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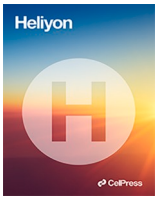

Review article

Ferroptosis in diabetic cardiomyopathy: Advances in cardiac fibroblast-cardiomyocyte interactions

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ABSTRACT

Diabetic cardiomyopathy (DCM) is a common complication of diabetes, and its pathogenesis remains elusive. Ferroptosis, a process dependent on iron-mediated cell death, plays a crucial role in DCM via disrupted iron metabolism, lipid peroxidation, and weakened antioxidant defenses. Hyperglycemia, oxidative stress, and inflammation may exacerbate ferroptosis in diabetes. This review emphasizes the interaction between cardiac fibroblasts and cardiomyocytes in DCM, influencing ferroptosis occurrence. By exploring ferroptosis modulation for potential therapeutic targets, this article offers a fresh perspective on DCM treatment. The study systematically covers the interplay, mechanisms, and targeted drugs linked to ferroptosis in DCM development.

1. Introduction

The increasing global prevalence of diabetes has become a serious health challenge worldwide. According to the statistics from the International Diabetes Federation, as of 2019, the global diabetic population reached 463 million, and it is projected to increase to 700 million by 2045. This puts immense pressure on individual health and healthcare systems [1]. Among the complications of diabetes, diabetic cardiomyopathy has gained significant attention. Since its initial proposal by Rubler et al., in 1972, approximately one-fifth of diabetic patients develop diabetic cardiomyopathy (DCM), with an even higher proportion in those with a long-term disease [2,3]. This illness not only lowers quality of life and compromises cardiac function, but it also greatly raises the risk of cardiovascular events like myocardial infarction, heart failure, and sudden cardiac death [4–7].

In the intricate system of the heart, different types of cells closely work together to maintain normal physiological functions. These cells include cardiomyocytes and cardiac fibroblasts. Although there are fewer cardiomyocytes compared to non-cardiomyocytes, cardiac fibroblasts are a major component of non-muscle cells in all species [8–10]. About 30 % of cardiomyocytes and 70 % of non-cardiomyocytes are involved in heart function impairment [11]. Among these cells, cardiac fibroblasts have a crucial role in maintaining the structural stability of the heart tissue, repairing damage, and regulating the inflammatory response and fibrosis processes. The interaction between cardiac fibroblasts and cardiomyocytes is particularly important in the pathological mechanism of DCM. Studies have shown that under diabetic conditions, activated fibroblasts transform into myofibroblasts, which worsens cardiac fibrosis and sustained inflammation [12–14]. Furthermore, through the release of growth factors and cytokines, fibroblasts have a direct impact on the metabolism, electrical activity, and signal transduction of cardiomyocytes. This in turn has an impact on the

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heart's remodeling process and general function [15–18].

The notion of ferroptosis, which was first presented in 2012, offers a fresh viewpoint on the pathogenic mechanisms underlying DCM. It is a form of cell death driven by iron-dependent lipid peroxidation processes [19,20]. Unlike apoptosis, ferroptosis does not involve nuclear DNA fragmentation or caspase activation [21,22]. Compared to necrosis, ferroptosis does not cause inflammatory reactions or immediate release of cellular contents [23]. In cardiovascular diseases, especially DCM, ferroptosis has become a focal point of research [24]. Iron metabolism can be disrupted and oxidative stress can be increased by elevated blood sugar and insulin resistance, which can lead to ferroptosis [25–27]. Exploring the interaction between cardiac fibroblasts and cardiomyocytes and ferroptosis not only enhances our understanding of the pathological mechanisms of DCM, but also provides a new research direction for innovative therapeutic strategies. This review aims to systematically summarize current research on this topic and explore prospects for future research directions and clinical applications.

2. Interaction between cardiac fibroblasts and cardiomyocytes in diabetic cardiomyopathy

2.1. Origin of cardiomyocytes and fibroblasts

Cardiac fibroblasts are produced throughout embryonic development from cells originating from the outside myocardium, called epicardial-derived cells [28,29]. Furthermore, mesangioblasts, which are multipotent precursor cells, have the ability to transform into cardiac fibroblasts or vascular tissues like endothelial cells by going through the epithelial-mesenchymal transition process [6,30]. Several studies have shown that various cell types, including epithelial cells, endothelial cells, hematopoietic fibroblast progenitor cells, macrophages, and pericytes, can also undergo epithelial-mesenchymal or endothelial-mesenchymal cell transitions to become cardiac fibroblasts [31–38]. The contribution of these diverse sources collectively leads to the diversity and dynamics of cardiac fibroblasts [13].

Cardiomyocytes are derived from mesodermal tissues during embryonic development. They originate from precursor cells of the heart, which form the primitive heart structure including the endocardium, myocardium, and the intervening cardiac jelly in the early stages of embryonic development. As development progresses, these precursor cells differentiate into mature cardiomyocytes, eventually forming mature cardiac muscle tissue with complex functionality [39–41]. Three transcription factors—Gata4, myocyte-specific enhancer factor 2C (Mef2C), and T-box 5 (Tbx5)—have been shown in recent studies to play a critical role in the conversion of fibroblasts into viable cardiomyocytes. These transcription factors are key players in cell differentiation and cardiac development, allowing fibroblasts to acquire cardiomyocyte characteristics and perform cardiomyocyte functions through the regulation of gene expression [42]. To gain a comprehensive understanding of cardiomyocyte and fibroblast origin and formation processes, it is essential to explore both physiological and pathological processes in the heart (Fig. 1).

