ damage (93,94). Furthermore, ubiquitination and proteasomal degradation of TFR1 counteract abnormal iron accumulation and ferroptosis, mitigating acute liver injury (95). During ferroptosis, endocytosis of extracellular ferritin increases Fe^{2+} levels in lysosomes. The release of free Fe^{2+} from lysosomes accelerates ROS formation and accumulation of lysosomal LPO. This generates 4-HNE and HNE adducts, leading to lysosomal membrane permeabilization. Detection of HNE adducts in the cytoplasm suggests that LPO diffuses from the lysosome into the cytosol (96).

Cystine/Glutamate Antiporter (system Xc^-)/GSH/GPX4 axis is a key pathway that inhibits ferroptosis (32). System Xc^-, composed of SLC7A11 and solute carrier family 3 member 2, transports cystine into cells. Cystine is reduced to cysteine, which combines with glycine and glutamate to form GSH. GPX4 catalyzes reduction of H_2O_2 and LPO, while GSH is oxidized to GSSG. During IR, downregulation of SLC7A11 expression impairs system Xc^- activity, decreasing GPX4 activity and depleting GSH. This results in the accumulation of toxic lipid ROS and triggers ferroptosis (97,98). Overexpression of GPX4 protects mouse cardiomyocytes during IR, whereas GPX4 deficiency exacerbates damage (89). Selenium, a key cofactor for GPX4, increases GPX4 expression, inhibits ferroptosis and protects neurons from IRI (99). In addition, the ferroptosis promoter ferric ammonium citrate notably increases ROS and MDA levels in chondrocytes. These oxidative species induce P53 and acyl-coA synthetase long chain family member 4 (ACSL4) expression while inhibiting expression of GPX4 and SLC7A11 (100). 4-HNE directly induces ferroptosis in cardiomyocytes by interacting with the cysteine residue of GPX4 and deubiquitinating enzyme ovarian tumor deubiquitinase 5(OTUD5), resulting in increased ubiquitination and degradation of GPX4 (35).

3. ALDH2 and programmed cell death

Numerous studies have highlighted the involvement of cell death modalities in IRI, including apoptosis, necrosis, necroptosis, autophagy, pyroptosis and ferroptosis (14-16,85,86). A central focus of research is potential interactions between cell death pathways and the identification of common upstream regulatory mechanisms (101). Cells proceed through different death pathways at distinct stages of IR. For example, in cerebral ischemic stroke, brain tissue exhibits varying patterns of cell death based on ischemic duration, oxygenation levels and residual blood flow (96,97). Moderate injury may activate autophagy as a protective mechanism to preserve cell viability and facilitate recovery. By contrast, severe injury typically leads to irreversible necrosis, apoptosis and ferroptosis (102,103). ALDH2 is a key regulator of cellular autophagy, apoptosis, necroptosis and ferroptosis during IRI (7,20,37). A growing body of evidence underscores the dynamic nature of cell death processes in IRI and highlights the multifaceted role of ALDH2 in regulating cell fate in various pathological contexts (15,101-103). Further investigation into the interplay between cell death pathways and ALDH2-mediated regulation may unveil novel therapeutic strategies for mitigating IRI.

ALDH2 and apoptosis in IRI. Apoptosis, a form of programmed cell death, is characterized by morphological changes and is energy-dependent. In the early stages, apoptosis is marked by cell shrinkage, chromatin pyknosis (condensation), a reduction in cell volume and an increase in cytoplasmic density, along with more compact organelles (101,104). Pyknosis of chromatin, or the condensation of nuclear material, is a hallmark of apoptosis. Biochemically, apoptosis typically progresses through a caspase-dependent cascade (101,104). Historically, apoptosis has been considered to occur through two main pathways, the extrinsic (death receptor-mediated) and the intrinsic (mitochondria-mediated) pathway. Both pathways activate caspases, which initiate the apoptotic process (101,105). The extrinsic pathway involves interaction of cell surface death receptors [for example, Fas/CD95; TNF-related apoptosis-inducing ligand-receptor (TRAIL-R); TNF-receptor1 (TNFR1)] with their respective ligands, triggering recruitment of proteins that activate caspases (101,105). By contrast, the intrinsic pathway is driven by mitochondrial outer membrane permeabilization and loss of mitochondrial integrity, a process regulated by the Bcl-2 family of proteins. This pathway is characterized by balance between pro-apoptotic proteins such as Bax and anti-apoptotic proteins such as Bcl-2. Following mitochondrial permeabilization, pro-apoptotic factors, including cytochrome *c*, are released into cytosol, leading to the formation of a caspase-activating complex (101,105). These apoptotic pathways have been implicated in IRI, as studies have shown their involvement in organ damage during ischemia and reperfusion (106,107). ALDH2 is a key regulator of apoptosis in IRI in different organs. In a myocardial IRI model, ALDH2 activation was shown to reduce the production of toxic aldehydes such as 4-HNE and MDA, protecting the myocardium via the ERK/p38 signaling pathway (3). In a renal IRI model, ALDH2 activation attenuates inflammation and decreases kidney injury by modulating the IκBα/NF-κB/IL-17C pathway (4). Similarly, in the liver, ALDH2 activation by Alda-1 induces autophagy via the AKT/mTOR and AMPK pathways, thereby protecting the liver from IRI-induced hepatocyte apoptosis (11). Furthermore, the role of ALDH2 in apoptosis regulation extends to the nervous system (15). In the intrinsic apoptotic pathway, the AKT signaling pathway regulates balance between pro-apoptotic Bax and anti-apoptotic Bcl-2 proteins (108). In a pig heart IR model, upregulation of ALDH2 increases Bcl-2/Bax ratio and decreases activation of caspase-3 (109). In humans, ALDH2 activation enhances mitochondrial membrane potential via the PI3K/AKT/mTOR pathway, thereby decreasing ROS production and inhibiting IR-induced apoptosis of cardiomyocytes (18).

ALDH2 and necroptosis in IRI. Cell death is typically classified into two categories: RCD and accidental cell death (ACD). Apoptosis represents RCD, while necrosis, driven by non-physiological stimuli such as physical, mechanical or chemical stressors, typifies ACD (110). Necrosis is characterized by cell swelling, membrane rupture and release of cytoplasmic contents. Necroptosis, a form of programmed necrosis, is primarily regulated by post-translational modification of receptor-interacting protein kinase (RIPK) 1, RIPK3 and mixed lineage kinase domain-like protein (MLKL) (111). The TNF signaling pathway is key for necroptosis. Following

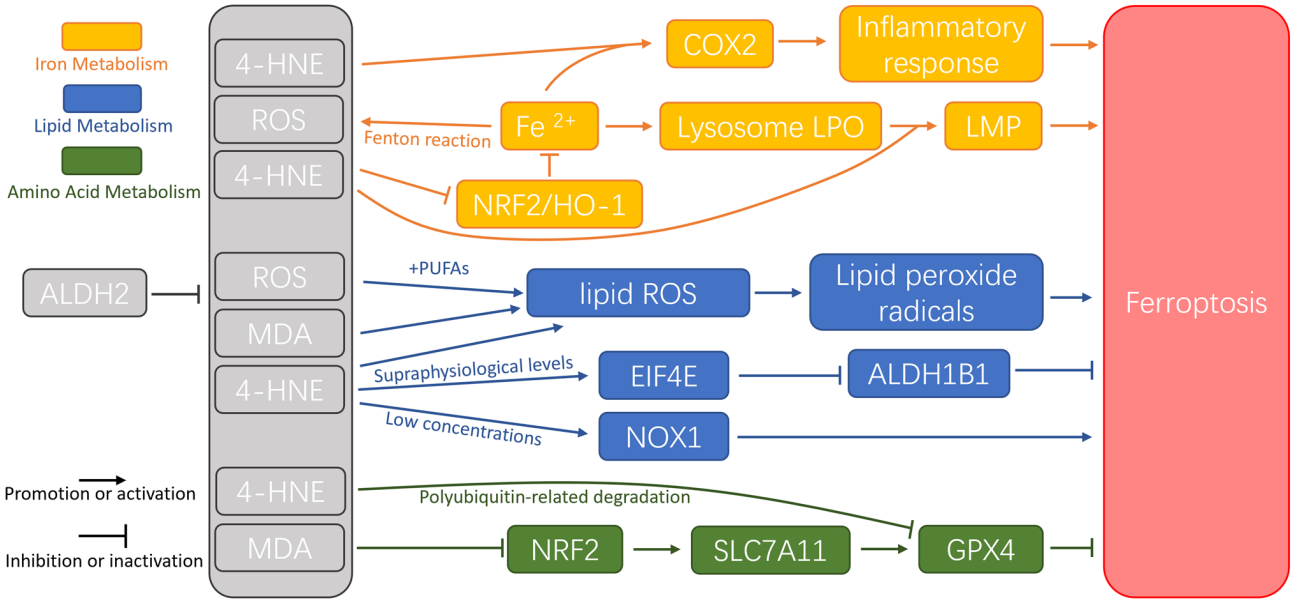

Figure 5. Association between ALDH2 and ferroptosis in ischemia-reperfusion injury. ROS, 4-HNE, and MDA promote ferroptosis by affecting iron metabolism, lipid metabolism, and amino acid metabolism. In this process, ALDH2 participates in ROS reduction and the degradation of 4-HNE and MDA, thereby inhibiting ferroptosis. LPO, lipid peroxidation; LMP, lysosomal membrane permeabilization; ROS, reactive oxygen species; COX2, cyclooxygenase-2; PUFA, polyunsaturated fatty acids; EIF4E, eukaryotic translation initiation factor 4E; ALDH1B1, aldehyde dehydrogenase 1 family member B1; NRF2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4. Figure created using Adobe Illustrator 2021 and PowerPoint 2021.

TNF binding to TNFR1, a cascade leads to the formation of complex I, which includes TNF-receptor-associated death domain protein, TNF-receptor-associated factor 2, cellular inhibitor of apoptosis protein 1 or 2 and the linear ubiquitin chain assembly complex. This complex facilitates linear ubiquitination of receptor-interacting serine/threonine-protein kinase 1 at the K63 site, enabling recruitment of downstream proteins (112). If complex I formation is disrupted, TNF signaling activates complex IIa or IIb, which comprise Fas-associated protein with death domain and caspase-8, proteins that have key roles in apoptosis execution (113). Other stimuli, including death receptors such as Fas [CD95 or apoptosis-related protein (Apo)-1], death receptor 3 (DR3) (Apo-3), DR4 (Apo-2 or TRAIL-R1), DR5 (TRAIL-R2) and DR6, initiate necroptosis via RIPK3. Additionally, pattern recognition receptors, including toll-like receptor (TLR) 3 and TLR4, mediate necroptosis through the formation of necroptotic bodies via toll/interleukin-receptor (TRIF), IFN-β, RIPK3 and MLKL, especially in the presence of caspase inhibitors (113).

The inhibition of ROS clearance and calcium overload triggers necroptosis through inflammatory factors such as TNF-α. RIP3, a key factor in necroptosis, can also drive inflammation and ROS production (114,115). Necroptosis generally occurs during the late reperfusion phase and can persist for an extended period (34). In the early reperfusion phase (within 10 min), inhibiting RIP3 does not mitigate cardiac injury, suggesting that during the initial phase of IRI, RIP3 primarily mediates damage through the regulation of oxidative stress and mitochondrial function, rather than necroptosis (116). Studies have revealed that the necroptosis inhibitor necrostatin-1 provides notable protection in the late stages of infarction, improving IR organ function over time, however, its efficacy is limited when administered early during infarction (117,118).

