Research status and molecular mechanisms of disulfidptosis in cardiovascular diseases (Review)

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Abstract. Cardiovascular diseases (CVDs) remain the primary cause of death worldwide. Exploring novel therapeutic targets is important for defining future research directions in cardiovascular medicine. Considering the notable role of cell death in disease pathogenesis, targeting disulfidptosis may represent a valuable therapeutic strategy for CVDs. However, current research increasingly centers on cancer, and the role of disulfidptosis in the cardiovascular field remains insufficiently explored. Accordingly, the present review examines the mechanisms of disulfidptosis across different cardiac cell types: Cardiomyocytes, vascular smooth muscle cells, endothelial cells and fibroblasts. Furthermore, the review discusses existing evidence for disulfidptosis in CVDs and potential intervention strategies, aiming to provide new perspectives for preventing and treating CVDs.

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1. Introduction

In 2023, the World Heart Federation released the World Heart Report, which highlighted that cardiovascular diseases (CVDs) will remain the primary cause of death globally for decades (1). In 2023, Liu *et al* (2) identified a novel form of cell death termed disulfidptosis, which is triggered in cells with high expression of the cystine transporter solute carrier family 7 member 11 (SLC7A11) under glucose deprivation. Elevated SLC7A11 levels increase cystine uptake; however, under glucose-deficient or oxidative stress conditions, the depletion of nicotinamide adenine dinucleotide phosphate (NADPH) impairs the reduction of cystine to cysteine. This leads to disulfide stress (3), causing cytoskeletal dysfunction and, ultimately, cell death.

Since disulfidptosis was first discovered in cancer cells, existing studies have primarily focused on its role in oncology (4,5). Nevertheless, emerging research has suggested a potential link between disulfidptosis and CVDs (6-9). Disulfide stress, a key step in disulfidptosis, promotes antioxidant system collapse and reactive oxygen species (ROS) accumulation, exacerbating oxidative stress and potentially triggering cellular inflammation, autophagy and other pathological processes through cascade signaling pathways, worsening CVD progression (10). Given these findings, the present review aimed to explore the molecular mechanisms of disulfidptosis, emphasizing its pathophysiological impact on CVDs, and discussing novel perspectives for prevention and therapeutic intervention.

2. Search strategy

The present study is a narrative review, aiming to provide a comprehensive and critical discussion on the current research status, molecular mechanisms and potential implications of the novel cell death modality disulfidptosis in the field of CVDs. The PubMed database (https://pubmed.ncbi.nlm.nih.gov/) was searched using the following search strategy: [‘disulfidptosis’ (Title/Abstract) OR ‘disulfide stress’ (Title/Abstract) OR ‘SLC7A11’ (Title/Abstract) OR ‘xCT’ (Title/Abstract) OR ‘system Xc-’ (Title/Abstract)] AND [‘cardiovascular’ (Title/Abstract) OR ‘heart’ (Title/Abstract) OR ‘myocardial’ (Title/Abstract) OR ‘cardiomyocyte’ (Title/Abstract) OR ‘vascular smooth muscle cell’ (Title/Abstract) OR ‘endothelial cell’ (Title/Abstract) OR ‘fibroblast’ (Title/Abstract)

OR 'atherosclerosis' (Title/Abstract) OR 'ischemia' (Title/Abstract) OR 'heart failure' (Title/Abstract)]. The present review primarily focused on original research articles, reviews, commentaries, and letters related to the molecular mechanisms of disulfidptosis and its potential role in CVDs, including myocardial infarction (MI), heart failure, aortic dissection and hypertrophic cardiomyopathy. The search was limited to articles published in English.

3. Disulfidptosis

SLC7A11: Core of disulfidptosis. SLC7A11regulates the uptake of extracellular cystine concurrent with the secretion of intracellular glutamate (11), a subunit of the cystine/glutamate antiporter system Xc-(xCT). Within the cell, cystine is reduced to cysteine, which is the rate-limiting precursor for glutathione (GSH) synthesis. GSH, a tripeptide composed of cysteine, glutamate and glycine, is the primary intracellular antioxidant. GSH effectively neutralizes ROS and maintains redox homeostasis (12).

Under glucose-sufficient conditions, NADPH generated via the pentose phosphate pathway (PPP) and glycolysis-tricarboxylic acid cycle coupling facilitates the reduction of cystine to cysteine, promoting GSH synthesis and antioxidant defense (13). However, glucose deprivation suppresses PPP activity, impairs NADPH production and halts cystine reduction. This leads to intracellular cystine accumulation (14). SLC7A11 acts as the trigger switch for disulfidptosis as its upregulation drives excessive cystine uptake. Disulfide stress is directly induced by glucose deficiency (2), initiating a disulfidptosis cascade (Fig. 1).

Actin cytoskeleton: The ultimate target of disulfide cross-linking. The actin cytoskeleton is a biopolymeric network composed primarily of microtubules, microfilaments and intermediate filaments. It provides structural rigidity and is required for diverse mechanical functions, including cell motility, shape changes, division, mechanosensing and tension homeostasis (15). Actin maintains cytoskeletal dynamics by forming filamentous actin (F-actin) (15). Key cysteine residues, such as Cys374 in actin (16), and Cys988 and Cys1379 in non-muscle myosin heavy chain (MYH)9 (2), as well as other cytoskeletal proteins, such as vinculin, are rich in free thiol (-SH) groups. Under conditions of disulfide stress, such as SLC7A11 upregulation and glucose deprivation, these-SH groups undergo spontaneous oxidation, leading to aberrant intra- and intermolecular disulfide bond formation in globular actin (17). This disrupts dynamic polymerization and causes F-actin rigidification.