2.2. Activation and transformation mechanisms of cardiac fibroblasts

Cardiac fibroblasts play a crucial role in maintaining the structure of cardiac tissue, aiding in injury repair, and regulating the synthesis and degradation of the extracellular matrix (ECM). Normally, these fibroblasts remain in a quiescent state, characterized by a small cell volume and minimal cell protrusions [43,44]. Nonetheless, in individuals with diabetes, cardiac fibroblasts undergo a series of activation and transformation processes [45], driven by several molecular mechanisms: 1) Oxidative Stress: Elevated glucose levels

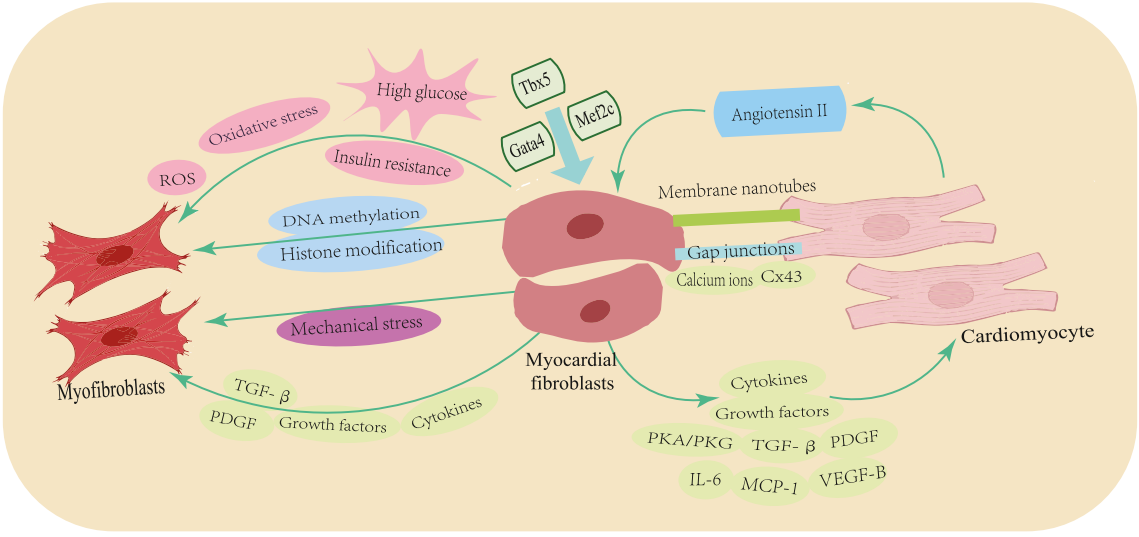

Fig. 1. Activation and transformation processes of myocardial fibroblasts and interaction of myocardial fibroblasts with cardiomyocytes in diabetic cardiomyopathy.

and insulin resistance result in increased oxidative stress, leading to the production of reactive oxygen species (ROS). This activation triggers the transformation of fibroblasts into myofibroblasts [14,46,47]. 2) Cytokines and Growth Factors: Inflammatory reactions release cytokines such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF), which directly or indirectly stimulate the proliferation and activation of fibroblasts [48,49]. 3) Changes in Mechanical Stress: Dysfunction in myocardial function in individuals with DCM can cause alterations in mechanical stress, further stimulating the activation and transformation of fibroblasts [50–52]. The exact mechanisms of mechanical signal transduction between cardiomyocytes and fibroblasts are not yet fully understood. 4) Epigenetic Regulation: Epigenetic changes, including DNA methylation and histone modifications, may also contribute to the activation and transformation of fibroblasts [53,54]. All of these processes work together to control how cardiac fibroblasts operate when diabetic (Fig. 1).

2.3. The role of cardiac fibroblasts in myocardial fibrosis and inflammatory responses

Cardiac fibroblasts are essential to the processes of myocardial fibrosis and inflammatory responses in DCM. First, activated fibroblasts synthesize and secrete ECM components such as collagen and fibronectin, leading to excessive deposition of myocardial tissue and triggering myocardial fibrosis [51,55]. Additionally, fibroblasts regulate the degradation and remodeling of ECM through the secretion of enzymes like matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) [56–59]. Second, activated fibroblasts secrete various cytokines and chemokines, such as Tumour necrosis factor alpha (TNF-α), interleukin 6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), to attract and activate macrophages and lymphocytes, exacerbating the inflammatory response [60–63]. Furthermore, by expressing adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), fibroblasts enhance the interaction between immune cells and Cardiomyocytes [64,65].

2.4. Direct and indirect communication pathways between cardiac fibroblasts and cardiomyocytes

The communication between cardiac fibroblasts and cardiomyocytes involves both direct physical contact and indirect signal transduction, forming a complex interactive network [66–68]. Direct communication includes gap junctions and adhesion molecule-mediated mechanical force transmission. Gap junctions allow for the rapid transfer of small molecules (such as calcium ions, connexin 43 (Cx43), etc.) between cells, influencing the electrophysiological activity and contractile function of cardiomyocytes [18,69–73]. By mediating mechanical force and signal transduction between cells, adhesion molecules regulate the morphology and function of cardiomyocytes [74]. Indirect communication occurs through the secretion of growth factors and cytokines by cardiac fibroblasts, which regulate the biological behavior of cardiomyocytes [75]. For example, natriuretic peptide receptor C (NPRC) deficiency can induce cardiomyocyte hypertrophy and fibrosis through the activation of protein kinase A (PKA)/protein kinase G (PKG) and TGF-β Smad signaling pathways [76–78]; PDGF stimulates fibroblast proliferation and migration [79]; cytokines such as IL-6 and MCP-1 promote inflammation and the recruitment of immune cells [63,80]. Conversely, soluble mediators released by cardiomyocytes also affect fibroblast proliferation. For instance, cardiomyocyte-derived angiotensin II increases fibroblast release of TGF-β [81–83]. An important part of the contact between cardiomyocytes and fibroblasts is played by membrane nanotubes, a unique long-distance structural and functional link [16,84–86]. Vascular endothelial growth factor-B (VEGF-B) indirectly influences their interaction in heart diseases by regulating angiogenesis, metabolism, and inflammatory responses [87,88]. Although these communication pathways have been identified as crucial in cardiac physiological and pathological processes, many details and unknowns remain regarding the exact nature and mechanisms of soluble mediator interactions. For a better comprehension of the pathogenic mechanisms of DCM and the investigation of novel therapeutic approaches, these findings are crucial (Fig. 1).