ALDH2 inhibits necroptosis primarily by eliminating superoxide and reactive aldehydes, thereby maintaining intracellular Ca^{2+} homeostasis and stabilizing mitochondrial function (119). The protective effects of ALDH2 are mediated by several mechanisms: ALDH2 downregulation activates caspase-associated pathways, which subsequently promote necroptosis induction (120). Oxidative stress upregulates the RIP1/RIP3/MLKL signaling cascade, leading to enhanced necroptosis. In a glutamate-induced retinal excitotoxic model of glaucoma, reduced ALDH2 expression is associated with increased expression of RIP1/RIP3/MLKL signaling proteins, indicating elevated necroptosis (121). In alcohol-induced cardiac injury, decreased ALDH2 activity activates the caspase pathway and necroptosis through RIP1/RIP3/MLKL signaling (122). Inhibition of ALDH2 activity leads to the accumulation of 4-HNE, which promotes myocardial cell necroptosis by inhibiting RIP1 ubiquitination and proteasomal degradation. In mice, perfusion with 4-HNE exacerbates necroptosis in a time- and concentration-dependent manner (123). Similarly, in high-glucose-induced rats and cell necroptosis models, decreased ALDH2 expression is associated with increased ROS production and upregulation of RIP1, RIP3 and MLKL, resulting in enhanced necroptosis (7,124). These findings highlight the key role of ALDH2 in mitigating necroptosis via antioxidative and aldehyde detoxification activities.

ALDH2 and ferroptosis in IRI. ALDH2 exhibits potent anti-inflammatory, anti-free radical and anti-LPO activity, which intersect with ferroptosis during IRI (39,98) (Fig. 5). ALDH2 serves a key role in mitigating ferroptosis by metabolizing LPO products such as 4-HNE and MDA,

thereby decreasing oxidative stress-induced cellular damage. Additionally, ALDH2 enhances antioxidant defenses by activating SLC7A11, which promotes intracellular GSH synthesis and decreases free iron (Fe^{2+}) levels, alleviating ferroptosis-mediated cell injury (125). For example, in a calcium oxalate kidney stone model, ALDH2 activation considerably reduces renal crystal deposition and ferroptosis (125). In acute lung injury, ALDH2 provides protection by suppressing both pyroptosis and ferroptosis (69). During post-cardiopulmonary resuscitation organ damage, ALDH2 protects renal, intestinal and pulmonary function by mitigating LPO and ferroptosis. Furthermore, ALDH2 regulates the Nrf2/GPX4 signaling pathway to increase cellular antioxidant capacity and diminish ferroptosis-associated inflammatory damage. In periodontitis, ALDH2 activation alleviates inflammation and promotes osteogenic differentiation of periodontal ligament stem cells by inhibiting ferroptosis via Nrf2 activation (126). Similarly, in gastric ulcers, ALDH2 activation decreases inflammation and oxidative stress while suppressing ferroptosis-associated damage via inhibition of the nucleotide-binding domain, leucine-rich repeat and pyrin domain-containing protein 3 inflammasome (127). Notably, ALDH2 deficiency or decreased activity increases cellular sensitivity to ferroptosis inducers or chemotherapeutic agents (128). In lung adenocarcinoma, decreased ALDH2 expression increases sensitivity to platinum-based chemotherapies by promoting ferroptosis (128).

Ferroptosis is driven by iron overload, free radical generation, LPO and activation of cell death effectors, culminating in membrane rupture. ALDH2 intervenes in multiple facets of ROS clearance, inhibition of LPO and maintenance of mitochondrial homeostasis during IR, all of which are associated with ferroptosis. In IRI following cardiopulmonary resuscitation, ALDH2 effectively protects organ function by alleviating LPO and ferroptosis in the kidney, intestine and lung (19,22). ACSL4, a key enzyme in LPO associated with ferroptosis, is regulated by ALDH2. In a murine model of Alzheimer's disease, ALDH2 suppresses special protein 1/ACSL4-mediated LPO and ferroptosis by modulating downregulation of GPX4 and SLC7A11, while upregulating NCOA4, thereby rescuing cardiac abnormality induced by amyloid precursor protein/presenilin-1 mutations (129). During IR, LPO products such as 4-HNE and MDA serve as markers for ferroptosis. Specifically, 4-HNE carbonylates cysteine residues at C93 of GPX4 and C247 of OTUD5, hindering their interaction and aggravating K48-linked polyubiquitin-related degradation of GPX4. ALDH2 activation mitigates this effect, preserving GPX4 function and inhibiting ferroptosis (35). ALDH2 also stabilizes mitochondrial morphology and function, protecting against cardiac dysfunction by activating the Nrf1-FUN14 domain-containing protein 1 (FUNDC1) cascade (130). Further mechanistic research reveals that FUNDC1 interacts with GPX4 to facilitate its recruitment into mitochondria via the translocase of the outer membrane/translocase of the inner membrane (TIM) complex, enhancing mitochondrial protection by ALDH2 (36). Regarding iron metabolism, intracellular and extracellular ALDH2 decreases 4-HNE, activates the Nrf2/HO-1 pathway to decrease intracellular iron accumulation and mitigates hepatic cell ferroptosis through Parkin-mediated mitochondrial autophagy (131). Additionally, ALDH2 is associated with serum ferritin levels; ALDH2 mutant genotypes are associated with lower serum ferritin levels in human males (132). These findings underscore the multifaceted role of ALDH2 in modulating ferroptosis and highlight its potential as a therapeutic target for IRI.

4. Preventive measures

Targeting ALDH2. Therapies targeting ALDH2 date from the late 1940s with the introduction of disulfiram for the treatment of alcohol addiction (30). Disulfiram functions as a non-selective ALDH2 inhibitor, causing acetaldehyde accumulation following alcohol consumption, which induces symptoms such as nausea, vomiting and facial flushing (31). Despite early adoption of ALDH2 inhibitors such as disulfiram, to the best of our knowledge, no clinically approved ALDH2 agonists exist for the treatment of IRI. In IRI, ALDH2 expression is often decreased and its enzymatic activity is impaired, leading to exacerbated tissue damage. However, development of ALDH2 agonists offers promising potential for the prevention and treatment of IRI. These agonists may restore ALDH2 activity, mitigate oxidative stress and alleviate IR-induced tissue injury (133-135). Research into ALDH2 agonists as therapeutic agents for IRI is essential for identifying viable treatment options in clinical practice. Determining the mechanisms underlying ALDH2 activation and its protective effects against IRI may facilitate development of novel compounds that target ALDH2 activation, paving the way for clinically applicable therapy.

Alda-1. Alda-1, a prominent ALDH2 agonist, was discovered in 2008 by Chen *et al* (133). Alda-1 was identified through high-throughput screening as a small molecule capable of enhancing ALDH2 activity. The aforementioned study showed that Alda-1 effectively increases activity of both the ALDH2 1*2 and ALDH2 2*2 variants, bringing them closer to the activity levels of wild-type ALDH2. Alda-1 results in a 60% reduction in area of rat myocardial infarction (133). Compared with the wild-type enzyme, Alda-1 demonstrates superior ability to activate dehydrogenase activity of the ALDH2 2*2 variant, an inactive mutated form of ALDH2 found in ~40% of the East Asian population (133). Alda-1 enhances acetaldehyde oxidation by ~1.5-fold in the ALDH 2*1 variant and 6-fold in ALDH2 2*2, highlighting its efficacy (129). Additionally, Alda-1 stimulates esterase activities in both enzyme variants, with a particularly pronounced effect on ALDH2 2*2, where esterase activity increases by 100-fold, compared with a 10-fold increase in wild-type ALDH2 (134). Alda-1 doubles the activity of wild-type ALDH2 and increases activity of ALDH2 2*2 by 11-fold (1). These findings underscore the potential of Alda-1 as a therapeutic agent for modulating ALDH2 activity and mitigating IRI effects, especially in individuals with the ALDH2 2*2 variant.

The decreased activity of the ALDH2 2*2 variant stems from a single amino acid substitution, where lysine replaces glutamate, resulting in a 200-fold increase in the K_M (which represents the affinity of an enzyme for its substrate) for NAD^+ binding. Research has shown that Alda-1 does not bind near the site of the ALDH2 2*2 mutation but rather closer to the exit of the substrate-binding tunnel (135). Its binding site overlaps with that of daidzin and extends toward the active site,

leaving key residues such as Cys302 and Glu268 unmodified, enabling them to perform catalytic functions (135). The E487K substitution in ALDH2 2*2, where glutamate is replaced by lysine at position 487, leads to decreased electron density near key residues, particularly those involved in forming helix αG (residues 245-262) and the active-site loop (residues 466-478). While Alda-1 does not interact directly with these residues, it facilitates restoration of the α helix and loop structures, bringing them closer to their native conformation (135). By restricting substrate diffusion within the substrate-to-coenzyme tunnel, Alda-1 increases the effective concentration of reactive groups at the active site, thereby enhancing dehydrogenase activity (135). This mechanism illustrates how Alda-1 can restore enzymatic function in the ALDH2 2*2 variant, presenting therapeutic potential for conditions associated with ALDH2 dysfunction, such as IRI.

4-HNE serves as both a substrate for ALDH2 and an inhibitor of its activity. ALDH2 contains a reactive Cys nucleophile in its active site, which is modified by 4-HNE. This lipid aldehyde forms covalent adducts by modifying protein thiols and amines. At low micromolar concentrations, inhibition of ALDH2 by 4-HNE is reversible, but at higher concentrations, when the active site thiols are covalently modified, inhibition becomes irreversible (136). Alda-1 has been shown to preserve ALDH2 catalytic activity in the presence of high concentrations of 4-HNE, protecting the enzyme from 4-HNE-induced inactivation (26). This protective effect is likely due to the ability of Alda-1 to decrease interaction of 4-HNE with key residues such as Cys302, Cys301 and Cys303, thereby preventing formation of aldehyde adducts (26). This mechanism reveals how Alda-1 maintains activity in structurally intact ALDH2, distinguishing it from its effect on the ALDH2 2*2 variant.

The activation of Alda-1 of ALDH2 has demonstrated efficacy in improving IRI *in vivo* (133-135), suggesting that ALDH2 activators may have therapeutic potential for conditions such as acute myocardial infarction, coronary artery bypass surgery and heart transplantation, where free radical generation, 4-HNE production and mitochondrial dysfunction contribute to irreversible damage. Alda-1 may also benefit patients with peripheral artery disease or angina who develop tolerance to glyceryl trinitrate (GTN) by preventing GTN-induced ALDH2 inactivation (137). Furthermore, the ability of Alda-1 to restore the activity of the mutant ALDH2 2*2 variant (133) suggests that patients carrying this mutation may become more responsive to GTN treatment following Alda-1 therapy. This highlights the potential of Alda-1 as a therapeutic intervention to address consequences of ALDH2 dysfunction in clinical contexts. However, clinical studies of alda-1 are scarce (137), pharmacokinetics and potential adverse reactions of Alda-1 require further investigation before clinical application.

GTN. GTN is used in clinical practice to treat conditions such as angina pectoris, myocardial infarction and heart failure (138). Its therapeutic effects are primarily mediated by bioactivation of GTN in vascular smooth muscle cells and platelets, leading to vasodilation of large veins and arteries, inhibition of platelet aggregation and increased levels of nitric oxide (NO) or S-nitrosothiol, as well as elevated cyclic guanosine monophosphate levels (139). However, prolonged use of organic nitrates such as GTN can result in development of nitrate tolerance, characterized by increased oxidative stress, endothelial dysfunction and sympathetic nerve activation (139,140). ALDH2 is the primary enzyme responsible for bioactivating organic nitrates, catalyzing the conversion of GTN to NO (141). In human individuals with ALDH2-inactivating genotypes (ALDH2 1*2 and ALDH2 2*2) exhibit decreased bioactivation of GTN, which leads to reduced vasodilatory effects (142). A clinical trial indicated that ALDH2 gene polymorphisms affect the pharmacokinetics and hemodynamics of GTN in human participants (143). In cardiovascular IRI, the accumulation of free radicals exacerbates NO reactions with superoxide, leading to the formation of peroxynitrite, which causes nitration of ALDH2. This nitration impairs ALDH2 catalytic activity and contributes to nitrate tolerance (144). Nitrates, including GTN, can inhibit ALDH2 activity (139,140). *In vitro*, GTN rapidly and effectively inactivates ALDH2 (145). Additionally, *in vivo* a study in nitrate-tolerant rats revealed an association between nitrate tolerance, ROS accumulation and loss of ALDH2 activity (146). Therefore, when targeting ALDH2 therapeutically, it is important to consider potential antagonistic or competitive interactions with clinically used drugs, such as nitrates. Strategies aimed at modulating ALDH2 activity should be evaluated to avoid unintended consequences, as interventions that appear beneficial in one context may have adverse effects in another.

