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REVIEW

Obesity-Associated Cardiac Fibrosis: Mechanisms and Emerging Therapeutic Targets

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Abstract: Obesity and cardiovascular disease are major, globally prevalent, and closely interrelated health challenges. Cardiac fibrosis represents the common pathological endpoint of multiple cardiac diseases. This review systematically synthesizes the mechanisms underlying obesity-related cardiac fibrosis. It elaborates on how inflammatory factors, cytokines, and miRNAs, acting on adipose tissue and cardiac cells, drive a series of biological processes—including oxidative stress, activation of the renin-angiotensin-aldosterone system, autophagy dysregulation, and metabolic dysfunction—ultimately leading to obesity-associated cardiomyopathy characterized by ventricular remodeling, heart failure, and atrial fibrillation. Potential therapeutic targets for this condition are also examined. Furthermore, this review discusses potential therapeutic targets for this condition, which will provide a critical theoretical foundation for the development of novel strategies aimed at preventing or even reversing obesity-related fibrotic heart disease.

Keywords: obesity, cardiac fibrosis, cardiac dysfunction, inflammation, cytokine, RAAS, autophagy

Introduction

Obesity is a chronic disease defined by the World Health Organization (WHO) as a pathological state characterized by excessive fat accumulation. It is typically assessed using Body Mass Index (BMI), which is calculated as weight (in kilograms) divided by height (in meters) squared. According to the WHO's classification, individuals with a BMI exceeding 30 kg/m^2 are defined as obese.[1,2] Obesity represents a serious global health challenge.[3] Over the past three decades, the obesity rates in countries including the United States, United Kingdom, China, and India have nearly doubled. Projections suggest that by 2030, over half of the global population will be affected by obesity, with the prevalence of severe obesity reaching 11%.[4] Consequently, obesity has emerged as a significant public health concern.

Obesity is not only one of the main risk factors for heart disease but also closely associated with other independent risk factors for heart attacks, such as hypertension, high cholesterol levels, diabetes, and obstructive sleep apnea.[5,6] Moreover, obesity itself imposes the burden on the heart, affecting its structure and pumping function, leading to the development of heart disease. Cardiac fibrosis is a significant physiological and pathological process in heart disease, representing a complication of various cardiac conditions. It entails the gradual replacement of normal myocardial fibers with fibrous tissue in the myocardium. Myocardial fibers play a crucial role in conducting electrical signals and maintaining the structural integrity of the heart in normal cardiac function. Cardiac fibrosis typically involves the proliferation of fibrous proteins, such as collagen, leading to the substitution of originally elastic and contractile myocardium with rigid fibrous tissue.[7–9] These alterations can profoundly impact the structure and function of the heart, leading to diminished contractile ability, ventricular dilation, and ultimately culminating in heart failure (HF) and

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other cardiac diseases. Additionally, mounting evidence indicates that individuals affected by obesity face an elevated risk of developing HF.[10,11] Without lifestyle interventions and targeted medication treatment, obesity can lead to structural and functional damage to the heart.[12–14] Indeed, prevention and treatment of obesity are paramount. In-depth research into the mechanisms underlying obesity is essential for effectively addressing this issue.

This review aims to elucidate the molecular and pathophysiological mechanisms underlying obesity-related cardiac fibrosis and to identify potential therapeutic targets.

Obesity-Induced Cardiac Fibrosis: Clinical Phenotypes

Obesity represents a global health crisis characterized by excessive adipose tissue accumulation, which poses a substantial risk for a wide range of non-communicable diseases. According to the WHO, over one billion people worldwide are currently living with obesity. Obesity is associated with a spectrum of systemic diseases—including cardiac disorders, hypertension, stroke, hepatic and renal diseases, diabetes, atherosclerosis, and sleep apnea syndrome—among which its link to cardiac diseases is particularly robust. These conditions are directly or indirectly related to the development of cardiac fibrosis (Figure 1). Early evidence from the Framingham Heart Study demonstrated that obesity significantly increases the risk of coronary artery disease, HF, and cardiovascular death, independent of common risk factors such as age, sex, smoking, cholesterol, blood pressure, and glucose intolerance, providing foundational