Further experiments have revealed that glucose starvation induces F-actin retraction from the cell cortex and stress fibers, physically detaching it from the plasma membrane. This demonstrates that the actin network, a sensitive target, loses its dynamic equilibrium due to disulfide crosslinking, ultimately resulting in cytoskeletal collapse and cell death (2).

WAVE regulatory complex (WRC) complex and Rac1: Amplifiers of disulfidptosis. In disulfidptosis, the WRC and Rac1 GTPase act as synergistic amplifiers of cytoskeletal collapse, notably exacerbating the lethal effects of disulfide stress. Rac1, a member of the Rho GTPase family, serves as a fundamental regulator of the actin cytoskeleton and serves important roles in cell motility, polarity and migration (18). Rac1 has also been implicated in CVDs (19). The WRC is a pentameric complex comprising Nck-associated protein 1 (NCKAP1), WAVE proteins such as WAVE2, cytoplasmic FMR1-interacting protein (CYFIP)1/2, Abl interactor 2 and protein BRICK1 (20). Rac1 activates WAVE proteins by interacting with the WRC component CYFIP1/2, which subsequently recruits and activates the actin-related protein 2/3 complex via the WRC's VCA (verprolin-homology, cofilin-homology, acidic) domain (21). This process drives F-actin nucleation and lamellipodia formation (22).

Recent studies have revealed that NCKAP1-deficient cells (UMRC6 cells) maintain normal SLC7A11 levels, cystine uptake and $NADP^+$:NADPH ratios, and exhibit attenuated glucose starvation-induced disulfide bond formation, F-actin retraction and plasma membrane detachment. Conversely, in *in vitro* experiments using cancer cell lines with high SLC7A11 expression, overexpression of a constitutively active Rac1 mutant promotes lamellipodia formation and exacerbates disulfidptosis. These findings demonstrate that Rac1/WRC-mediated lamellipodia formation accelerates disulfidptosis, likely because the branched actin networks within lamellipodia provide important substrates for additional disulfide cross-linking between cytoskeletal proteins (2).

4. Crosstalk between disulfidptosis and ferroptosis

In the complex pathology of CVDs, disulfidptosis is likely to form intricate dialogue networks with other cell death modalities, collectively determining cellular fate and tissue outcome. The present review focused primarily on the crosstalk between disulfidptosis and ferroptosis, as disulfidptosis and ferroptosis share the most direct and close relationship. Similar to disulfidptosis, ferroptosis is notably linked to SLC7A11 and GSH (23).

In 2003, Dolma *et al* (24) discovered a novel compound, erastin, which could selectively eliminate tumor cells that expressed SV40 large T antigen (ST) and mutant Ras. This induced a new non-apoptotic form of cell death. In 2008, Yang and Stockwell (25) discovered two new compounds: RSL5 and RSL3. Similar to erastin, these compounds induced the iron-dependent, non-apoptotic cell death of tumor cells containing mutant Ras, which could be inhibited by the iron chelator deferoxamine and vitamin E. In 2012, the Stockwell laboratory formally named this cell death process ferroptosis (26).

Morphologically, ferroptosis is characterized by the loss of plasma membrane integrity, cell membrane rupture, mitochondrial shrinkage, rupture of the mitochondrial outer membrane, reduction or loss of cristae, and increased membrane thickening (27). At the molecular level, the key cause of ferroptosis is the inactivation of GSH peroxidase 4 (GPX4) (28). This results in failure to clear lipid peroxides promptly, which are subsequently catalyzed by divalent iron ions (Fe^{2+}) via the Fenton reaction (29), ultimately damaging the integrity of the cell membrane system.

Initially, the inhibition of xCT on the cell membrane, whose key component is SLC7A11, prevents cystine uptake. This