Isoflurane (ISO). ISO is a commonly used volatile anesthetic with a well-established safety profile that exerts protective effects in IRI across various types of organs. ISO therapy can mitigate infarction volume and intracranial hemorrhage in tissue-type plasminogen activator-exaggerated brain injury at low concentrations (147). ISO may be associated with a lower rate of postoperative myocardial infarction and hemodynamic complications in patients undergoing coronary artery bypass grafting (148). Protective effects of ISO have also been observed in the heart (149), kidney (150) and liver (151). The mechanism underlying protective effects of ISO in IRI may involve the activation of ALDH2. ISO pretreatment decreases mitochondrial translocation of PKCδ and enhances ALDH2 phosphorylation (152). This leads to decreased release of myocardial injury markers such as lactate dehydrogenase and creatine kinase-myocardial band. Conversely, activation of PKCε facilitates the protective effects of ISO (152). These findings suggest that ISO exerts its protective effects in IRI through ALDH2 activation and modulation of PKC signaling pathways, offering insight into potential therapeutic strategies for mitigating tissue damage in IRI.

Ischemic preconditioning (IPC). IPC refers to the phenomenon where brief episodes of ischemia before prolonged ischemic events confer cell protection against subsequent IRI (39). To the best of our knowledge, there are no effective clinical interventions for established IRI; however, IPC has been studied as a potential therapeutic strategy to mitigate tissue damage associated with IRI (140-145). In 1997, a clinical trial showed that IPC exerts functional protection against simulated IRI (153); numerous trials have confirmed its effectiveness in alleviating

IRI in the heart, kidney, intestine and liver (154-156). Genetic or pharmacological inhibition of ALDH2 impairs the cardioprotective effects of IPC, highlighting the role of ALDH2 activation in mediating protection against IRI (157). The protective mechanism of ALDH2 in IPC involves sequential activation of PKCε and ALDH2 (158). PKCε translocates into the mitochondria, where it interacts with ALDH2, increasing its enzyme activity (159). This interaction is essential for the protective effects of IPC against IRI. Overall, these findings underscore the central role of ALDH2 activation in IPC-mediated protection against IRI and offer insights into the mechanisms involved. Further research into ALDH2 activation may facilitate development of novel therapeutic strategies to prevent and treat IRI.

Ethanol/acetaldehyde exposure. Ethanol and acetaldehyde exposure are pharmacological interventions that mimic the cardioprotective effects of IPC, although the effects are limited at lower doses. For example, brief exposure to ethanol (10-50 mM) before ischemia has been shown to reduce myocardial damage caused by prolonged ischemia (160). Cardioprotective effects of ethanol are mediated by activation of ALDH2 (161). Similarly, pretreatment with 50 μM acetaldehyde enhances ALDH2 activity and decreases myocardial damage in wild-type mouse hearts, without considerably altering cardiac acetaldehyde levels (157). However, in ALDH2 2*2 mice, acetaldehyde pretreatment leads to a three-fold increase in cardiac acetaldehyde levels, exacerbating IRI (157). The underlying mechanism of ALDH2 activation by ethanol and acetaldehyde involves activation of PKCε in cardiomyocytes (157,160).

In addition to ethanol and acetaldehyde, other compounds activate ALDH2, although the exact mechanisms remain incompletely understood. Estrogen (162), heat shock factor 1 (163) and melatonin (164) have been proposed to increase ALDH2 activity by promoting mitochondrial import of PKCε. Antioxidants such as lipoic acid (130), resveratrol (165) and vitamins D (166), C (167) and E (168) activate ALDH2 through various signaling pathways. Notably, flurbiprofen, a non-steroidal anti-inflammatory drug, activates ALDH2 in the context of its anti-obesity effects (169). In summary, pharmacological activation of ALDH2 offers potential therapeutic avenues for IRI; further investigation into specific drugs targeting ALDH2 activation is essential for minimizing side effects and improving clinical outcomes.

ALDH bright (ALDHbr) cells. ALDH activity is notably elevated in certain stem or progenitor cells, designated ALDHbr cells. These cells have been identified and isolated from numerous types of normal tissue, including human cord blood, bone marrow, mobilized peripheral blood, skeletal muscle and breast tissue, as well as rodent brain, pancreas and prostate tissue, using flow cytometry techniques (141,170). In a preclinical ischemic disease model ALDHbr cell administration has considerable efficacy in promoting tissue repair and local neovascularization and may have clinical application (170). In patients with ischemic heart failure, ALDHbr cell therapy is considered safe, potentially enhancing perfusion and functional recovery (171). Additionally, clinical trials investigating intermittent claudication have reported therapeutic effects consistent with ALDH2 isozyme functions, such as improved ischemic tolerance, angiogenesis and mitochondrial metabolism (172,173). However, the specific ALDH isozyme targeted by these therapies is unclear. PCR array has demonstrated a marked increase in ALDH2 expression in ALDHbr cells following ischemic injury (174). By contrast, a clinical trial involving patients with claudication and infrainguinal peripheral artery disease, who received ten injections of ALDHbr in the thigh and calf, showed no improvement in peripheral artery disease outcomes, potentially due to sample size limitations (173). While ALDHbr cell therapy offers promising therapeutic potential, its widespread application is constrained by its high cost and complexity (173), with modest effects on clinical outcome.

Targeting ferroptosis. Targeting ferroptosis is a promising strategy for mitigating IRI. Several small-molecule compounds designed to intervene at various stages of the ferroptotic cascade have been developed. Deferoxamine, a widely studied iron chelator, has demonstrated considerable efficacy in inhibiting ferroptosis (175-177). Deferoxamine decreases lactate dehydrogenase release, highlighting its therapeutic potential in alleviating tissue damage caused by IR in isolated wild-type mouse hearts (175). In a randomized controlled trial, deferoxamine effectively limited generation of ROS by chelating redox-active iron, thereby alleviating oxidative stress without reducing infarct size (176). Dexrazoxane, the only US Food and Drug Administration-approved drug for doxorubicin-induced cardiotoxicity, also serves as an iron chelator. In a murine model of doxorubicin-induced cardiomyopathy and IR, dexrazoxane decreases non-heme iron levels in the heart and mitigates doxorubicin-induced liver iron accumulation (177). Ferrostatin-1 (Fer-1) has been identified as a potent inhibitor of LPO (178). Li *et al* (178) reported that Fer-1 decreases levels of pro-ferroptotic AA-PE, thereby preventing cardiomyocyte death. Additionally, by inhibiting the TLR4/TRIF/type I IFN signaling pathway associated with ferroptosis, Fer-1 impedes neutrophil adhesion to coronary endothelial cells, thereby mitigating inflammation (178). Liproxstatin-1 is another selective ferroptosis inhibitor. Administering Liproxstatin-1 1 h before ischemia in a mouse model of intestinal IRI induces expression of GPX4 and decreases COX2 expression, as well as levels of 12- and 15-hydroxyeicosatetraenoic acid, LPO products and serum markers such as lactate dehydrogenase, TNF-α and IL-6 (179). Several drugs target multiple stages of ferroptosis simultaneously. For example, puerarin, used clinically for heart failure, exerts a multifaceted protective effect against IRI. Liu *et al* (180) showed that puerarin decreases erastin-induced ferroptosis in cardiomyocytes by downregulating NADPH oxidase 4 expression, upregulating GPX4 and inhibiting both iron overload and LPO. In Alzheimer's disease, the beneficial effects of puerarin are associated with changes in expression of iron metabolism-associated proteins in neuronal cells, including divalent metal ion transporter 1 and TFR1. By mitigating iron metabolism-related damage, puerarin improves cognitive function and memory in neurodegenerative disease (181). Despite these advances, no specific drug targeting ferroptosis has been developed for treatment of IRI. Further research into the specific regulatory mechanisms and targets of ferroptosis in IRI is essential for identifying

Table II. Targeting ferroptosis in treatment of IRI.

A, Small molecules

First author, year	Compound	Disease	Mechanism	Model	(Refs.)
Eleftheriadis *et al*, 2021	Vitamin E	Renal IRI	Inhibition of lipid peroxidation	Primary C57BL/6 murine RPTECs	(182)
Chen *et al*, 2020; Lu *et al*, 2020; Stamenkovic *et al*, 2021; Tuo *et al*, 2017; Wu *et al*, 2021	Ferrostatin-1	Cerebral, myocardial, lung and liver, intestinal IRI	Inhibition of lipid peroxidation	MCAO mice and rats, rat ventricular cardiomyocytes, mouse hepatic and lung IRI model	(183-187)
Li *et al*, 2019; Tuo *et al*, 2017; Friedmann Angeli *et al*, 2014; Xu *et al*, 2020	liproxstatin-1	Cerebral, myocardial, lung, liver and renal IRI	Inhibition of lipid peroxidation	MCAO mice and rats, intestinal IRI C57BL/6 mice, GPX4(-/-) acute renal failure ARF mice; lung IRI mice and cell	(179,186, 188,189)
Yamada *et al*, 2020; Zhou *et al*, 2022; Tu *et al*, 2021	Deferoxamine	Myocardial, liver and renal IRI	Iron chelation	Mouse hepatic and renal IRI, rat IRI; H9c2 cells	(190-192)
Shi *et al*, 2022	Selenium compounds	Cerebral IRI	Increased levels of GPX4	MCAO mouse	(193)
Fang *et al*, 2019	Dexrazoxane	Myocardial IRI	Iron chelation	Canonical apoptosis and/ or necroptosis-defective RIPK3-/-, MLKL-/- or FADD-/-MLKL-/- mice	(177)
Lv *et al*, 2021	Etomidate	Myocardial IRI	Upregulation of Nrf2 and HO-1 protein expression	MIRI rat	(194)
Yang *et al*, 2022	Entacapone	Renal IRI	Increased expression of SLC7A11	AKI mice; HK-2 cells	(195)
Chen *et al*, 2023	SRS11-92	Cerebral IRI	Upregulation of Nrf2 signal pathway	MCAO mice	(196)

B, Natural products

First author, year	Compound	Disease	Mechanism	Model	(Refs.)
Li *et al*, 2024; Ding *et al*, 2023	Puerarin	Myocardial IRI	Nrf2-Keap1 dynamics and increased GPX4 protein expression	PC12 and H9C2 cells, mouse IRI	(197,198)
Guan *et al*, 2019	Carvacrol	Cerebral IRI	Increased expression of GPX4	Gerbil cerebral IRI	(199)
Fu *et al*, 2022	Rehmannioside A	Cerebral IRI	Activation of PI3K/AKT/Nrf2 and SLC7A11/GPX4 signaling pathways	MCAO rat, SH-SY5Y cells	(200)
Yang *et al*, 2023	Galangin	Myocardial IRI	Targeting the Nrf2/Gpx4 signaling pathway	MIRI mice	(201)
Guo *et al*, 2021	Carthamin yellow	Cerebral IRI	Deactivation of the NF-κB/NLRP3 inflammasome signaling pathway	MCAO rat	(202)
Yuan *et al*, 2021	Kaempferol	Cerebral IRI	Activation of Nrf2/SLC7A11/GPX4 signaling	E16 mouse embryos; primary mouse cortical neurons	(203)

Table II. Continued.