3. Role of ferroptosis in diabetic cardiomyopathy

3.1. Molecular mechanisms and biomarkers of ferroptosis

Ferroptosis is a unique form of cell death that occurs due to the iron-dependent process of lipid peroxidation. There are three main components to this molecular mechanism: 1) Imbalance in Iron Metabolism: Iron ions play a crucial role in various cellular processes, such as oxygen transport, DNA synthesis, and energy metabolism. In ferroptosis, disruptions in iron ion metabolism lead to their abnormal accumulation, particularly within the mitochondria and endoplasmic reticulum [89–93]. 2) Lipid Peroxidation: The interaction between iron ions and hydrogen peroxide initiates the production of hydroxyl radicals, which triggers lipid peroxidation. Among all cellular components, phospholipids are particularly vulnerable to oxidative damage. The byproducts of lipid peroxidation, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), have detrimental effects on the structure and function of cell membranes, ultimately resulting in cell death [91,94–96]. 3) Inhibition of Antioxidant Defense Systems: Ferroptosis involves the suppression of critical enzymes in the antioxidant defense system, including glutathione peroxidase 4 (GPX4). This inhibition impairs the effective clearance of excess lipid peroxidation products by cells, thereby exacerbating oxidative damage [20,25,97–100].

3.2. The role of ferroptosis in cardiomyocyte injury and death

In the context of DCM, ferroptosis plays a significant role in the processes of cardiomyocyte injury and death, negatively affecting both myocardial function and structure. The specific ways in which this occurs are as follows: 1) Impaired Cardiomyocyte Function: Ferroptosis causes damage to the membranes of cardiomyocytes, leading to lipid peroxidation. This disruption interferes with their

electrophysiological activity and contractile function, ultimately resulting in myocardial dysfunction and heart failure [101–103]. 2) Cardiomyocyte Death: Ferroptosis, as a distinct form of cell death, directly contributes to the death and apoptosis of cardiomyocytes, further worsening the extent and severity of myocardial injury [104–106]. 3) Interaction with Other Cell Death Modalities: Ferroptosis interacts with and influences complex relationships with other forms of cell death, such as apoptosis and autophagy [107–109]. For example, ferroptosis can either trigger or enhance other forms of cell death, while other cell death modalities, like copper-dependent autophagy degradation, can induce ferroptosis [110,111].

3.3. *Factors and signaling pathways promoting ferroptosis in the diabetic state*

The elevated rate of ferroptosis in the diabetic condition may be caused by a number of causes. These factors include: 1) Hyperglycemia: Elevated blood glucose levels can induce endoplasmic reticulum stress and unfolded protein response (UPR), activating signaling pathways like IRE1 and c-Jun N-terminal kinase (JNK). This activation inhibits the expression and activity of GPX4, which promotes the occurrence of ferroptosis [20,25,97,98,109]. 2) Oxidative Stress: Diabetes leads to increased oxidative stress, which in turn inhibits the function of the antioxidant defense system. This promotes lipid peroxidation and the process of ferroptosis [25,26,112,113]. 3) Inflammatory Response: The inflammatory response in diabetes results in the production of cytokines and chemokines, which activate fibroblasts and immune cells. This leads to increased production of ROS and inflammatory factors, thereby promoting ferroptosis [114–117]. Through pathways such as nuclear factor-κB (NF-κB) and NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, inflammation and oxidative stress can also upregulate the expression of Acyl-CoA synthetase long-chain family member 4 (ACSL4). This increases the generation of lipid peroxidation products and ROS, ultimately promoting ferroptosis [26,118–121].

Numerous important molecular targets and signaling pathways are involved in the regulation of ferroptosis. These pathways include: 1) GPX4 Signaling Pathway: GPX4 is an important enzyme in the antioxidant defense system. Reduced GPX4 activity is a defining characteristic of ferroptosis. Research has shown that Hydroxy safflower yellow A can inhibit ferroptosis and reduce myocardial ischemia/reperfusion injury by activating the Hypoxia induicible factor-1 alpha (HIF-1α)/Solute carrier family 7 member 11 (SLC7A11)/GPX4 signaling pathway [122]. Therefore, enhancing GPX4 activity or inhibiting its inhibitors may be a strategy to suppress ferroptosis [20,25,97–100,111,123]. 2) TGF-β Signaling Pathway: TGF-β is a cytokine that plays a crucial role in fibrosis and inflammatory responses. Excessive activation of TGF-β can promote fibroblast proliferation and ECM deposition. Additionally, it can promote ferroptosis by inhibiting GPX4 activity [97,98,124–127]. 3) Nuclear factor erythroid 2-related factor 2 (Nrf2) Signaling Pathway: Nrf2 is a key transcription factor in cellular antioxidant defense. Ferroptosis and lipid peroxidation can be inhibited by upregulating antioxidant enzyme production and activity through activation of the Nrf2 signaling pathway. Therefore, activating the Nrf2 signaling pathway may be a strategy to inhibit ferroptosis [24,128–134].