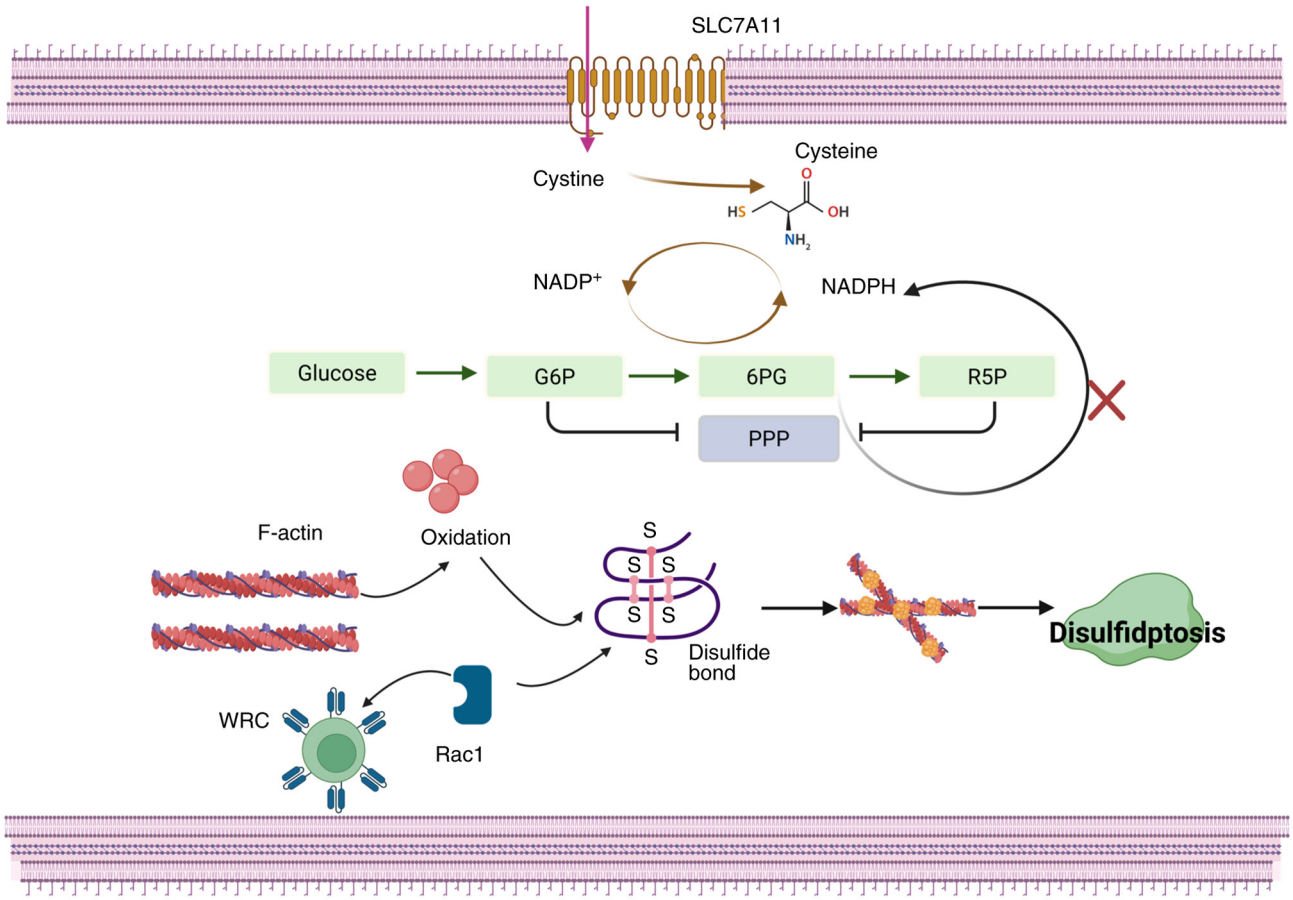

Figure 1. Disulfidptosis mechanism. The cystine transporter SLC7A11 imports extracellular cystine. Under glucose-sufficient conditions, NADPH produced via the PPP and glycolysis-tricarboxylic acid cycle coupling supports cystine reduction to cysteine. Glucose deprivation suppresses PPP activity, depleting NADPH, halting cystine reduction and leading to cystine accumulation. The resulting disulfide stress causes spontaneous oxidation of free sulfhydryl groups on F-actin, forming aberrant intra- and intermolecular disulfide bonds. This crosslinking disrupts the actin cytoskeleton, ultimately triggering cell death. The WRC and Rac1 GTPase accelerate disulfidptosis by promoting lamellipodia formation, which provides additional actin networks for disulfide crosslinking in SLC7A11-upregulated cells. G6P, glucose 6-phosphate; 6PG, 6-phosphogluconate; R5P, ribose 5-phosphate; WRC, WAVE regulatory complex; SLC7A11, solute carrier family 7 member 11; F-actin, filamentous actin; NADPH, nicotinamide adenine dinucleotide phosphate; PPP, pentose phosphate pathway.

leads to intracellular cysteine depletion and an insufficient amount of raw material for GSH synthesis (30). Consequently, GPX4 becomes functionally stagnant due to the lack of its required cofactor (30). Long-chain polyunsaturated fatty acids (PUFAs), such as arachidonic acid, are recognized and activated by acyl-CoA synthetase long chain family member 4 (31). Subsequently, under the action of lysophosphatidylcholine acyltransferase 3 (32), they are esterified and incorporated into membrane phospholipids. This results in cellular membranes, especially plasma and mitochondrial membranes, being enriched with PUFA-containing phospholipids (PUFA-PLs), which are notably susceptible to oxidation due to their bis-allylic structures (33). These membrane PUFA-PLs are catalyzed by various oxidase systems, generating phospholipid hydroperoxides (PL-PUFA-OOH) (34). Unstable intracellular Fe^{2+}, via the Fenton reaction, convert PL-PUFA-OOH into highly reactive lipid radicals and lipid peroxyl radicals. Ferroptosis occurs when the clearance capacity of GPX4 is overwhelmed by the generation of lipid peroxides. In this process, the inhibition of SLC7A11 is one of the primary causes of GPX4 inactivation (35).

Under glucose starvation conditions, high SLC7A11 expression steers cells toward disulfidptosis, whereas if SLC7A11 is inhibited, cells tend to undergo ferroptosis. Thus, SLC7A11 acts as a common molecular switch for disulfidptosis and ferroptosis. In this way, cell fate depends on SLC7A11 activity and glucose availability (36). Simultaneously, the depletion of GSH during disulfidptosis creates a reduced cellular environment that is prone to ferroptosis. Furthermore, the disruption of cell membrane integrity caused by disulfidptosis might accelerate the diffusion of lipid peroxides and, thus, the process of ferroptosis (37).