B, Natural products

First author, year	Compound	Disease	Mechanism	Model	(Refs.)
Lin *et al*, 2021	Gossypol acetic acid	Myocardial IRI	Decreased ACSL4 and NRF2 and increased GPX4 protein levels	MIRI rat, H9c2 cells	(204)
Du *et al*, 2023	Cyanidin-3-glucoside	Renal IRI	Activation of the AMPK pathway	AKI mice model	(205)
Xu *et al*, 2021	Naringenin	Myocardial IRI	Regulation of the Nrf2/System xc-/GPX4 pathway	MIRI rat	(206)
Li *et al*, 2022; Zhu *et al*, 2022; Wang *et al*, 2023	Resveratrol	Cerebral, myocardial and intestinal IRI	Regulation of USP19/Beclin1-induced autophagy and activation of the SIRT3/FoxO3a pathway	MIRI and MCAO rat, intestinal IR mice	(207-209)
Zhang *et al*, 2021	Irisin	Renal IRI	Upregulation of GPX4	AKI mice	(210)

ARF, acute renal failure; AKI, acute renal injury; MCAO, middle cerebral artery occlusion; MIRI, myocardial ischemia-reperfusion injury; RPTEC, renal proximal tubular epithelial cell; GPX4, GSH peroxidase 4; RIPK, receptor-interacting protein kinase; MLKL, mixed lineage kinase domain-like protein; Fadd, Fas-associated death domain; HO-1, hemeoxygenase-1; SLC7A11, solute carrier family 7 member 11; USP, ubiquitin-specific protease.

potential therapeutic strategies. Additionally, upstream signaling pathways that regulate ferroptosis remain unclear and the interaction between ALDH2 and ferroptosis, along with the precise mechanisms involved, have yet to be fully elucidated. Given the dynamic nature of pathological changes in IRI, temporal progression of ferroptosis during IRI should be further investigated. Potential therapies targeting ferroptosis are summarized in Table II.

5. Conclusion

IRI is a complex complication in clinical practice, where damage initiated during ischemia can persist and worsen upon reperfusion. The mechanisms underlying IRI involve a number of cellular injury processes, including autophagy, necrosis, apoptosis, necroptosis and ferroptosis (101). Among the key factors in this cascade, ALDH2 is a cellular oxidoreductase responsible for acetaldehyde metabolism, which is associated with antioxidant defense (28). The present review highlights the key role of ALDH2 in IRI, particularly in scavenging ROS and limiting LPO accumulation. Additionally, ALDH2 regulates cell death pathways under oxidative stress conditions (7,20). The interaction between ALDH2 and ferroptosis suggests these as potential therapeutic targets for mitigating IRI. The present review summarizes the role of ALDH2 in regulation of ferroptosis and other cell death pathways, aiming to uncover intersections with ferroptosis and enhance understanding of its role in IRI. However, the mechanisms by which activators of ALDH2 and ferroptosis inhibitors mitigate IRI remain incompletely understood. To the best of our knowledge, clinical studies on the role of ALDH2 and ferroptosis in IRI are scarce. Moreover, the aforementioned studies research on these compounds has primarily been conducted in rodent models of IR, highlighting the need for clinical trials to evaluate their safety and efficacy. Future research should investigate the detailed mechanisms through which ALDH2 and ferroptosis inhibitors protect against IRI to develop more effective treatment strategies and improve management and prevention of IRI in clinical practice.

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Authors' contributions

LH constructed figures and wrote the manuscript. WZ conceived and designed the study and edited the manuscript. Data authentication is not applicable. Both authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

References

1. Panisello-Rosello A, Lopez A, Folch-Puy E, Carbonell T, Rolo A, Palmeira C, Adam R, Net M and Roselló-Catafau J: Role of aldehyde dehydrogenase 2 in ischemia reperfusion injury: An update. World J Gastroenterol 24: 2984-2994, 2018.
2. Zhang M, Liu Q, Meng H, Duan H, Liu X, Wu J, Gao F, Wang S, Tan R and Yuan J: Ischemia-reperfusion injury: Molecular mechanisms and therapeutic targets. Signal Transduct Target Ther 9: 12, 2024.
3. Bai X, Zhang J, Yang H, Linghu K and Xu M: SNHG3/miR-330-5p/HSD11B1 alleviates myocardial ischemia-reperfusion injury by regulating the ERK/p38 signaling pathway. Protein Pept Lett 30: 699-708, 2023.
4. Chen Y, Xiong Y, Luo J, Hu Q, Lan J, Zou Y, Ma Q, Yao H, Liu Z, Zhong Z, *et al*: Aldehyde dehydrogenase 2 protects the kidney from Ischemia-reperfusion injury by suppressing the I κ B α/NF-κ B/IL-17C pathway. Oxid Med Cell Longev 2023: 2264030, 2023.
5. Diao M, Xu J, Wang J, Zhang M, Wu C, Hu X, Zhu Y, Zhang M and Hu W: Alda-1, an activator of ALDH2, improves postresuscitation cardiac and neurological outcomes by inhibiting pyroptosis in swine. Neurochem Res 47: 1097-1099, 2022.
6. Gao R, Lv C, Qu Y, Yang H, Hao C, Sun X, Hu X, Yang Y and Tang Y: Remote ischemic conditioning mediates cardio-protection after myocardial ischemia/reperfusion injury by reducing 4-HNE levels and regulating autophagy via the ALDH2/SIRT3/HIF1alpha signaling pathway. J Cardiovasc Transl Res 17: 169-182, 2024.
7. Kang P, Wang J, Fang D, Fang T, Yu Y, Zhang W, Shen L, Li Z, Wang H, Ye H and Gao Q: Activation of ALDH2 attenuates high glucose induced rat cardiomyocyte fibrosis and necroptosis. Free Radic Biol Med 146: 198-210, 2020.
8. Li M, Xu M, Li J, Chen L, Xu D, Tong Y, Zhang J, Wu H, Kong X and Xia Q: Alda-1 ameliorates liver Ischemia-Reperfusion injury by activating aldehyde dehydrogenase 2 and enhancing autophagy in mice. J Immunol Res 2018: 9807139, 2018.
9. Lin D, Xiang T, Qiu Q, Leung J, Xu J, Zhou W, Hu Q, Lan J, Liu Z, Zhong Z, *et al*: Aldehyde dehydrogenase 2 regulates autophagy via the Akt-mTOR pathway to mitigate renal ischemia-reperfusion injury in hypothermic machine perfusion. Life Sci 253: 117705, 2020.
10. Lin L, Tao JP, Li M, Peng J, Zhou C, Ouyang J and Si YY: Mechanism of ALDH2 improves the neuronal damage caused by hypoxia/reoxygenation. Eur Rev Med Pharmacol Sci 26: 2712-2720, 2022.
11. Liu Z, Ye S, Zhong X, Wang W, Lai CH, Yang W, Yue P, Luo J, Huang X, Zhong Z, *et al*: Pretreatment with the ALDH2 activator Alda-1 protects rat livers from ischemia/reperfusion injury by inducing autophagy. Mol Med Rep 22: 2373-2385, 2020.
12. Ma LL, Ding ZW, Yin PP, Wu J, Hu K, Sun AJ, Zou YZ and Ge JB: Hypertrophic preconditioning cardioprotection after myocardial ischaemia/reperfusion injury involves ALDH2-dependent metabolism modulation. Redox Biol 43: 101960, 2021.
13. Pan G, Roy B and Palaniyandi SS: Diabetic aldehyde dehydrogenase 2 Mutant (ALDH2*2) mice are more susceptible to cardiac Ischemic-Reperfusion injury due to 4-Hydroxy-2-Nonenal induced coronary endothelial cell damage. J Am Heart Assoc 10: e021140, 2021.
14. Papatheodorou I, Galatou E, Panagiotidis GD, Ravingerova T and Lazou A: Cardioprotective effects of PPARbeta/delta activation against ischemia/reperfusion injury in rat heart are associated with ALDH2 upregulation, amelioration of oxidative stress and preservation of mitochondrial energy production. Int J Mol Sci 22: e021140, 2021.
15. Qu Y, Liu Y and Zhang H: ALDH2 activation attenuates oxygen-glucose deprivation/reoxygenation-induced cell apoptosis, pyroptosis, ferroptosis and autophagy. Clin Transl Oncol 25: 3203-1326, 2023.
16. Sidramagowda Patil S, Hernandez-Cuervo H, Fukumoto J, Krishnamurthy S, Lin M, Alleyn M, Breitzig M, Narala VR, Soundararajan R, Lockey RF, *et al*: Alda-1 attenuates hyperoxia-induced acute lung injury in mice. Front Pharmacol 11: 597942, 2020.
17. Sun X, Gao R, Li W, Zhao Y, Yang H, Chen H, Jiang H, Dong Z, Hu J, Liu J, *et al*: Alda-1 treatment promotes the therapeutic effect of mitochondrial transplantation for myocardial ischemia-reperfusion injury. Bioact Mater 6: 2058-2069, 2021.
18. Tan X, Chen YF, Zou SY, Wang WJ, Zhang NN, Sun ZY, Xian W, Li XR, Tang B, Wang HJ, *et al*: ALDH2 attenuates ischemia and reperfusion injury through regulation of mitochondrial fusion and fission by PI3K/AKT/mTOR pathway in diabetic cardiomyopathy. Free Radic Biol Med 195: 219-230, 2023.
19. Wu H, Xu S, Diao M, Wang J, Zhang G and Xu J: Alda-1 treatment alleviates lung injury after cardiac arrest and resuscitation in swine. Shock 58: 464-469, 2022.
20. Xu T, Guo J, Wei M, Wang J, Yang K, Pan C, Pang J, Xue L, Yuan Q, Xue M, *et al*: Aldehyde dehydrogenase 2 protects against acute kidney injury by regulating autophagy via the Beclin-1 pathway. JCI Insight 6: e138183, 2021.
21. Yoval-Sanchez B, Calleja LF, de la Luz Hernandez-Esquivel M and Rodriguez-Zavala JS: Piperlonguminine a new mitochondrial aldehyde dehydrogenase activator protects the heart from ischemia/reperfusion injury. Biochim Biophys Acta Gen Subj 1864: 129684, 2020.
22. Yu Q, Gao J, Shao X, Lu W, Chen L and Jin L: The Effects of Alda-1 treatment on renal and intestinal injuries after cardiopulmonary resuscitation in pigs. Front Med (Lausanne) 9: 892472, 2022.
23. Zhang R, Xue MY, Liu BS, Wang WJ, Fan XH, Zheng BY, Yuan QH, Xu F, Wang JL and Chen YG: Aldehyde dehydrogenase 2 preserves mitochondrial morphology and attenuates hypoxia/reoxygenation-induced cardiomyocyte injury. World J Emerg Med 11: 246-254, 2020.
24. Zhang ZX, Li H, He JS, Chu HJ, Zhang XT and Yin L: Remote ischemic postconditioning alleviates myocardial ischemia/reperfusion injury by up-regulating ALDH2. Eur Rev Med Pharmacol Sci 22: 6475-6484, 2018.
25. Zhou T, Wang X, Wang K, Lin Y, Meng Z, Lan Q, Jiang Z, Chen J, Lin Y, Liu X, *et al*: Activation of aldehyde dehydrogenase-2 improves ischemic random skin flap survival in rats. Front Immunol 14: 1127610, 2023.
26. Chen CH, Ferreira JC, Gross ER and Mochly-Rosen D: Targeting aldehyde dehydrogenase 2: New therapeutic opportunities. Physiol Rev 94: 1-34, 2014.
27. Lamb RJ, Griffiths K, Lip GYH, Sorokin V, Frenneaux MP, Feelisch M ansd Madhani M: ALDH2 polymorphism and myocardial infarction: From alcohol metabolism to redox regulation. Pharmacol Ther 259: 108666, 2024.
28. Yoshida A, Hsu LC and Yasunami M: Genetics of human alcohol-metabolizing enzymes. Prog Nucleic Acid Res Mol Biol 40: 255-287, 1991.
29. Mali VR and Palaniyandi SS: Regulation and therapeutic strategies of 4-hydroxy-2-nonenal metabolism in heart disease. Free Radic Res 48: 251-263, 2014.
30. Schneider C, Porter NA and Brash AR: Routes to 4-hydroxynonenal: Fundamental issues in the mechanisms of lipid peroxidation. J Biol Chem 283: 15539-15543, 2008.
31. Kimura M, Yokoyama A and Higuchi S: Aldehyde dehydrogenase-2 as a therapeutic target. Expert Opin Ther Targets 23: 955-966, 2019.
32. Ke K, Li L, Lu C, Zhu Q, Wang Y, Mou Y, Wang H and Jin W: The crosstalk effect between ferrous and other ions metabolism in ferroptosis for therapy of cancer. Front Oncol 12: 916082, 2022.
33. Fang X, Ardehali H, Min J and Wang F: The molecular and metabolic landscape of iron and ferroptosis in cardiovascular disease. Nat Rev Cardiol 20: 7-23, 2023.