4. The impact of the interaction between cardiac fibroblasts and cardiomyocytes on ferroptosis

4.1. *Regulation of myocardial cell iron metabolism and oxidative stress by factors secreted from cardiac fibroblasts*

In cardiomyocytes, cardiac fibroblasts are essential for controlling oxidative stress and iron metabolism. They do this via secreting different enzymes, cytokines, and growth factors. In the context of ferroptosis, the following key factors released by fibroblasts have

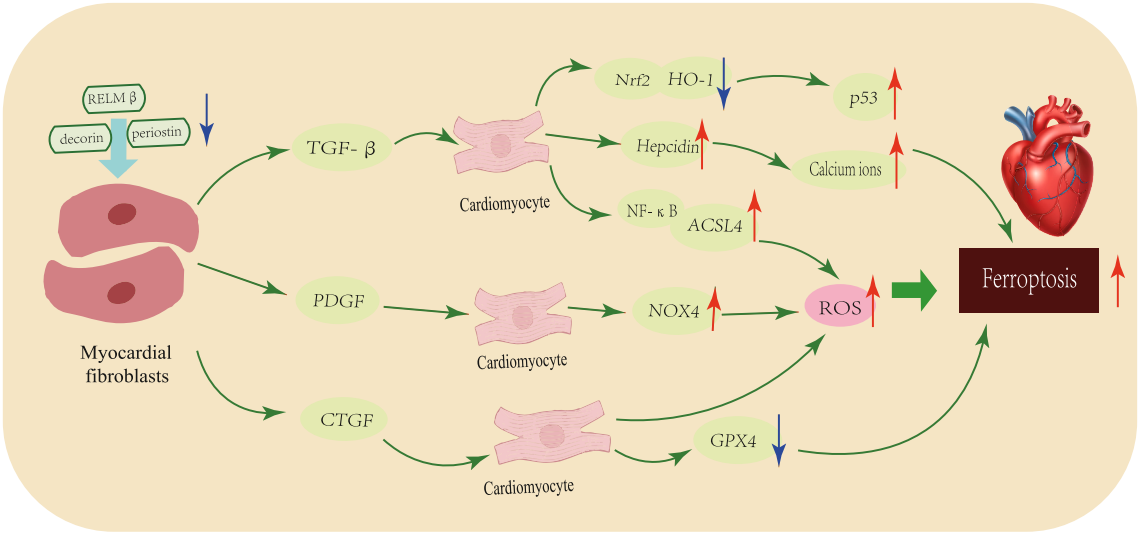

Fig. 2. Interplay between cardiac fibroblasts and cardiomyocytes in modulating ferroptosis pathways.

important implications: 1) TGF-β: TGF-β, a key fibrotic factor, induces hepcidin expression in cardiomyocytes. This, in turn, inhibits iron absorption and release in intestinal and liver cells, leading to reduced serum iron levels and the accumulation of iron ions in cardiac tissues. This process increases the risk of ferroptosis [77,135–141]. 2) PDGF: Inducing oxidative stress in cardiomyocytes, PDGF promotes fibroblast activation and proliferation. It affects iron metabolism and promotes ferroptosis by activating members of the Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Oxidase (NOXs) family, which increases the generation of ROS [26,142–146]. 3) CTGF (Connective Tissue Growth Factor): CTGF, another significant fibrotic factor, promotes ferroptosis by upregulating hepcidin expression and inhibiting the antioxidant defense system [142,147–149]. These factors, released by fibroblasts, modulate the expression of important genes and enzymes such as hepcidin and GPX4. Consequently, they impact cardiomyocytes' oxidative stress status and iron balance, which in turn influences the development of ferroptosis [20,25,26,100,123] (Fig. 2).

4.2. Regulation of gene expression associated with ferroptosis by factors secreted from cardiac fibroblasts

Through distinct signaling pathways and transcription factors, cardiac fibroblasts release a variety of growth factors and cytokines that impact the expression of genes linked to ferroptosis. Studies have shown that TGF-β, through both small mother against decapentaplegic (Smad) and non-Smad signaling pathways, increases the expression of genes such as ACSL4 and NADPH oxidase 4 (Nox4). This leads to a higher production of lipid peroxidation products and ROS, which in turn promotes ferroptosis [103,129,150,151]. Furthermore, TGF-β increases the vulnerability of cardiomyocytes to oxidative stress and cell death by suppressing the antioxidant defense system of Nrf2/Heme oxygenase-1 (HO-1) and upregulating the expression of genes associated with apoptosis, such as p53 [26,128,129,152–154]. On the other hand, some anti-fibrotic and anti-inflammatory factors, such as decorin, periostin, and resistin-like molecule β (RELMβ), reduce inflammation and fibrotic processes by downregulating signaling pathways like TGF-β and NF-κB. At the same time, they increase the expression of antioxidant genes like Nrf2 and HO-1, preventing ferroptosis from occurring [100,129,131,155,156] (Fig. 2).

4.3. Cardiomyocyte regulation of fibroblast activity and its dysregulation in diabetic cardiomyopathy

Cardiomyocytes, through a sophisticated network of paracrine signals, actively regulate fibroblast function and phenotype. Among these signals, TGF-β and CTGF emerge as key mediators, orchestrating fibroblast proliferation and transdifferentiation into myofibroblasts, a process pivotal to extracellular matrix remodeling and subsequent myocardial stiffness [77,97,98,135,140,147–149]. Importantly, in the setting of diabetic cardiomyopathy, ferroptosis-induced cardiomyocyte death introduces a new dimension to this dialogue. The release of iron and ROS from dying cardiomyocytes fosters a pro-fibrotic microenvironment, potentiating fibroblast activation and contributing to the vicious cycle of tissue fibrosis [103,129,150,151]. Furthermore, the metabolic perturbations intrinsic to diabetes mellitus, such as hyperglycemia, disrupt normal cardiomyocyte metabolism and secretory profiles. This metabolic dysfunction is increasingly recognized as a driving force behind altered cytokine and growth factor secretion, which may skew the fibroblast response towards a predominantly pro-fibrotic state, exacerbating disease progression [48,49,124–127].