5. Cell types and disulfidptosis in the cardiovascular system

The heart comprises intricately coordinated cell types, including contractile cardiomyocytes, pacemaker cells, supporting cells, immune cells and neural cells (38). Understanding the characteristics and interaction mechanisms of disulfidptosis in these cells is important for investigating CVD pathogenesis and developing targeted therapies. The following section discusses the effects of disulfidptosis on cardiomyocytes, vascular smooth muscle cells (VSMCs), endothelial cells (ECs), fibroblasts and macrophages (Fig. 2).

Cardiomyocytes. As terminally differentiated cells, cardiomyocytes rely on stable oxidative metabolism and intact

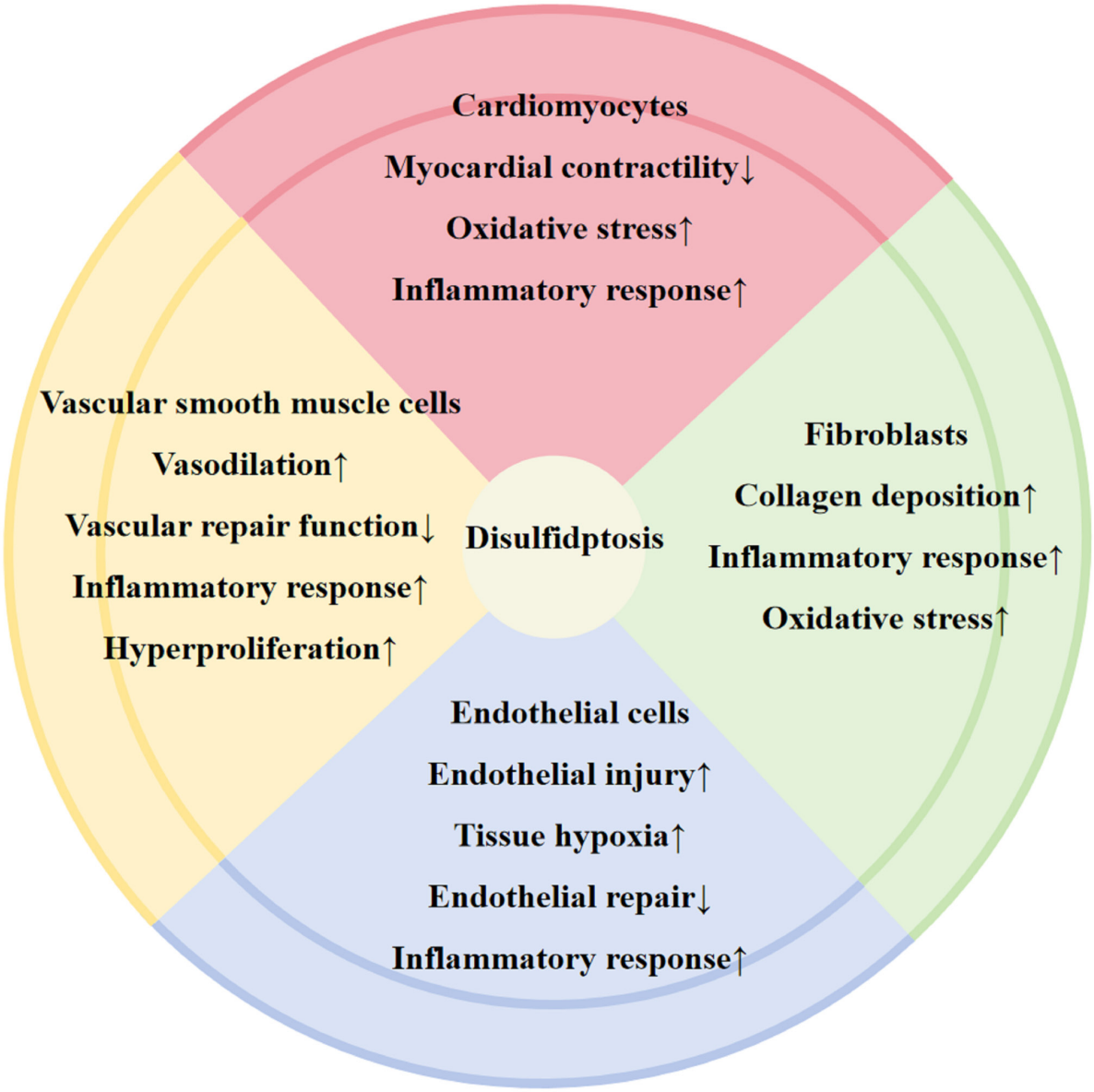

Figure 2. Disulfidptosis in the cardiovascular system.