34. Xiang Q, Yi X, Zhu XH, Wei X and Jiang DS: Regulated cell death in myocardial ischemia-reperfusion injury. Trends Endocrinol Metab 35: 219-234, 2024.
35. Liu L, Pang J, Qin D, Li R, Zou D, Chi K, Wu W, Rui H, Yu H, Zhu W, *et al*: Deubiquitinase OTUD5 as a novel protector against 4-HNE-triggered ferroptosis in myocardial ischemia/reperfusion injury. Adv Sci (Weinh) 10: e2301852, 2023.
36. Bi Y, Liu S, Qin X, Abudureyimu M, Wang L, Zou R, Ajoolabady A, Zhang W, Peng H, Ren J and Zhang Y: FUNDC1 interacts with GPx4 to govern hepatic ferroptosis and fibrotic injury through a mitophagy-dependent manner. J Adv Res 55: 45-60, 2024.
37. Zhu W, Feng D, Shi X, Wei Q and Yang L: The potential role of mitochondrial acetaldehyde dehydrogenase 2 in urological cancers from the perspective of ferroptosis and cellular senescence. Front Cell Dev Biol 10: 850145, 2022.
38. Droge W: Free radicals in the physiological control of cell function. Physiol Rev 82: 47-95, 2002.
39. Chen CH, Sun L and Mochly-Rosen D: Mitochondrial aldehyde dehydrogenase and cardiac diseases. Cardiovasc Res 88: 51-57, 2010.
40. Wilson DF and Matschinsky FM: Ethanol metabolism: The good, the bad, and the ugly. Med Hypotheses 140: 109638, 2020.
41. Hink U, Daiber A, Kayhan N, Trischler J, Kraatz C, Oelze M, Mollnau H, Wenzel P, Vahl CF, Ho KK, *et al*: Oxidative inhibition of the mitochondrial aldehyde dehydrogenase promotes nitroglycerin tolerance in human blood vessels. J Am Coll Cardiol 50: 2226-2232, 2007.
42. Xu Y, Yuan Q, Cao S, Cui S, Xue L, Song X, Li Z, Xu R, Yuan Q and Li R: Aldehyde dehydrogenase 2 inhibited oxidized LDL-induced NLRP3 inflammasome priming and activation via attenuating oxidative stress. Biochem Biophys Res Commun 529: 998-1004, 2020.
43. Moldovan L and Moldovan NI: Oxygen free radicals and redox biology of organelles. Histochem Cell Biol 122: 395-412, 2004.
44. Bielski BH, Arudi RL and Sutherland MW: A study of the reactivity of HO2/O2-with unsaturated fatty acids. J Biol Chem 258: 4759-4761, 1983.
45. Browne RW and Armstrong D: HPLC analysis of lipid-derived polyunsaturated fatty acid peroxidation products in oxidatively modified human plasma. Clin Chem 46: 829-836, 2000.
46. Schneider C, Boeglin WE, Yin H, Porter NA and Brash AR: Intermolecular peroxyl radical reactions during autoxidation of hydroxy and hydroperoxy arachidonic acids generate a novel series of epoxidized products. Chem Res Toxicol 21: 895-903, 2008.
47. Singh S, Brocker C, Koppaka V, Chen Y, Jackson BC, Matsumoto A, Thompson DC and Vasiliou V: Aldehyde dehydrogenases in cellular responses to oxidative/electrophilic stress. Free Radic Biol Med 56: 89-101, 2013.
48. Gao J, Hao Y, Piao X and Gu X: Aldehyde dehydrogenase 2 as a therapeutic target in oxidative stress-related diseases: Post-translational modifications deserve more attention. Int J Mol Sci 23: 2682, 2022.
49. Breitzig M, Bhimineni C, Lockey R and Kolliputi N: 4-Hydroxy-2-nonenal: A critical target in oxidative stress? Am J Physiol Cell Physiol 311: C537-C543, 2016.
50. Schaur RJ, Siems W, Bresgen N and Eckl PM: 4-Hydroxy-nonenal-a bioactive lipid peroxidation product. Biomolecules 5: 2247-337, 2015.
51. Forman HJ: Reactive oxygen species and alpha,beta-unsaturated aldehydes as second messengers in signal transduction. Ann N Y Acad Sci 1203: 35-44, 2010.
52. Shoeb M, Ansari NH, Srivastava SK and Ramana KV: 4-Hydroxynonenal in the pathogenesis and progression of human diseases. Curr Med Chem 21: 230-237, 2014.
53. Zhang H and Forman HJ: Signaling pathways involved in phase II gene induction by alpha, beta-unsaturated aldehydes. Toxicol Ind Health 25: 269-278, 2009.
54. Dalleau S, Baradat M, Gueraud F and Huc L: Cell death and diseases related to oxidative stress: 4-hydroxynonenal (HNE) in the balance. Cell Death Differ 20: 1615-1630, 2013.
55. Xue Z, Zhao K, Sun Z, Wu C, Yu B, Kong D and Xu B: Isorhapontigenin ameliorates cerebral ischemia/reperfusion injury via modulating Kinase Cepsilon/Nrf2/HO-1 signaling pathway. Brain Behav 11: e02143, 2021.
56. Wang Y, Li B, Liu G, Han Q, Diao Y and Liu J: Corilagin attenuates intestinal ischemia/reperfusion injury in mice by inhibiting ferritinophagy-mediated ferroptosis through disrupting NCOA4-ferritin interaction. Life Sci 334: 122176, 2023.
57. Endo J, Sano M, Katayama T, Hishiki T, Shinmura K, Morizane S, Matsuhashi T, Katsumata Y, Zhang Y, Ito H, *et al*: Metabolic remodeling induced by mitochondrial aldehyde stress stimulates tolerance to oxidative stress in the heart. Circ Res 105: 1118-1127, 2009.
58. Esterbauer H, Schaur RJ and Zollner H: Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. Free Radic Biol Med 11: 81-128, 1991.
59. Giera M, Lingeman H and Niessen WM: Recent advancements in the LC- and GC-Based analysis of malondialdehyde (MDA): A brief overview. Chromatographia 75: 433-440, 2012.
60. Esterbauer H and Zollner H: Methods for determination of aldehydic lipid peroxidation products. Free Radic Biol Med 7: 197-203, 1989.
61. Shen Z, Zhang Y, Bu G and Fang L: Renal denervation improves mitochondrial oxidative stress and cardiac hypertrophy through inactivating SP1/BACH1-PACS2 signaling. Int Immunopharmacol 141: 112778, 2024.
62. Tsikas D: Assessment of lipid peroxidation by measuring malondialdehyde (MDA) and relatives in biological samples: Analytical and biological challenges. Anal Biochem 524: 13-30, 2017.
63. Lankin VZ, Tikhaze AK and Melkumyants AM: Malondialdehyde as an important key factor of molecular mechanisms of vascular wall damage under heart diseases development. Int J Mol Sci 24: 128, 2022
64. Busch CJ and Binder CJ: Malondialdehyde epitopes as mediators of sterile inflammation. Biochim Biophys Acta Mol Cell Biol Lipids 1862: 398-406, 2017.
65. Agadjanyan ZS, Dmitriev LF and Dugin SF: A new role of phosphoglucose isomerase. Involvement of the glycolytic enzyme in aldehyde metabolism. Biochemistry (Mosc) 70: 1251-1255, 2005.
66. Liu H, Wu X, Luo J, Wang X, Guo H, Feng D, Zhao L, Bai H, Song M, Liu X, *et al*: Pterostilbene attenuates astrocytic inflammation and neuronal oxidative injury after Ischemia-reperfusion by inhibiting NF-κB phosphorylation. Front Immunol 10: 2408, 2019.
67. Qi D, Chen P, Bao H, Zhang L, Sun K, Song S and Li T: Dimethyl fumarate protects against hepatic ischemia-reperfusion injury by alleviating ferroptosis via the NRF2/SLC7A11/HO-1 axis. Cell Cycle 22: 818-828, 2023.
68. Wang IC, Lin JH, Lee WS, Liu CH, Lin TY and Yang KT: Baicalein and luteolin inhibit ischemia/reperfusion-induced ferroptosis in rat cardiomyocytes. Int J Cardiol 375: 74-86, 2023.
69. Cao Z, Qin H, Huang Y, Zhao Y, Chen Z, Hu J and Gao Q: Crosstalk of pyroptosis, ferroptosis, and mitochondrial aldehyde dehydrogenase 2-related mechanisms in sepsis-induced lung injury in a mouse model. Bioengineered 13: 4810-4820, 2022.
70. Yoval-Sanchez B and Rodriguez-Zavala JS: Differences in susceptibility to inactivation of human aldehyde dehydrogenases by lipid peroxidation byproducts. Chem Res Toxicol 25: 722-729, 2012.
71. Zhang T, Zhao Q, Ye F, Huang CY, Chen WM and Huang WQ: Alda-1, an ALDH2 activator, protects against hepatic ischemia/reperfusion injury in rats via inhibition of oxidative stress. Free Radic Res 52: 629-638, 2018.
72. Ma XH, Liu JH, Liu CY, Sun WY, Duan WJ, Wang G, Kurihara H, He RR, Li YF, Chen Y, *et al*: ALOX15-launched PUFA-phospholipids peroxidation increases the susceptibility of ferroptosis in ischemia-induced myocardial damage. Signal Transduct Target Ther 7: 288, 2022.
73. Yan HF, Tuo QZ, Yin QZ and Lei P: The pathological role of ferroptosis in ischemia/reperfusion-related injury. Zool Res 41: 220-230, 2020.
74. Wu X, Li Y, Zhang S and Zhou X: Ferroptosis as a novel therapeutic target for cardiovascular disease. Theranostics 11: 3052-3059, 2021.
75. Kagan VE, Mao G, Qu F, Angeli JP, Doll S, Croix CS, Dar HH, Liu B, Tyurin VA, Ritov VB, *et al*: Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol 13: 81-90, 2017.
76. Liu J, Kang R and Tang D: Signaling pathways and defense mechanisms of ferroptosis. FEBS J 289: 7038-7050, 2022.