4.4. Communication between cardiac fibroblasts and cardiomyocytes shapes the microenvironment of ferroptosis

The communication between cardiac fibroblasts and cardiomyocytes has a significant impact on the genes and signaling pathways associated with ferroptosis. This communication occurs through both direct and indirect pathways. Direct communication is facilitated by gap junctions and adhesion molecules, allowing the transfer of small molecules like calcium ions. This transfer affects the electrophysiological activities and contractile functions of cardiomyocytes [70,157–160]. In a high-glucose environment, cardiomyocytes release inflammatory factors that activate cardiac fibroblasts. This activation leads to oxidative stress and lipid peroxidation, which worsens cardiac damage [161]. Additionally, fibroblasts indirectly influence cardiomyocytes by secreting growth factors and cytokines, such as TGF-β/Smad, NF-κB, and Nrf2. These substances regulate the expression and activity of genes related to ferroptosis, including iron metabolism, antioxidant defense systems, and ferroptotic executor genes [128–130,150] (Fig. 2).

Therefore, these pathways and microenvironmental factors play a crucial role in the interaction between cardiac fibroblasts and cardiomyocytes during the process of ferroptosis. They provide important clues and targets for the development of novel therapeutic strategies.

5. Temporal characteristics of ferroptosis in type 1 diabetes (T1D) and type 2 diabetes (T2D) hearts and its differential role in the development of DCM and clinical implications

5.1. Presence and stage-specific distribution of ferroptosis in T1D and T2D hearts

Ferroptosis, a regulated form of cell death occurring under conditions of iron overload and oxidative stress, has emerged as a focal point in diabetes research, particularly in the context of T1D and T2D diabetes where meticulous examination is imperative. It is crucial to pinpoint the pivotal timepoints in the disease course where ferroptosis becomes significant, specifically when diabetic hearts exhibit enhanced susceptibility to ischemia-reperfusion injury compared to non-diabetic individuals. This distinction is crucial for clarifying the fundamental mechanisms that initiate ferroptosis, potentially revealing unique pathways for ferroptosis activation in T1D and T2D. Studies have documented differential expression patterns of ferroptosis across varying stages of T1D (early, middle, late), suggesting a stage-dependent characteristic [162,163]. In T2D, while ferroptosis is typically associated with later stages,

emerging evidence hints at its presence in earlier phases, underscoring the unique temporal profile of T2D [130,164,165].

5.2. Distinct mechanisms of ferroptosis across different stages of diabetes progression

T1D accounts for approximately 2 % of all diabetes cases, characterized by absolute insulin deficiency due to β-cell destruction, whereas T2D arises from progressive insulin secretory defects against a backdrop of insulin resistance [166,167]. The distinct mechanisms of ferroptosis in T1D and T2D underscore their divergent disease progressions. Research has highlighted that in the early stages of diabetes, animal models exhibit an augmented resistance to ischemic injury [168]. Specifically, during the early phase of T1D, approximately one week post-onset, the heart manifests a pronounced reinforcement of antioxidant systems, evidenced by elevated glutathione levels, reduced free iron content in the ischemia-reperfusion injury zone, and concomitant increases in ferritin, indicating a robust antioxidant barrier in early T1D hearts that combats oxidative stress and mitigates ischemic harm [163]. However, as the condition progresses, ferroptosis gradually escalates, becoming a pivotal mechanism of heightened sensitivity to ischemic injury in T1D hearts by the fifth week of disease development [163]. The therapeutic benefits of NAC, particularly its capacity to inhibit ferroptosis in later stages, further emphasize the necessity and significance of targeting ferroptosis as an intervention strategy.

5.3. Human evidence and pathogenic roles of ferroptosis in DCM across T1D & T2D

Currently, studies on ferroptosis in cardiovascular diseases predominantly focuses on animal models and in vitro experiments, with a relative dearth of clinical studies and human observational data. This gap hampers a comprehensive understanding of the precise pathophysiological pathways and regulatory mechanisms of ferroptosis within the intricate human physiological environment. Notably, diabetic patients exhibit a 2.45–2.99-fold higher risk of myocardial ischemia compared to non-diabetic individuals, highlighting the intimate link between diabetes and cardiovascular disorders [169]. Recent studies have illuminated the integral association of ferroptosis with the pathogenesis of DCM [130,170–172]. In various T2D mouse models, ferroptosis has been validated as a central mechanism driving the development of DCM [130,170]. Of particular interest, tissues prone to ischemia in diabetic individuals, such as the myocardium, display an increased propensity for ferroptosis, suggesting a pivotal role for ferroptosis in diabetes-related cardiovascular complications [173,174]. Serum ferritin levels have emerged as a useful biomarker for early detection of T2D, and iron overload is acknowledged as a significant risk factor for T2D [175–178]. Clinical and forensic evidence not only confirms the presence of ferroptosis in diabetic hearts but also underscores its clinical relevance through indicators of iron dysregulation and oxidative stress markers, including elevated ferritin and 4-hydroxynonenal. Furthermore, successful quantification and confirmation of ferroptosis in T2D mouse models and T2D patient hearts have laid an empirical foundation for further deciphering the role of ferroptosis in diabetic cardiac pathology [171,179].