cytoskeletal structure to maintain contractile function, making them notably susceptible to disulfidptosis. Cardiac contraction depends on cyclic contraction-relaxation generated by interactions between actin-based thin filaments and myosin thick filaments (39). Actin is the cytoskeletal protein most vulnerable to aberrant disulfide bonds in disulfidptosis, leading to actin intermolecular cross-linking and disruption of myofibrils in cardiomyocytes (40). Loss of disulfide homeostasis leads to cytoskeletal disintegration, causing morphological alterations in cardiomyocytes, such as shrinkage and fragmentation, that directly impair contractility and cardiac function (41). Additionally, disulfidptosis exacerbates oxidative stress and energy metabolism disorders (42). Cardiomyocytes exhibit high oxidative metabolism, generate ROS and require high GSH levels (43). However, GSH depletion in disulfidptosis induces oxidative stress in cardiomyocytes, damaging mitochondria and ultimately rendering ATP production insufficient to sustain contraction (44). Concurrently, oxidative stress activates pro-inflammatory signaling, such as the NF-κB pathway, in cardiomyocytes, promoting the release of cytokines, such as TNF-α and IL-6, which exacerbate local inflammation (45). Disulfidptosis-induced cardiomyocyte death is irreversible. Dying cells release damage-associated molecular patterns (DAMPs) that recruit immune cells such as macrophages, triggering excessive inflammation and secondary cardiomyocyte injury (46).

VSMCs. As the predominant cell type in the medial layer of blood vessels, VSMCs maintain vascular tone and participate in vascular remodeling, which includes processes such as contraction, proliferation and migration; these processes depend on stable redox homeostasis and dynamic cytoskeletal organization (47). The disulfide stress inherent to disulfidptosis could directly conflict with the redox-dependent activation mechanism of NADPH oxidase 1 (NOX1) in VSMCs. Specifically, the aberrant intermolecular disulfide bonding that characterizes disulfidptosis may competitively disrupt or dysregulate the precise formation of intermolecular disulfide

bonds between protein disulfide isomerase and p47phox, a known prerequisite for NOX1 activation. If NOX1 activity is thereby compromised, the resulting alteration in cellular redox balance could, in turn, affect the NADPH-mediated reduction of cystine to cysteine. This potential crosstalk suggests a mechanism whereby disulfidptosis might influence cellular redox signaling and cyst(e)ine metabolism through interference with NOX1 function (48). Disulfidptosis may markedly disrupt vascular homeostasis by targeting important physiological processes in VSMCs. VSMC contraction relies on phosphorylation of myosin light chain (MLC), which is mediated by MLC kinase (MLCK) (49). During disulfidptosis, GSH depletion elevates the intracellular oxidative potential, leading to the oxidation of free-SH groups in MLCK and the formation of abnormal disulfide bonds (50). This results in reduced or abolished enzymatic activity, impaired MLC phosphorylation and consequent vascular dysfunction, manifesting as excessive vasodilation or regional blood flow disturbances due to uneven contractility (51).

VSMC migration, proliferation and injury repair require the dynamic remodeling of cytoskeletal components, including microtubules and microfilaments (52). During disulfidptosis, the oxidation of -SH groups in tubulin and actin promotes aberrant protein polymerization through intermolecular disulfide bonding. For example, actin filaments may irreversibly cross-link into bundled structures, causing cytoskeletal rigidity (2). This stiffness inhibits VSMC migratory capacity and compromises vascular repair mechanisms (53). Dying VSMCs release DAMPs that recruit inflammatory cells, such as macrophages and monocytes, and initiate local inflammation (54). The cytokines secreted by these inflammatory cells, such as platelet-derived growth factor (PDGF) and TGF-β, act on surviving vascular smooth muscle cells (VSMCs), promoting their transition to a synthetic phenotype and enhancing proliferation, thereby exacerbating vascular wall thickening. PDGF and TGF-β primarily drive the phenotypic switch of VSMCs from a 'contractile' to a 'synthetic' state by regulating gene expression, intracellular signaling and cytoskeletal remodeling (55).

ECs. ECs are important for cardiovascular homeostasis, serving as a selective barrier between blood and tissues, and regulating vascular tone, anticoagulation, inflammatory responses and tissue perfusion (56). As their functions are highly dependent on an intact cytoskeleton and a precise redox balance, ECs may represent another notable target for the pathological effects of disulfidptosis. The following section extrapolates potential dysfunctions in ECs based on the core biochemical mechanisms of disulfidptosis, aberrant protein disulfide crosslinking and reductive power failure.

Members of the Rho family of guanine nucleotide exchange factors act as key regulators of Rho GTPase activity and differentially activate small GTPases, such as Rac1, a protein implicated in disulfidptosis. These Rho GTPases are primarily involved in actin cytoskeleton remodeling. In ECs, they modulate junctional stability, and serve important roles in angiogenesis and the maintenance of endothelial barrier integrity (57). Tight and adherens junctions form the structural basis of endothelial barrier integrity. It can be logically extrapolated that the pervasive oxidative-reductive imbalance and protein disulfide stress occurring during disulfidptosis could target the important sulfhydryl-rich domains of the relevant junctional proteins. If abnormal intra- or intermolecular disulfide crosslinking occurs, it directly disrupts the structure and function of junctional complexes, leading to abnormal increases in endothelial permeability (58). The consequence is plasma extravasation, which causes tissue edema and provides a pathway for the extravasation of inflammatory cells, such as neutrophils, exacerbating local inflammation (59). ECs regulate vasodilation primarily through nitric oxide (NO) production, which is catalyzed by endothelial NO synthase (eNOS). The activity of eNOS is strictly dependent on the reduced state of certain amino acid residues (60). Therefore, it is reasonable to hypothesize that the GSH depletion and ROS accumulation accompanying disulfidptosis alter the redox modification status of eNOS, impairing its function and leading to decreased NO bioavailability (61,62). Insufficient NO generation triggers abnormal microvascular constriction and reduced blood perfusion, such as in the myocardial or cerebral microcirculation, aggravating tissue hypoxia and promoting disease progression (63).