77. Liu C, Li Z, Li B, Liu W, Zhang S, Qiu K and Zhu W: Relationship between ferroptosis and mitophagy in cardiac ischemia reperfusion injury: A mini-review. PeerJ 11: e14952, 2023.
78. Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, Fulda S, Gascón S, Hatzios SK, Kagan VE, *et al*: Ferroptosis: A regulated cell death nexus linking metabolism, redox biology, and disease. Cell 171: 273-285, 2017.
79. Liang C, Zhang X, Yang M and Dong X: Recent progress in ferroptosis inducers for cancer therapy. Adv Mater 31: e1904197, 2019.
80. Yang WS, Kim KJ, Gaschler MM, Patel M, Shchepinov MS and Stockwell BR: Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. Proc Natl Acad Sci USA 113: E4966-E49675, 2016.
81. Haeggstrom JZ and Funk CD: Lipoxygenase and leukotriene pathways: Biochemistry, biology, and roles in disease. Chem Rev 111: 5866-5898, 2011.
82. Braughler JM, Duncan LA and Chase RL: The involvement of iron in lipid peroxidation. Importance of ferric to ferrous ratios in initiation. J Biol Chem 261: 10282-10289, 1986.
83. Matsuyama M, Nakatani T, Hase T, Kawahito Y, Sano H, Kawamura M and Yoshimura R: The expression of cyclooxygenases and lipoxygenases in renal ischemia-reperfusion injury. Transplant Proc 36: 1939-1942, 2004.
84. Jiang M, Jike Y, Liu K, Gan F, Zhang K, Xie M, Zhang J, Chen C, Zou X, Jiang X, *et al*: Exosome-mediated miR-144-3p promotes ferroptosis to inhibit osteosarcoma proliferation, migration, and invasion through regulating ZEB1. Mol Cancer 22: 113, 2023.
85. Yang R, Gao W, Wang Z, Jian H, Peng L, Yu X, Xue P, Peng W, Li K and Zeng P: Polyphyllin I induced ferroptosis to suppress the progression of hepatocellular carcinoma through activation of the mitochondrial dysfunction via Nrf2/HO-1/GPX4 axis. Phytomedicine 122: 155135, 2024.
86. Chen X, Huang J, Yu C, Liu J, Gao W, Li J, Song X, Zhou Z, Li C, Xie Y, *et al*: A noncanonical function of EIF4E limits ALDH1B1 activity and increases susceptibility to ferroptosis. Nat Commun 13: 6318, 2022.
87. Jang EJ, Jeong HO, Park D, Kim DH, Choi YJ, Chung KW, Park MH, Yu BP and Chung HY: Src Tyrosine kinase activation by 4-hydroxynonenal upregulates p38, ERK/AP-1 signaling and COX-2 expression in YPEN-1 Cells. PLoS One 10: e0129244, 2015.
88. Lee J and Hyun DH: The interplay between intracellular iron homeostasis and neuroinflammation in neurodegenerative diseases. Antioxidants (Basel) 12: 918, 2023.
89. Miyamoto HD, Ikeda M, Ide T, Tadokoro T, Furusawa S, Abe K, Ishimaru K, Enzan N, Sada M, Yamamoto T, *et al*: Iron overload via heme degradation in the endoplasmic reticulum triggers ferroptosis in myocardial ischemia-reperfusion injury. JACC Basic Transl Sci 7: 800-819, 2022.
90. Ito J, Omiya S, Rusu MC, Ueda H, Murakawa T, Tanada Y, Abe H, Nakahara K, Asahi M, Taneike M, *et al*: Iron derived from autophagy-mediated ferritin degradation induces cardiomyocyte death and heart failure in mice. Elife 10: e62174, 2021.
91. Tang LJ, Zhou YJ, Xiong XM, Li NS, Zhang JJ, Luo XJ and Peng J: Ubiquitin-specific protease 7 promotes ferroptosis via activation of the p53/TfR1 pathway in the rat hearts after ischemia/reperfusion. Free Radic Biol Med 162: 339-352, 2021.
92. Masaldan S, Clatworthy SAS, Gamell C, Meggyesy PM, Rigopoulos AT, Haupt S, Haupt Y, Denoyer D, Adlard PA, Bush AI and Cater MA: Iron accumulation in senescent cells is coupled with impaired ferritinophagy and inhibition of ferroptosis. Redox Biol 14: 100-115, 2018.
93. Li W, Li W, Wang Y, Leng Y and Xia Z: Inhibition of DNMT-1 alleviates ferroptosis through NCOA4 mediated ferritinophagy during diabetes myocardial ischemia/reperfusion injury. Cell Death Discov 7: 267, 2021.
94. Fan Z, Cai L, Wang S, Wang J and Chen B: Baicalin prevents myocardial ischemia/reperfusion injury through inhibiting ACSL4 mediated ferroptosis. Front Pharmacol 12: 628988, 2021.
95. Wu Y, Jiao H, Yue Y, He K, Jin Y, Zhang J, Zhang J, Wei Y, Luo H, Hao Z, *et al*: Ubiquitin ligase E3 HUWE1/MULE targets transferrin receptor for degradation and suppresses ferroptosis in acute liver injury. Cell Death Differ 29: 1705-1718, 2022.
96. Bresgen N, Jaksch H, Lacher H, Ohlenschlager I, Uchida K and Eckl PM: Iron-mediated oxidative stress plays an essential role in ferritin-induced cell death. Free Radic Biol Med 48: 1347-1357, 2010.
97. Ma S, Sun L, Wu W, Wu J, Sun Z and Ren J: USP22 Protects against myocardial Ischemia-Reperfusion Injury via the SIRT1-p53/SLC7A11-dependent inhibition of Ferroptosis-induced cardiomyocyte death. Front Physiol 11: 551318, 2020.
98. Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, Cheah JH, Clemons PA, Shamji AF, Clish CB, *et al*: Regulation of ferroptotic cancer cell death by GPX4. Cell 156: 317-331, 2014.
99. Alim I, Caulfield JT, Chen Y, Swarup V, Geschwind DH, Ivanova E, Seravalli J, Ai Y, Sansing LH, Ste Marie EJ, *et al*: Selenium drives a transcriptional adaptive program to block ferroptosis and treat stroke. Cell 177: 1262-1279.e25, 2019.
100. Yao X, Sun K, Yu S, Luo J, Guo J, Lin J, Wang G, Guo Z, Ye Y and Guo F: Chondrocyte ferroptosis contribute to the progression of osteoarthritis. J Orthop Translat 27: 33-43, 2021.
101. Zhang Q, Jia M, Wang Y, Wang Q and Wu J: Cell death mechanisms in cerebral Ischemia-Reperfusion injury. Neurochem Res 47: 3525-3542, 2022.
102. Kalogeris T, Baines CP, Krenz M and Korthuis RJ: Cell biology of ischemia/reperfusion injury. Int Rev Cell Mol Biol 298: 229-317, 2012.
103. Guo J, Tuo QZ and Lei P: Iron, ferroptosis, and ischemic stroke. J Neurochem 165: 487-520, 2023.
104. Elmore S: Apoptosis: A review of programmed cell death. Toxicol Pathol 35: 495-516, 2007.
105. Green DR and Llambi F: Cell death signaling. Cold Spring Harb Perspect Biol 7: a006080, 2015.
106. Pang Q, Zhao Y, Chen X, Zhao K, Zhai Q and Tu F: Apigenin protects the brain against Ischemia/Reperfusion injury via Caveolin-1/VEGF in vitro and in vivo. Oxid Med Cell Longev 2018: 7017204, 2018.
107. Liu J, Li J, Yang Y, Wang X, Zhang Z and Zhang L: Neuronal apoptosis in cerebral ischemia/reperfusion area following electrical stimulation of fastigial nucleus. Neural Regen Res 9: 727-734, 2014.
108. Teijido O and Dejean L: Upregulation of Bcl2 inhibits apoptosis-driven BAX insertion but favors BAX relocalization in mitochondria. FEBS Lett 584: 3305-3310, 2010.
109. Andreka G, Vertesaljai M, Szantho G, Font G, Piroth Z, Fontos G, Juhasz ED, Szekely L, Szelid Z, Turner MS, *et al*: Remote ischaemic postconditioning protects the heart during acute myocardial infarction in pigs. Hear 93: 749-752, 2007.
110. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L, Amelio I, Andrews DW, *et al*: Molecular mechanisms of cell death: Recommendations of the nomenclature committee on cell death 2018. Cell Death Differ 25: 486-541, 2018.
111. Guerrero-Mauvecin J, Villar-Gomez N, Rayego-Mateos S, Ramos AM, Ruiz-Ortega M, Ortiz A and Sanz AB: Regulated necrosis role in inflammation and repair in acute kidney injury. Front Immunol 14: 1324996, 2023.
112. Annibaldi A and Meier P: Checkpoints in TNF-Induced cell death: Implications in inflammation and cancer. Trends Mol Med 24: 49-65, 2018.
113. Seo J, Nam YW, Kim S, Oh DB and Song J: Necroptosis molecular mechanisms: Recent findings regarding novel necroptosis regulators. Exp Mol Med 53: 1007-117, 2021.
114. Luedde T, Kaplowitz N and Schwabe RF: Cell death and cell death responses in liver disease: Mechanisms and clinical relevance. Gastroenterology 147: 765-83.e4, 2014.
115. Koike A, Hanatani M and Fujimori K: Pan-caspase inhibitors induce necroptosis via ROS-mediated activation of mixed lineage kinase domain-like protein and p38 in classically activated macrophages. Exp Cell Res 380: 171-179, 2019.
116. Horvath C, Young M, Jarabicova I, Kindernay L, Ferenczyova K, Ravingerova T, Lewis M and Suleiman MS: Inhibition of cardiac RIP3 mitigates early reperfusion injury and Calcium-induced mitochondrial swelling without altering necroptotic signalling. Int J Mol Sci 22: 7983, 2021.
117. Oerlemans MI, Liu J, Arslan F, den Ouden K, van Middelaar BJ, Doevendans PA and Sluijter JP: Inhibition of RIP1-dependent necrosis prevents adverse cardiac remodeling after myocardial ischemia-reperfusion in vivo. Basic Res Cardiol 107: 270, 2012.
118. Luo Y, Apaijai N, Liao S, Maneechote C, Chunchai T, Arunsak B, Benjanuwattra J, Yanpiset P, Chattipakorn SC and Chattipakorn N: Therapeutic potentials of cell death inhibitors in rats with cardiac ischaemia/reperfusion injury. J Cell Mol Med 26: 2462-2476, 2022.