In summary, this section highlights the complex, stage-dependent roles of ferroptosis in T1D and T2D hearts, its implications for diabetic cardiomyopathy, and the need for advanced human-focused research. Recognizing ferroptosis' variable impacts across disease stages and its links to cardiovascular risks, future studies must prioritize understanding its precise mechanisms in humans to effectively target this process as a therapeutic avenue, ultimately reducing diabetes-related heart complications.

6. Exploration and strategies for novel therapeutic targets

6.1. Intervention strategies targeting the interaction between cardiac fibroblasts and cardiomyocytes

Intervention strategies that target the interaction between cardiac fibroblasts and cardiomyocytes show promise for treating DCM and inhibiting ferroptosis. Here are some potential strategies: 1) Anti-fibrotic drugs, such as pirfenidone and nintedanib, have been shown to reduce fibrosis progression and inflammation by inhibiting signaling pathways like TGF-β and PDGF. This inhibition leads to

Table 1
Drugs and compounds targeting ferroptosis in DCM: Focus on cardiac fibroblast and cardiomyocyte interactions.

No.	Category	Drugs/Compounds	Mechanism of Action	Target/Effects	References
1	Antifibrotic Drugs	Pirfenidone, Nintedanib	Inhibit TGF-β and PDGF pathways, reducing fibrosis and inflammation	Decrease cardiac fibroblast proliferation and ECM deposition	[180–184]
2	Extracellular Matrix-Degrading Enzymes	Collagenases, MMPs	Degrade ECM components	Alleviate fibrosis and improve heart function	[56, 185–187]
3	Immunomodulators	Interferon-γ, IL-10	Regulate functions of immune cells and cardiac fibroblasts, reducing inflammation and fibrosis	Modulate immune response and reduce fibrotic changes	[188–190]
4	Iron Chelators	Deferiprone, Deferoxamine	Bind and remove free iron ions	Reduce risk of ferroptosis and manage iron overload	[130, 193–195]
5	Antioxidants	Vitamin C, Vitamin E, NAC	Neutralize ROS and lipid peroxidation products	Enhance antioxidant defense and inhibit ferroptosis initiation	[113,196, 197]
6	Nrf2 Activators	Bardoxolone methyl, Dimethyl fumarate	Upregulate antioxidant genes and suppress inflammatory gene expression, boosting cellular defense against oxidative stress	Enhance antioxidant capacity and mitigate ferroptosis	[130,131, 200–202]

decreased proliferation of cardiac fibroblasts and synthesis of ECM components [180–184]. 2) Extracellular matrix-degrading enzymes, including collagenases and MMPs, offer a way to break down ECM components, alleviating fibrosis and improving heart function. However, caution is necessary as excessive ECM degradation may disrupt tissue structure and increase the risk of bleeding [56,185–187]. 3) Immune modulators, such as interferon-γ and IL-10, can regulate the functions of immune cells and cardiac fibroblasts, reducing inflammation and fibrosis [188–190]. Additionally, novel immunotherapeutic techniques like immune checkpoint inhibitors and Chimeric antigen receptor T (CAR-T) cell therapy may provide new possibilities for treating DCM [191,192]. These tactics may indirectly affect cardiomyocytes' oxidative stress status and iron metabolism by regulating the activity and function of cardiac fibroblasts, which may in turn affect the development of ferroptosis [26] (Table 1).

6.2. Potential drugs and therapies for inhibiting ferroptosis

Current research suggests that specific drugs and therapies demonstrate potential for inhibiting ferroptosis. These include: 1) Iron Chelators: Iron chelating agents, such as deferiprone and deferoxamine, can bind to and eliminate free iron ions in the body. This action reduces the risk of ferroptosis. However, cautious use of these drugs is essential since excessive chelation of iron ions may lead to anemia and other side effects [130,193–195]. 2) Antioxidants: Lipid peroxidation products and reactive oxygen species (ROS) are immediately neutralized by antioxidants such as vitamin C, vitamin E, and N-acetylcysteine (NAC). By doing this, they prevent ferroptosis from occurring and increase the capability of the antioxidant defense system [113,196,197]. However, it should be emphasized that long-term or high-dose antioxidant use may have negative effects, such as promoting tumor growth and inhibiting normal cell communication [198,199]. 3) Nrf2 Activators: Nrf2 is a critical antioxidant transcription factor. Upon activation, it boosts cellular antioxidant defenses by upregulating antioxidant genes and suppressing inflammatory gene expression [128]. Some Nrf2 activators, including bardoxolone methyl and dimethyl fumarate, have entered clinical trial phases and shown certain efficacy and safety profiles [130,131,200–202]. In this context, the mechanisms of action for these drugs and therapies primarily involve regulating iron metabolism, clearing ROS, or enhancing the antioxidant defense system to prevent the onset of ferroptosis (Table 1).

6.3. Targeting ferroptosis-related genes and pathways using gene editing and cell therapy

The development of targeted therapeutics targeting ferroptosis-related genes and pathways has led to the emergence of novel techniques in gene editing and cell therapy. Here are some potential methods: 1) Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated nuclease 9 (Cas9) Gene Editing: This efficient gene editing tool can precisely disable or repair specific genes, including those associated with ferroptosis. For example, disabling genes such as ACSL4 or GPX4 can inhibit ferroptosis, while restoring genes like inositol-requiring enzyme type 1 (IRE1) or JNK can restore their normal function [100,123,145,203–208]. 2) Cell Therapy: This includes stem cell therapy and CAR-T cell therapy, where modified cells are transplanted into the patient to replace or modulate damaged cardiomyocytes and cardiac fibroblasts [209–211]. Transplanting genetically engineered mesenchymal stem cells or induced pluripotent stem cells and developing them into cardiac fibroblasts and cardiomyocytes, for example, can decrease fibrosis and improve heart function [212–218]. In summary, gene editing and cell therapy provide new targets and strategies for the interaction between cardiac fibroblasts and cardiomyocytes and the treatment of ferroptosis [219]. Further in-depth research and optimization are required to ensure the safety, efficacy, and personalized treatment plans of these methods, in order to achieve improved therapeutic outcomes and quality of life. Furthermore, customized treatment programs must to take into account each patient's unique characteristics and disease progression.