A healthy endothelium maintains an anticoagulant phenotype through the surface expression of molecules such as thrombomodulin (64). Extrapolating from the general outcome of cell damage caused by disulfidptosis: EC death or dysfunction exposes the pro-thrombotic subendothelial matrix and activates platelets and the coagulation cascade, predisposing patients to local thrombosis and exacerbating ischemia (65). Simultaneously, dying or stressed ECs secrete DAMPs, such as high mobility group box 1. These molecules can activate innate immune cells, including macrophages and neutrophils, amplifying the release of pro-inflammatory cytokines, such as IL-1β and TNF-α, via pathways such as the NF-κB pathway, establishing a cycle of endothelial damage, inflammation and thrombosis (65). Although the endothelium possesses a certain capacity for regeneration and repair, it has been extrapolated that disulfidptosis may hinder this process through two potential mechanisms: i) Abnormal crosslinking of cytoskeletal proteins, such as actin and tubulin, could directly impair the migratory capacity of surviving ECs toward the injury site; and ii) the persistent oxidative stress and inflammatory microenvironment triggered by disulfidptosis may suppress the mobilization, homing and differentiation of endothelial progenitor cells (66). Prolonged impairment of repair leaves the vascular wall continuously exposed to detrimental stimuli, creating conditions conducive to abnormal VSMC proliferation, lipid depositions and pathological vascular remodeling (67).

Fibroblasts. Fibroblasts are the central cells responsible for producing and remodeling the extracellular matrix (ECM), and their dysfunction is a notable factor in the fibrosis of tissues such as the myocardium and blood vessels. The ECM is a dynamic network composed of collagen, including types I, III and IV, fibronectin, laminin, elastin and proteoglycans. An imbalance between ECM synthesis and degradation is key to the development of fibrosis (68).

Based on the core characteristics of disulfidptosis, involving the collapse of intracellular reductive power, which is caused by factors such as GSH depletion and a decreased

$NADPH:NADP^+$ ratio, and the consequent risk of widespread protein oxidation and aberrant disulfide bond formation, a testable scientific hypothesis can be proposed: This abnormal redox environment may disrupt the normal metabolic balance of ECM in fibroblasts. The synthesis and secretion of ECM components such as collagen is a multistep, intricate process involving enzymes such as prolyl hydroxylase, which catalyzes post-translational modifications in the endoplasmic reticulum (69). It is hypothesized that the activity of these enzymes could be impaired if their important sulfhydryl groups are oxidized, or if the function of the cytoskeletal and vesicular transport systems, such as tubulin-dependent dynein transport, that are responsible for intracellular trafficking were hindered due to abnormal protein crosslinking. Theoretically, this could affect the proper processing and secretion of procollagen (70).

ECM degradation is primarily performed by the matrix metalloproteinase (MMP) family. Their catalytic centers contain conserved cysteine residues within the zinc-binding domain, which must remain in a reduced state for enzymatic activity (71). Therefore, it is reasonable to speculate that the highly oxidative environment induced by disulfidptosis could oxidize these key sulfhydryl groups, potentially inhibiting MMP activity. If the synthesis and degradation pathways are concurrently disrupted, it could theoretically lead to increased net deposition of ECM, which is a hallmark of fibrosis (72). Another potential link between disulfidptosis and the fibrotic process may be established through abnormal fibroblast activation and the inflammatory microenvironment. Oxidative stress induces fibroblast activation and transformation into highly secretory myofibroblasts (73). Consequently, it has been hypothesized that the GSH depletion and ROS accumulation accompanying early-stage disulfidptosis may activate signaling pathways such as the NF-κB pathway within fibroblasts, promoting the expression of pro-fibrotic factors such as TGF-β. This could drive fibroblasts toward a pathological phenotype in a paracrine or autocrine manner (31). When disulfidptosis reaches the threshold of cellular collapse, fibroblast lysis and the subsequent release of DAMPs can recruit and activate immune cells such as macrophages, initiating and perpetuating local chronic inflammation. Notably, chronic inflammation is a key driver of fibrosis progression (74).

6. Evidence for disulfidptosis in CVDs

In a recent study, a natural resin extracted from Dracaena cochinchinensis demonstrated anti-inflammatory and neuroprotective properties against ischemic brain injury. Molecular docking analysis suggested that this resin may downregulate genes associated with disulfidptosis, including *Flna*, *Iqgap1*, *Tln1* and *Myh9*. This indicates that its neuroprotective effects may be achieved through modulating these genes and thereby potentially influencing the disulfidptosis pathway. However, whether disulfidptosis is directly involved in mediating the resin's effects requires further experimental confirmation (75).

In the context of type A aortic dissection (TAAD), a recent study utilized machine learning to analyze disulfidptosis-related genes. Compared with healthy controls, CAPZB, PDLIM1, and MYH10 were identified as three hub genes, all of which exhibited lower expression levels in TAAD samples. This study also revealed marked differences in immune cell infiltration in TAAD tissues. These associative findings suggested that alterations in the expression of disulfidptosis-related genes may have been linked to changes in the immune microenvironment of TAAD; however, the specific causal mechanisms underlying this association warrant further investigation (8).