119. Guo R and Ren J: Alcohol dehydrogenase accentuates ethanol-induced myocardial dysfunction and mitochondrial damage in mice: Role of mitochondrial death pathway. PLoS One 5: e8757, 2010.
120. Gao Y, Xu Y, Hua S, Zhou S and Wang K: ALDH2 attenuates Dox-induced cardiotoxicity by inhibiting cardiac apoptosis and oxidative stress. Int J Clin Exp Med 8: 6794-6803, 2015.
121. Liu M, Li H, Yang R, Ji D and Xia X: GSK872 and necrostatin-1 protect retinal ganglion cells against necroptosis through inhibition of RIP1/RIP3/MLKL pathway in glutamate-induced retinal excitotoxic model of glaucoma. J Neuroinflammation 19: 262, 2022.
122. Shen C, Wang C, Han S, Wang Z, Dong Z, Zhao X, Wang P, Zhu H, Sun X, Ma X, *et al*: Aldehyde dehydrogenase 2 deficiency negates chronic low-to-moderate alcohol consumption-induced cardioprotecion possibly via ROS-dependent apoptosis and RIP1/RIP3/MLKL-mediated necroptosis. Biochim Biophys Acta Mol Basis Dis 1863: 1912-1918, 2017.
123. Zhai X, Wang W, Sun S, Han Y, Li J, Cao S, Li R, Xu T, Yuan Q, Wang J, *et al*: 4-Hydroxy-2-nonenal promotes cardiomyocyte necroptosis via stabilizing receptor-interacting serine/threonine-protein kinase 1. Front Cell Dev Biol 9: 721795, 2021.
124. Fang T, Cao R, Wang W, Ye H, Shen L, Li Z, Hu J and Gao Q: Alterations in necroptosis during ALDH2-mediated protection against high glucose-induced H9c2 cardiac cell injury. Mol Med Rep 18: 2807-2815, 2018.
125. Zhang J, Wang R, Xie L, Ren H, Luo D, Yang Y, Xie H, Shang Z and Liu C: Pharmacological activation of aldehyde dehydrogenase 2 inhibits ferroptosis via SLC7A11/GPX4 axis to reduce kidney stone formation. Eur J Pharmacol 986: 177132, 2025.
126. Chen J, Hu C, Lu X, Yang X, Zhu M, Ma X and Yang Y: ALDH2 alleviates inflammation and facilitates osteogenic differentiation of periodontal ligament stem cells in periodontitis by blocking ferroptosis via activating Nrf2. Funct Integr Genomics 24: 184, 2024.
127. Zhang Y, Yuan Z, Chai J, Zhu D, Miao X, Zhou J and Gu X: ALDH2 ameliorates ethanol-induced gastric ulcer through suppressing NLPR3 inflammasome activation and ferroptosis. Arch Biochem Biophys 743: 109621, 2023.
128. Shan G, Bian Y, Yao G, Liang J, Shi H, Hu Z, Zheng Z, Bi G, Fan H and Zhan C: Targeting ALDH2 to augment platinum-based chemosensitivity through ferroptosis in lung adenocarcinoma. Free Radic Biol Med 224: 310-324, 2024.
129. Zhu ZY, Liu YD, Gong Y, Jin W, Topchiy E, Turdi S, Gao YF, Culver B, Wang SY, Ge W, *et al*: Mitochondrial aldehyde dehydrogenase (ALDH2) rescues cardiac contractile dysfunction in an APP/PS1 murine model of Alzheimer's disease via inhibition of ACSL4-dependent ferroptosis. Acta Pharmacol Sin 43: 39-49, 2022.
130. Li W, Yin L, Sun X, Wu J, Dong Z, Hu K, Sun A and Ge J: Alpha-lipoic acid protects against pressure overload-induced heart failure via ALDH2-dependent Nrf1-FUNDC1 signaling. Cell Death Dis 11: 599, 2020.
131. Ma X, Luo Q, Zhu H, Liu X, Dong Z, Zhang K, Zou Y, Wu J, Ge J and Sun A: Aldehyde dehydrogenase 2 activation ameliorates CCl4-induced chronic liver fibrosis in mice by up-regulating Nrf2/HO-1 antioxidant pathway. J Cell Mol Med 22: 3965-3978, 2018.
132. Tao Y, Huang X, Xie Y, Zhou X, He X, Tang S, Liao M, Chen Y, Tan A, Chen Y, *et al*: Genome-wide association and gene-environment interaction study identifies variants in ALDH2 associated with serum ferritin in a Chinese population. Gene 685: 196-201, 2019.
133. Chen CH, Budas GR, Churchill EN, Disatnik MH, Hurley TD and Mochly-Rosen D: Activation of aldehyde dehydrogenase-2 reduces ischemic damage to the heart. Science 321: 1493-1495, 2008.
134. Beretta M, Gorren AC, Wenzl MV, Weis R, Russwurm M, Koesling D, Schmidt K and Mayer B: Characterization of the East Asian variant of aldehyde dehydrogenase-2: Bioactivation of nitroglycerin and effects of Alda-1. J Biol Chem 285: 943-952, 2010.
135. Perez-Miller S, Younus H, Vanam R, Chen CH, Mochly-Rosen D and Hurley TD: Alda-1 is an agonist and chemical chaperone for the common human aldehyde dehydrogenase 2 variant. Nat Struct Mol Biol 17: 159-1564, 2010.
136. Doorn JA, Hurley TD and Petersen DR: Inhibition of human mitochondrial aldehyde dehydrogenase by 4-hydroxynon-2-enal and 4-oxonon-2-enal. Chem Res Toxicol 19: 102-110, 2006.
137. Budas GR, Disatnik MH and Mochly-Rosen D: Aldehyde dehydrogenase 2 in cardiac protection: A new therapeutic target? Trends Cardiovasc Med 19: 158-164, 2009.
138. Malyshev Y, Neuzil P, Petru J, Funasako M, Hala P, Kopriva K, Schneider C, Achyutha A, Vanderper A, Musikantow D, *et al*: Nitroglycerin to ameliorate coronary artery spasm during focal Pulsed-Field ablation for atrial fibrillation. JACC Clin Electrophysiol 10: 885-896, 2024.
139. Mollace V, Muscoli C, Dagostino C, Giancotti LA, Gliozzi M, Sacco I, Visalli V, Gratteri S, Palma E, Malara N, *et al*: The effect of peroxynitrite decomposition catalyst MnTBAP on aldehyde dehydrogenase-2 nitration by organic nitrates: Role in nitrate tolerance. Pharmacol Res 89: 29-35, 2014.
140. Salvemini D, Pistelli A and Mollace V: Release of nitric oxide from glyceryl trinitrate by captopril but not enalaprilat: In vitro and in vivo studies. Br J Pharmacol 109: 430-436, 1993.
141. Munzel T and Daiber A: The potential of aldehyde dehydrogenase 2 as a therapeutic target in cardiovascular disease. Expert Opin Ther Targets 22: 217-231, 2018.
142. Li Y, Zhang D, Jin W, Shao C, Yan P, Xu C, Sheng H, Liu Y, Yu J, Xie Y, *et al*: Mitochondrial aldehyde dehydrogenase-2 (ALDH2) Glu504Lys polymorphism contributes to the variation in efficacy of sublingual nitroglycerin. J Clin Invest 116: 506-511, 2006.
143. Nagano T, Ushijima K, Taga N, Takeuchi M, Kawada MA, Aizawa K, Imai Y and Fujimura A: Influence of the aldehyde dehydrogenase 2 polymorphism on the vasodilatory effect of nitroglycerin in infants with congenital heart disease and pulmonary arterial hypertension. Eur J Clin Pharmacol 75: 1361-1367, 2019.
144. Maiuolo J, Oppedisano F, Carresi C, Gliozzi M, Musolino V, Macri R, Scarano F, Coppoletta A, Cardamone A, Bosco F, *et al*: The generation of nitric oxide from aldehyde Dehydrogenase-2: The role of dietary nitrates and their implication in cardiovascular disease management. Int J Mol Sci 23: 15454, 2022.
145. Marini E, Giorgis M, Leporati M, Rolando B, Chegaev K, Lazzarato L, Bertinaria M, Vincenti M and Di Stilo A: Multitarget antioxidant NO-donor organic nitrates: A novel approach to overcome nitrates tolerance, an ex vivo study. Antioxidants (Basel) 11: 166, 2022.
146. Chen YR, Nie SD, Shan W, Jiang DJ, Shi RZ, Zhou Z, Guo R, Zhang Z and Li YJ: Decrease in endogenous CGRP release in nitroglycerin tolerance: Role of ALDH-2. Eur J Pharmacol 571: 44-50, 2007.
147. Kim EJ, Kim SY, Lee JH, Kim JM, Kim JS, Byun JI and Koo BN: Effect of isoflurane post-treatment on tPA-exaggerated brain injury in a rat ischemic stroke model. Korean J Anesthesiol 68: 281-286, 2015.
148. Zangrillo A, Lomivorotov VV, Pasyuga VV, Belletti A, Gazivoda G, Monaco F, Nigro Neto C, Likhvantsev VV, Bradic N, Lozovskiy A, *et al*: Effect of volatile anesthetics on myocardial infarction after coronary artery surgery: A post hoc analysis of a randomized trial. J Cardiothorac Vasc Anesth 36: 2454-2462, 2022.
149. Yuan J and Fu X: MicroRNA-21 mediates the protective role of emulsified isoflurane against myocardial ischemia/reperfusion injury in mice by targeting SPP1. Cell Signal 86: 110086, 2021.
150. Ku HC, Huang CW and Lee SY: Technical refinement of a bilateral renal Ischemia-reperfusion mouse model for acute kidney injury research. J Vis Exp: Nov 3, 2023 doi: 10.3791/63957.
151. Obeid PCI, Natalini CC and Howell GE: Exposure to emulsified isoflurane and sevoflurane protects canine primary hepatocytes against hypoxia-induced apoptosis. Am J Vet Res: 1-8, 2023 doi: 10.2460/ajvr.23.08.0192 (Epub ahead of print).
152. Li H and Lang XE: Protein kinase C signaling pathway involvement in cardioprotection during isoflurane pretreatment. Mol Med Rep 11: 2683-2688, 2015.
153. Cleveland JC Jr, Meldrum DR, Rowland RT, Banerjee A and Harken AH: Adenosine preconditioning of human myocardium is dependent upon the ATP-sensitive K+ channel. J Mol Cell Cardiol 29: 175-182, 1997.
154. Zhao Z, Shi Q, Guo Q, Peng L, Li X, Rao L and Li M: Remote ischemic preconditioning can extend the tolerance to extended drug-coated balloon inflation time by reducing myocardial damage during percutaneous coronary intervention. Int J Cardiol 353: 3-8, 2022.