7. Limitations of the review

Our narrative review aspires to deliver a thorough examination of ferroptosis within diabetic cardiomyopathy, emphasizing cardiac fibroblast and cardiomyocyte interactions. Despite meticulous efforts, certain constraints are recognized: Firstly, Our search focused on English literature, possibly neglecting valuable non-English contributions and narrowing geographic and cultural perspectives. Broader linguistic inclusivity is advisable for future reviews. Secondly, The swift pace of research advancements means our analysis may not capture the absolute latest developments, due to the inherent delay between study conduct and publication. Ongoing updates are critical. Thirdly, Varied study designs and quality among included articles could affect result synthesis. Differences in assessing ferroptosis complicate interpretations. Lastly, As a narrative review, our work leans on author discretion, risking bias, in contrast to the more standardized, quantitative methods of systematic reviews or meta-analyses. These limitations highlight the necessity for ongoing exploration and updates in this rapidly advancing domain. Addressing them in future studies will deepen our comprehension and foster tailored interventions for managing this multifaceted condition.

8. Conclusion

This article explores the relationship between cardiac fibroblasts and cardiomyocytes in triggering ferroptosis in DCM. Cardiac fibroblasts release specific factors that influence intracellular iron metabolism and oxidative stress in cardiomyocytes, exacerbating myocardial fibrosis, ischemic damage, and promoting ferroptosis. The communication network between these two cell types is crucial in regulating the expression of genes related to ferroptosis and signaling pathways. In summary, understanding the interplay between cardiac fibroblasts and cardiomyocytes, as well as the role of ferroptosis in DCM, offers new research perspectives and treatment strategies. A comprehensive understanding of the molecular mechanisms and pathophysiological significance of these processes can

lead to more effective and safe treatment methods, ultimately improving the quality of life and prognosis for patients with DCM. Progress in this area will be fueled by continued efforts and interdisciplinary collaboration.

9. Outstanding questions

Future research directions in the field of DCM are poised to address several critical questions that hold promise for advancing therapeutic strategies. Firstly, while key signaling pathways involved in ferroptosis have been identified in DCM, a deeper understanding of the precise molecular mechanisms and interactions between soluble mediators within these pathways is essential. This includes elucidating their functional roles in disease pathogenesis. Secondly, there is an urgent need to develop novel interventional strategies targeting the intricate crosstalk between cardiac fibroblasts and cardiomyocytes. Such strategies could potentially modulate their interactions to inhibit or reverse fibrosis, inflammation, and ferroptosis in DCM patients. Thirdly, comprehensive investigation into the complex signaling networks under diabetic conditions, particularly focusing on how specific growth factors like VEGF-B and other mediators influence the dynamic communication between cardiac cells at various stages of disease progression, can pave the way for more effective interventions. Fourth, innovative targeted therapies should be developed and validated for their efficacy in suppressing the activation, proliferation, and transformation of cardiac fibroblasts, with concurrent evaluation of their impact on iron-mediated cell death and overall heart function. Fifth, identifying and validating new biomarkers that accurately reflect the state of ferroptosis and correlate well with DCM diagnosis and prognosis is crucial. These markers could also serve as potential therapeutic targets or tools for monitoring disease progression. Sixth, exploring the intricate interplay between ferroptosis and other cell death modalities (apoptosis, autophagy) under diabetic conditions will aid in designing multi-targeted intervention strategies that simultaneously tackle multiple cell death pathways. Seventh, continued exploration into the fine-tuning of critical signaling pathways such as GPX4, TGF-β, and Nrf2 in diabetes-related ferroptosis is vital to guide the development of more targeted *anti*-ferroptotic drugs. Eighth, employing gene editing technologies like CRISPR/Cas9 to study the effectiveness and safety of targeting genes linked to ferroptosis, such as ACSL4 and GPX4, could lead to new avenues for therapeutic intervention. Ninth, optimizing and expanding the application of stem cell therapy and CAR-T cell therapy in repairing cardiac damage, inhibiting fibrosis, and regulating ferroptosis is another promising area for future research. Tenth, personalizing treatment approaches based on individual patient characteristics and