Regarding ischemic cardiomyopathy (IC), Tan *et al* (7) utilized bioinformatics and machine learning approaches to identify *MYH9*, *NUBPL*, *MYL6*, *MYH10* and *NCKAP1* as potential diagnostic biomarkers. These genes were associated with processes such as myocardial structure and immune cell infiltration. A diagnostic model based on these five genes demonstrated high predictive accuracy across multiple datasets, which was supported by preliminary validation in a mouse model of IC. Notably, this study primarily provided associative evidence at the gene expression level and has not directly confirmed the occurrence of disulfidptosis as a cell death event in IC models (7). Furthermore, studies on other CVDs, such as heart failure and hypertrophic cardiomyopathy, have observed changes in the expression of disulfidptosis-related genes, implying a potential association between disulfidptosis and CVDs (6,9,76).

In summary, thus far, research has predominantly focused on bioinformatics analyses and associative validation of expression changes in disulfidptosis-related genes across various CVDs. These findings offer important evidence and hypotheses that disulfidptosis may be involved in the pathological processes of CVDs. However, it must be emphasized that the association between these pathologies at the gene expression level does not equate to the functional activation of this cell death program. There is still a lack of key experimental evidence that directly confirms the occurrence of disulfidptosis, such as by detecting characteristic protein disulfide cross-linking and cytoskeletal collapse, in CVD models, both *in vivo* and *in vitro*. Therefore, future research should move beyond associative analyses and focus on verifying the specific mechanistic role of disulfidptosis in CVDs through direct molecular and functional experiments (Table I) (6-9,75).

7. Therapeutic targets and intervention strategies

Directly inhibiting SLC7A11 activity may be an effective approach for ameliorating disulfidptosis. SLC7A11 is the specific subunit of the xCT transporter on the cell membrane that is responsible for exchanging extracellular cystine for intracellular glutamate. Sulfasalazine, which is similar to the known xCT inhibitor erastin, effectively inhibits the expression and transport function of xCT, leading to GSH depletion in MDA-MB-231 and MDA-MB-468 cells (triple-negative breast cancer cell lines) (77). This mechanism has been shown to improve heart failure (78).

Furthermore, supplementing NAD^+ represents another therapeutic strategy. NAD is a notable coenzyme required for cellular energy metabolism and redox homeostasis (79). Supplementation with NAD precursors can markedly increase myocardial NAD levels, improving cardiac function (80-82). Also, activators of malic enzyme can promote NADPH generation (83), which has been shown to alleviate pulmonary hypertension (84,85).

As disulfide bond formation is central to disulfidptosis, reducing the formation of aberrant disulfide bonds is

Table I. Summary of bioinformatics and experimental studies linking disulfidptosis to specific cardiovascular diseases.

First author, year	Study model or source of evidence	Key findings	Evidence strength and rationale	(Refs.)
Fan *et al*, 2024	Bioinformatics: Publicly available datasets from patients with HCM.	Discovered differential expression of disulfidptosis-related genes in HCM and constructed an associated risk model.	Medium: Bioinformatics associations provided preliminary evidence for a transcriptional link between disulfidptosis and HCM.	(6)
Tan *et al*, 2025	1. Bioinformatics: Human myocardial tissue transcriptomic data for IC from the GEO database. 2. *In vivo* validation: Mouse model of IC.	1. Identified a diagnostic gene signature, including MYH9, NUBPL, MYL6, MYH10 and NCKAP1, related to disulfidptosis in IC. 2. Observed concordant mRNA expression trends for some key genes in mouse myocardial tissue.	Medium: Strong bioinformatics associations with diagnostic potential were observed and preliminary *in vivo* mRNA-level validation was obtained in a disease model. Direct evidence of protein-level modification and a functional demonstration of disulfide disulfidptosis in cardiomyocytes was lacking.	(7)
Wang *et al*, 2025	Bioinformatics: Transcriptomic data from patients with TAAD vs. normal aortic tissues.	Identified disulfidptosis-related genes, such as *CAPZB*, *PDLIM1* and *MYH10*, which were differentially expressed in TAAD, and associated with immune cell infiltration and metabolic alterations.	Medium: Bioinformatics associations suggested a potential link between disulfidptosis-related gene expression and TAAD pathology. Requires functional validation to establish causality.	(8)
Zhao *et al*, 2024	Bioinformatics: Publicly available datasets of patients with HF.	Revealed that disulfidptosis-related genes were associated with characteristics of the immune microenvironment in HF.	Medium: Bioinformatics associations indicated a potential role of disulfidptosis-related pathways in the immune landscape of HF.	(9)
Xu *et al*, 2025	1. *In vivo*: Mouse model of ischemic brain injury. 2. *In silico*: Molecular docking study.	1. Dragon's blood resin treatment alleviated brain injury. 2. Predicted that the active components of the resin bound to and modulated disulfidptosis-related proteins, such as *FLNA*, *IQGAP1*, *TLN1* and *Myh9*.	Weak and indirect: Indirect protective evidence in a related ischemic model and computational speculation on the mechanism was provided. The study did not directly measure or modulate disulfidptosis itself, leaving the proposed mechanism hypothetical.	(75)