155. Amador A, Grande L, Marti J, Deulofeu R, Miquel R, Sola A, Rodriguez-Laiz G, Ferrer J, Fondevila C, Charco R, *et al*: Ischemic pre-conditioning in deceased donor liver transplantation: A prospective randomized clinical trial. Am J Transplant 7: 2180-2189, 2007.
156. Hardt J, Seyfried S, Brodrecht H, Khalil L, Buttner S, Herrle F, Reissfelder C and Rahbari NN: Remote ischemic preconditioning versus sham-control for prevention of anastomotic leakage after resection for rectal cancer (RIPAL trial): A pilot randomized controlled, triple-blinded monocenter trial. Int J Colorectal Dis 39: 65, 2024.
157. Ueta CB, Campos JC, Albuquerque RPE, Lima VM, Disatnik MH, Sanchez AB, Chen CH, de Medeiros MHG, Yang W, Mochly-Rosen D and Ferreira JCB: Cardioprotection induced by a brief exposure to acetaldehyde: Role of aldehyde dehydrogenase 2. Cardiovasc Res 114: 1006-1015, 2018.
158. Marino A and Levi R: Salvaging the ischemic heart: Gi-coupled receptors in mast cells activate a PKCepsilon/ALDH2 pathway providing Anti-RAS cardioprotection. Curr Med Chem 25: 4416-4431, 2018.
159. Churchill EN, Disatnik MH and Mochly-Rosen D: Time-dependent and ethanol-induced cardiac protection from ischemia mediated by mitochondrial translocation of varepsilonPKC and activation of aldehyde dehydrogenase 2. J Mol Cell Cardiol 46: 278-284, 2009.
160. Chen CH, Gray MO and Mochly-Rosen D: Cardioprotection from ischemia by a brief exposure to physiological levels of ethanol: Role of epsilon protein kinase C. Proc Natl Acad Sci USA 96: 12784-12789, 1999.
161. Kang PF, Wu WJ, Tang Y, Xuan L, Guan SD, Tang B, Zhang H, Gao Q and Wang HJ: Activation of ALDH2 with low concentration of ethanol attenuates myocardial Ischemia/Reperfusion injury in diabetes rat model. Oxid Med Cell Longev 2016: 6190504, 2016.
162. Li D, Chen J, Ai Y, Gu X, Li L, Che D, Jiang Z, Li L, Chen S, Huang H, *et al*: Estrogen-related hormones induce apoptosis by stabilizing Schlafen-12 protein turnover. Mol Cell 75: 1103-16.e9, 2019.
163. Ji E, Jiao T, Shen Y, Xu Y, Sun Y, Cai Z, Zhang Q and Li J: Molecular mechanism of HSF1-Upregulated ALDH2 by PKC in ameliorating pressure overload-induced heart failure in mice. Biomed Res Int 2020: 3481623, 2020.
164. Wang S, Wang L, Qin X, Turdi S, Sun D, Culver B, Reiter RJ, Wang X, Zhou H and Ren J: ALDH2 contributes to melatonin-induced protection against APP/PS1 mutation-prompted cardiac anomalies through cGAS-STING-TBK1-mediated regulation of mitophagy. Signal Transduct Target Ther 5: 119, 2020.
165. Luo G, Huang B, Qiu X, Xiao L, Wang N, Gao Q, Yang W and Hao L: Resveratrol attenuates excessive ethanol exposure induced insulin resistance in rats via improving NAD+ /NADH ratio. Mol Nutr Food Res: 61, 2017 doi: 10.1002/mnfr.201700087.
166. Zhang H, Xue L, Li B and Zhang Z and Tao S: Vitamin D protects against alcohol-induced liver cell injury within an NRF2-ALDH2 feedback loop. Mol Nutr Food Res 63: e1801014, 2019.
167. He JD and Parker JD: The effect of vitamin C on nitroglycerin-mediated vasodilation in individuals with and without the aldehyde dehydrogenase 2 polymorphism. Br J Clin Pharmacol 89: 2767-2774, 2023.
168. Rodriguez-Gutierrez G, Duthie GG, Wood S, Morrice P, Nicol F, Reid M, Cantlay LL, Kelder T, Horgan GW, Fernández-Bolaños Guzmán J and de Roos B: Alperujo extract, hydroxytyrosol, and 3,4-dihydroxyphenylglycol are bioavailable and have antioxidant properties in vitamin E-deficient rats-a proteomics and network analysis approach. Mol Nutr Food Res 56: 1137-1147, 2012.
169. Hosoi T, Yamaguchi R, Noji K, Matsuo S, Baba S, Toyoda K, Suezawa T, Kayano T, Tanaka S and Ozawa K: Flurbiprofen ameliorated obesity by attenuating leptin resistance induced by endoplasmic reticulum stress. EMBO Mol Med 6: 335-346, 2014.
170. Balber AE: Concise review: Aldehyde dehydrogenase bright stem and progenitor cell populations from normal tissues: Characteristics, activities, and emerging uses in regenerative medicine. Stem Cells 29: 570-575, 2011.
171. Perin EC, Silva GV, Zheng Y, Gahremanpour A, Canales J, Patel D, Fernandes MR, Keller LH, Quan X, Coulter SA, *et al*: Randomized, double-blind pilot study of transendocardial injection of autologous aldehyde dehydrogenase-bright stem cells in patients with ischemic heart failure. Am Heart J 163: 415-421.e1, 2012.
172. Perin EC, Murphy M, Cooke JP, Moye L, Henry TD, Bettencourt J, Gahremanpour A, Leeper N, Anderson RD, Hiatt WR, *et al*: Rationale and design for PACE: Patients with intermittent claudication injected with ALDH bright cells. Am Heart J 168: 667-673, 2014.
173. Perin EC, Murphy MP, March KL, Bolli R, Loughran J, Yang PC, Leeper NJ, Dalman RL, Alexander J, Henry TD, *et al*: Evaluation of cell therapy on exercise performance and limb perfusion in peripheral artery disease: The CCTRN PACE trial (Patients with intermittent claudication injected with ALDH bright cells). Circulation 135: 1417-1428, 2017.
174. Sun X, Zhu H, Dong Z, Liu X, Ma X, Han S, Lu F, Wang P, Qian S, Wang C, *et al*: Mitochondrial aldehyde dehydrogenase-2 deficiency compromises therapeutic effect of ALDH bright cell on peripheral ischemia. Redox Biol 13: 196-206, 2017.
175. Gao M, Monian P, Quadri N, Ramasamy R and Jiang X: Glutaminolysis and transferrin regulate ferroptosis. Mol Cell 59: 298-308, 2015.
176. Chan W, Taylor AJ, Ellims AH, Lefkovits L, Wong C, Kingwell BA, Natoli A, Croft KD, Mori T, Kaye DM, *et al*: Effect of iron chelation on myocardial infarct size and oxidative stress in ST-elevation-myocardial infarction. Circ Cardiovasc Interv 5: 270-278, 2012.
177. Fang X, Wang H, Han D, Xie E, Yang X, Wei J, Gu S, Gao F, Zhu N, Yin X, *et al*: Ferroptosis as a target for protection against cardiomyopathy. Proc Natl Acad Sci USA 116: 2672-2680, 2019.
178. Li W, Feng G, Gauthier JM, Lokshina I, Higashikubo R, Evans S, Kiertiburanakul S, Lee MP, Supparatpinyo K, Zhang F, *et al*: Ferroptotic cell death and TLR4/Trif signaling initiate neutrophil recruitment after heart transplantation. J Clin Invest 129: 2293-2304, 2019.
179. Li Y, Feng D, Wang Z, Zhao Y, Sun R, Tian D, Liu D, Zhang F, Ning S, Yao J and Tian X: Ischemia-induced ACSL4 activation contributes to ferroptosis-mediated tissue injury in intestinal ischemia/reperfusion. Cell Death Differ 26: 2284-2299, 2019.
180. Liu B, Zhao C, Li H, Chen X, Ding Y and Xu S: Puerarin protects against heart failure induced by pressure overload through mitigation of ferroptosis. Biochem Biophys Res Commun 497: 233-240, 2018.
181. Yu W, An S, Shao T, Xu H, Chen H, Ning J, Zhou Y and Chai X: Active compounds of herbs ameliorate impaired cognition in APP/PS1 mouse model of Alzheimer's disease. Aging (Albany NY) 11: 11186-11201, 2019.
182. Eleftheriadis T, Pissas G, Filippidis G, Liakopoulos V and Stefanidis I: Reoxygenation induces reactive oxygen species production and ferroptosis in renal tubular epithelial cells by activating aryl hydrocarbon receptor. Mol Med Rep 23: 41, 2021.
183. Chen K, Xu Z, Liu Y, Wang Z, Li Y, Xu X, Chen C, Xia T, Liao Q, Yao Y, *et al*: Irisin protects mitochondria function during pulmonary ischemia/reperfusion injury. Sci Transl Med 9: eaao6298, 2017.
184. Lu J, Xu F and Lu H: LncRNA PVT1 regulates ferroptosis through miR-214-mediated TFR1 and p53. Life Sci 260: 118305, 2020.
185. Stamenkovic A, O'Hara KA, Nelson DC, Maddaford TG, Edel AL, Maddaford G, Dibrov E, Aghanoori M, Kirshenbaum LA, Fernyhough P, *et al*: Oxidized phosphatidylcholines trigger ferroptosis in cardiomyocytes during ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 320: H1170-H1184, 2021.
186. Tuo QZ, Lei P, Jackman KA, Li XL, Xiong H, Li XL, Liuyang ZY, Roisman L, Zhang ST, Ayton S, *et al*: Tau-mediated iron export prevents ferroptotic damage after ischemic stroke. Mol Psychiatry 22: 1520-1530, 2017.
187. Wu S, Yang J, Sun G, Hu J, Zhang Q, Cai J, Yuan D, Li H, Hei Z and Yao W: Macrophage extracellular traps aggravate iron overload-related liver ischaemia/reperfusion injury. Br J Pharmacol 178: 3783-3796, 2021.
188. Friedmann Angeli JP, Schneider M, Proneth B, Tyurina YY, Tyurin VA, Hammond VJ, Herbach N, Aichler M, Walch A, Eggenhofer E, *et al*: Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. Nat Cell Biol 16: 1180-1191, 2014.
189. Xu Y, Li X, Cheng Y, Yang M and Wang R: Inhibition of ACSL4 attenuates ferroptotic damage after pulmonary ischemia-reperfusion. FASEB J 34: 16262-16275, 2020.

190. Yamada N, Karasawa T, Wakiya T, Sadatomo A, Ito H, Kamata R, Watanabe S, Komada T, Kimura H, Sanada Y, *et al*: Iron overload as a risk factor for hepatic Ischemia-Reperfusion injury in liver transplantation: Potential role of ferroptosis. Am J Transplant 20: 1606-1618, 2020.
191. Zhou L, Xue X, Hou Q and Dai C: Targeting ferroptosis attenuates interstitial inflammation and kidney fibrosis. Kidney Dis (Basel) 8: 57-71, 2022.
192. Tu H, Zhou YJ, Tang LJ, Xiong XM, Zhang XJ, Ali Sheikh MS, Zhang JJ, Luo XJ, Yuan C and Peng J: Combination of ponatinib with deferoxamine synergistically mitigates ischemic heart injury via simultaneous prevention of necroptosis and ferroptosis. Eur J Pharmacol 898: 173999, 2021.
193. Shi Y, Han L, Zhang X, Xie L, Pan P and Chen F: Selenium alleviates cerebral Ischemia/reperfusion injury by regulating oxidative stress, mitochondrial fusion and ferroptosis. Neurochem Res 47: 2992-3002, 2022.
194. Lv Z, Wang F, Zhang X, Zhang X, Zhang J and Liu R: Etomidate attenuates the ferroptosis in myocardial Ischemia/Reperfusion rat model via Nrf2/HO-1 pathway. Shock 56: 440-449, 2021.
195. Yang J, Sun X, Huang N, Li P, He J, Jiang L, Zhang X, Han S and Xin H: Entacapone alleviates acute kidney injury by inhibiting ferroptosis. FASEB J 36: e22399, 2022.
196. Chen Y, He W, Wei H, Chang C, Yang L, Meng J, Long T, Xu Q and Zhang C: Srs11-92, a ferrostatin-1 analog, improves oxidative stress and neuroinflammation via Nrf2 signal following cerebral ischemia/reperfusion injury. CNS Neurosci Ther 29: 1667-1677, 2023.
197. Li C and Liu Y: Puerarin reduces cell damage from cerebral ischemia-reperfusion by inhibiting ferroptosis. Biochem Biophys Res Commun 693: 149324, 2024.
198. Ding Y, Li W, Peng S, Zhou G, Chen S, Wei Y, Xu J, Gu H, Li J, Liu S and Liu B: Puerarin protects against myocardial Ischemia/Reperfusion injury by inhibiting ferroptosis. Biol Pharm Bull 46: 524-532, 2023.
199. Guan X, Li X, Yang X, Yan J, Shi P, Ba L, Cao Y and Wang P: The neuroprotective effects of carvacrol on ischemia/reperfusion-induced hippocampal neuronal impairment by ferroptosis mitigation. Life Sci 235: 116795, 2019.
200. Fu C, Wu Y, Liu S, Luo C, Lu Y, Liu M, Wang L, Zhang Y and Liu X: Rehmannioside A improves cognitive impairment and alleviates ferroptosis via activating PI3K/AKT/Nrf2 and SLC7A11/GPX4 signaling pathway after ischemia. J Ethnopharmacol 289: 115021, 2022.
201. Yang T, Liu H, Yang C, Mo H, Wang X, Song X, Jiang L, Deng P, Chen R, Wu P, *et al*: Galangin attenuates myocardial ischemic Reperfusion-Induced ferroptosis by targeting Nrf2/Gpx4 signaling pathway. Drug Des Devel Ther 17: 2495-2511, 2023.
202. Guo H, Zhu L, Tang P, Chen D, Li Y, Li J and Bao C: Carthamin yellow improves cerebral ischemia-reperfusion injury by attenuating inflammation and ferroptosis in rats. Int J Mol Med 47: 52, 2021.
203. Yuan Y, Zhai Y, Chen J, Xu X and Wang H: Kaempferol ameliorates Oxygen-glucose deprivation/reoxygenation-induced neuronal ferroptosis by activating Nrf2/SLC7A11/GPX4 Axis. Biomolecules 11: 923, 2021.
204. Lin JH, Yang KT, Ting PC, Luo YP, Lin DJ, Wang YS and Chang JC: Gossypol acetic acid attenuates cardiac ischemia/reperfusion injury in rats via an antiferroptotic mechanism. Biomolecules 11: 1667, 2021.
205. Du YW, Li XK, Wang TT, Zhou L, Li HR, Feng L, Ma H and Liu HB: Cyanidin-3-glucoside inhibits ferroptosis in renal tubular cells after ischemia/reperfusion injury via the AMPK pathway. Mol Med 29: 42, 2023.
206. Xu S, Wu B, Zhong B, Lin L, Ding Y, Jin X, Huang Z, Lin M, Wu H and Xu D: Naringenin alleviates myocardial ischemia/reperfusion injury by regulating the nuclear factor-erythroid factor 2-related factor 2 (Nrf2)/System xc-/glutathione peroxidase 4 (GPX4) axis to inhibit ferroptosis. Bioengineered 12: 10924-10934, 2021.
207. Li T, Tan Y, Ouyang S, He J and Liu L: Resveratrol protects against myocardial ischemia-reperfusion injury via attenuating ferroptosis. Gene 808: 145968, 2022.
208. Zhu H, Huang J, Chen Y, Li X, Wen J, Tian M, Ren J, Zhou L and Yang Q: Resveratrol pretreatment protects neurons from oxygen-glucose deprivation/reoxygenation and ischemic injury through inhibiting ferroptosis. Biosci Biotechnol Biochem 86: 704-716, 2022.
209. Wang X, Shen T, Lian J, Deng K, Qu C, Li E, Li G, Ren Y, Wang Z, Jiang Z, *et al*: Resveratrol reduces ROS-induced ferroptosis by activating SIRT3 and compensating the GSH/GPX4 pathway. Mol Med 29: 137, 2023.
210. Zhang J, Bi J, Ren Y, Du Z, Li T, Wang T, Zhang L, Wang M, Wei S, Lv Y and Wu R: Involvement of GPX4 in irisin's protection against ischemia reperfusion-induced acute kidney injury. J Cell Physiol 236: 931-945, 2021.