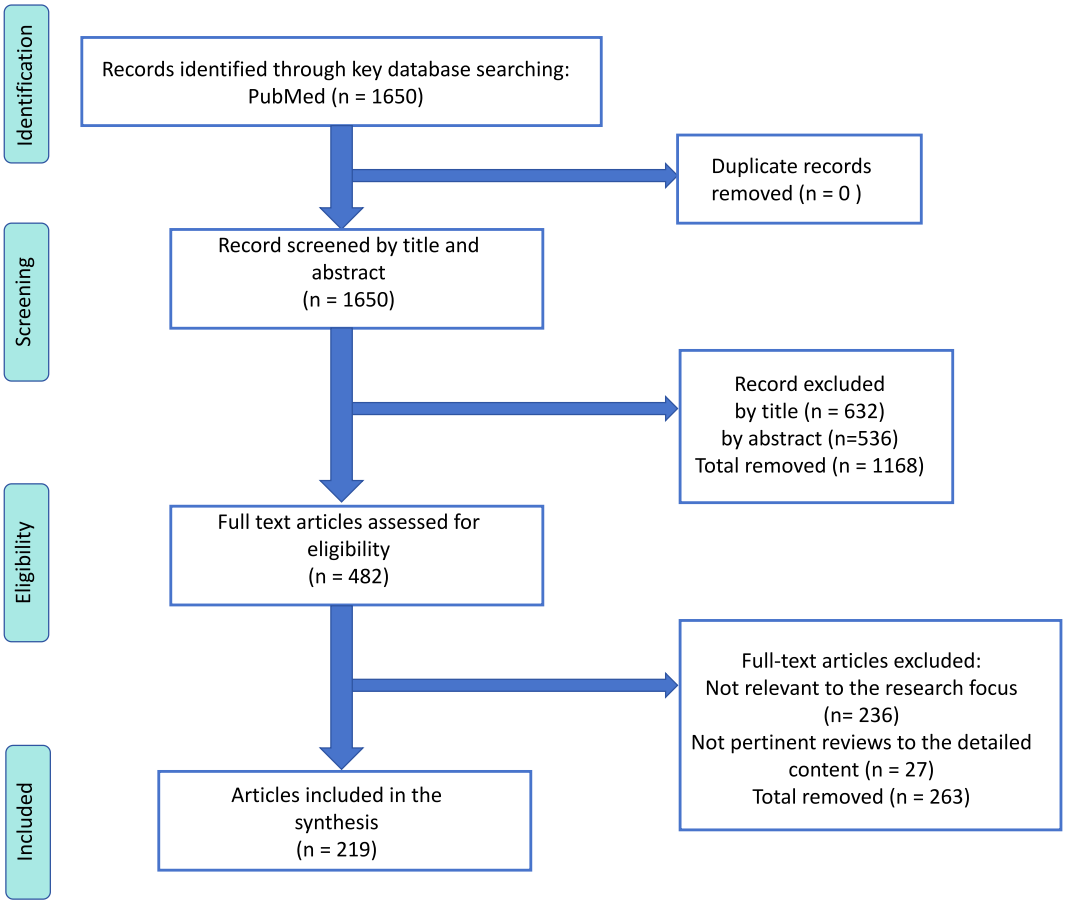

Fig. 3. Literature screening and inclusion process.

disease progression, including the tailored regulation of ferroptosis-related gene expression and signaling pathways, presents a compelling challenge and opportunity. Last but not least, bridging the gap between basic science findings and clinical practice necessitates conducting more preclinical and clinical trials investigating the safety and efficacy of novel drugs and therapies targeting the interaction between cardiac fibroblasts and cardiomyocytes, as well as ferroptosis pathways in DCM.

10. Search strategy and selection criteria

In preparing the review "Ferroptosis in Diabetic Cardiomyopathy: New Directions in Cellular Interplay," we extensively explored PubMed and scrutinized key references. Our search keywords – "ferroptosis," "diabetic cardiomyopathy," "heart fibroblasts," "heart muscle cells," and "cell cooperation" – helped us gather the most fitting and recent research.

Our literature selection was guided by a set of well-defined criteria, structured as follows: First, studies were included if they had explicit relevance to ferroptosis in the context of diabetic cardiomyopathy, ensuring a concentrated investigation into our central theme. Second, a key emphasis was placed on research examining heart fibroblasts or myocardial cells, with particular attention to their cooperative or communicative behavior, to deepen our understanding of cellular interactions. Third, to maintain recency and accessibility, English-language publications from the last five years were prioritized, with an exception made for historically pivotal works that significantly advanced comprehension in the field, even if they were published prior to this timeframe. Fourth, priority was given to studies presenting original empirical data or offering innovative insights; while comprehensive reviews and meta-analyses were utilized to orient the research landscape, they were not considered as primary data sources themselves. On the contrary, studies were excluded based on several grounds: divergence from the core theme of diabetic cardiomyopathy-related ferroptosis; concentration on non-diabetic cardiac conditions; deficiency in scientific rigor; and duplication. This structured approach ensured a methodical and focused selection process, enriching the quality and relevancy of our narrative review.

Our literature search encompassed key databases, with PubMed being the primary source, initially yielding 1650 records. Following the elimination of duplicates and an initial screening of titles and abstracts, 482 articles progressed to full-text review. Applying our rigorous assessment criteria, a total of 263 articles, including 27 review articles, were subsequently excluded, primarily due to their irrelevance to the focused research question, methodological inadequacies, or lack of original data contribution. As a result, a final selection of 219 publications, comprising primarily original research and a few highly informative reviews, stood as the cornerstone of our narrative review, reinforcing our in-depth analysis with a solid foundation of pertinent and high-quality research (Fig. 3).

Ethics statement

This narrative review has been prepared in accordance with the ethical standards outlined by Heliyon's publication guidelines. To ensure the authenticity and originality of our work, all sources cited within the text have been meticulously referenced following appropriate academic citation practices, thereby avoiding plagiarism and upholding the integrity of the scholarly record. Given the nature of this narrative review, which synthesizes existing literature without generating new empirical data, no ethical approval was necessary for conducting human or animal subjects research.

Data availability statement

The research presented in this article is a narrative review based on a synthesis of information from previously published studies. No primary data were generated or analyzed during this work. Consequently, there is no additional dataset associated with this article to deposit in a public repository. The list of references included in the text serves as the comprehensive data source for this review.

CRediT authorship contribution statement

Mengmeng Wang: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Degang Mo:** Writing – original draft, Visualization, Formal analysis, Conceptualization. **Ning Zhang:** Writing – review & editing, Supervision, Funding acquisition. **Haichu Yu:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

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

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