GEO, Gene Expression Omnibus; IC, ischemic cardiomyopathy; TAAD, type A aortic dissection; HF, heart failure; HCM, hypertrophic cardiomyopathy.

important for disease mitigation. For example, the disulfide reductant dithiothreitol can reduce abnormal disulfide bonds, but its application is limited because of its strong odor and toxicity (86). Thioredoxin-interacting protein (TXNIP) is a novel molecular target that enhances endogenous disulfide reductase capacity (87). A single study has shown that cardiomyocyte-specific TXNIP C247S mutation knock-in mice exhibit higher survival rates and smaller infarct sizes following MI than control mice. Inhibition of thioredoxin by TXNIP promotes mitochondrial antioxidant capacity in cardiomyocytes, protecting the heart from MI-induced oxidative damage. This protective mechanism involves potent regulation of the thioredoxin system via a disulfide bond exchange mechanism in adult mouse cardiomyocytes (87).

Additionally, inhibiting actin cross-linking to protect the cytoskeleton represents another strategy to suppress disulfidptosis. Reportedly, in HL-1 murine atrial cardiomyocytes exposed to 2% ethanol, the cytoskeleton was markedly disrupted during apoptosis and the anti-apoptotic transcriptional coactivator Yes-associated protein (YAP) was inactivated. Conversely, the retrovirus-induced expression of constitutively active YAP and jasplakinolide-mediated stabilization of the actomyosin cytoskeleton prevented cardiomyocyte cell death (88).

8. Discussion and conclusions

The present review systematically elaborated on the core molecular mechanisms of disulfidptosis, a novel form of regulated cell death, and explored its potential role in CVDs from the perspective of different cell types within the cardiovascular system. The core of disulfidptosis lies in the lethal imbalance between SLC7A11-mediated cystine metabolism and glucose-dependent NADPH regeneration. The resulting disulfide stress directly affects the cytoskeletal system, which maintains cell morphology and function, and ultimately leads to cellular collapse. For example, disulfidptosis can: i) Impair cardiomyocyte contractility; ii) exacerbate inflammatory responses; iii) promote the synthetic phenotype switch, proliferation and migration of VSMCs; iv) aggravate vascular wall thickening; v) disrupt endothelial barrier function; vi) activate platelets and the coagulation cascade, triggering thrombosis and worsening tissue ischemia; and vii) induce myofibroblast generation, leading to excessive ECM deposition and accelerated fibrosis. Given that glucose starvation is a primary trigger for disulfidptosis and pathological scenarios such as myocardial ischemia-reperfusion injury, the hypoglycemic environment within atherosclerotic plaques and diabetic cardiomyopathy represent typical glucose starvation conditions; as such, the present review hypothesized a close relationship between CVDs and disulfidptosis.

Particularly noteworthy is the mirror-image crosstalk between disulfidptosis and ferroptosis. These cell death modalities share SLC7A11 as a common molecular switch, yet their outcomes diverge based on the cellular metabolic environment; high SLC7A11 expression under glucose starvation steers cells toward disulfidptosis, whereas its inhibition directs cells toward ferroptosis. This nuanced relationship suggests that in pathological contexts with marked metabolic fluctuations, such as myocardial ischemia-reperfusion injury, these two death modalities may coexist or occur sequentially, collectively amplifying tissue damage. To definitively establish the role of disulfidptosis in CVDs, future research should focus on the development and application of direct experimental biomarkers. Key approaches should include, but are not limited to: i) Employing non-reducing gel electrophoresis to detect aberrant disulfide crosslinking in cytoskeletal proteins, such as actin; ii) monitoring the NADPH:GSH ratio to confirm reductive power collapse; iii) assessing SLC7A11 protein levels and cystine transport activity; and iv) rigorously distinguishing disulfidptosis from ferroptosis through morphological observations, for example F-actin staining, combined with specific inhibitors. Establishing and standardizing these detection criteria should be a notable research priority for the next phase in this field.

Although bioinformatics analyses have revealed notable alterations in key disulfidptosis-related genes in CVDs, such as IC and TAAD, providing preliminary evidence for their association with disulfidptosis, it is important to recognize the apparent limitations of current studies. The primary challenge is that the majority of evidence remains indirect, lacking definitive proof of disulfidptosis occurrence in CVD models, such as *in vivo* animal models or clinical samples, including the direct detection of aberrant disulfide bonds in cytoskeletal proteins (for example, actin), within myocardial or vascular tissues.

However, studies suggest that small molecule inhibitors directly targeting SLC7A11 activity or NAD^+ supplementation could be potential therapeutic strategies for mitigating disulfidptosis in CVDs. Their combined use may alleviate the adverse effects of NADPH depletion. Additionally, disulfide reductants, such as TXNIP, and the inhibition of actin cross-linking have shown potential in ameliorating the progression of CVDs. Therefore, this strategy represents a promising research topic.

Future investigations should explore the interaction mechanisms between disulfidptosis and ferroptosis by utilizing single-cell sequencing and multi-omics integration to identify novel therapeutic targets, providing novel options for the diagnosis and treatment of CVDs. Furthermore, it is important to precisely evaluate the contribution of disulfidptosis across a broader range of CVD models, such as hypertensive heart disease, myocarditis and heart failure, to clarify whether it acts as a primary driver or synergistic disruptor.

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Authors' contributions

XJ, ZC, XD and ZL designed the article and wrote the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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