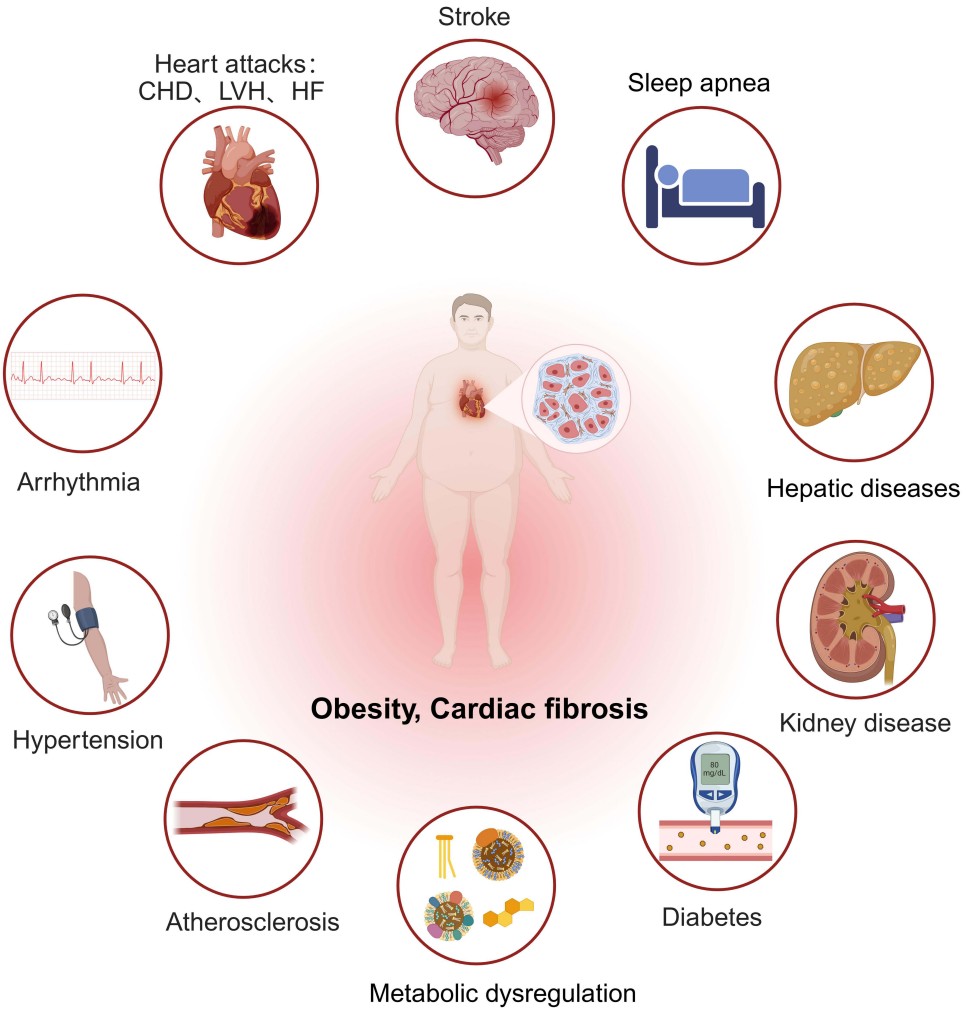

Figure 1 Obesity, Cardiac Fibrosis and Systemic Diseases. Cardiac fibrosis promoted by obesity is associated with a spectrum of systemic diseases, including cardiac disorders (coronary artery disease, left ventricular hypertrophy, heart failure, arrhythmia), hypertension, stroke, sleep apnea syndrome, hepatic diseases, renal diseases, diabetes, atherosclerosis, and metabolic dysregulation.

Abbreviations: CHD, coronary heart disease; LVH, left ventricular hypertrophy; HF, heart failure. Created with https:BioRender.com.

epidemiological support for this association.[15] Furthermore, population-based studies have established a strong correlation between increasing BMI and the incidence of early cardiovascular disease (CVD) or multiple cardiometabolic morbidities.[16,17]

Left Ventricular Remodeling

Numerous animal models and human studies have consistently demonstrated a close association between obesity and the initiation and progression of myocardial fibrosis. Various murine models of obesity have confirmed the development of cardiac fibrosis.[18–21] In obese individuals, there is often an increase in total blood volume and cardiac output (CO), resulting in left ventricular remodeling, hypertrophy, and diastolic dysfunction. Studies have shown that obese individuals are 3.5 times more likely to develop hypertension compared to those with normal weight, with over 60% of hypertension cases can be attributed to fat accumulation.[22] In mice models of hypertension, cardiac muscle exhibits impaired Ca^{2+} transport, alterations in cardiomyocytes ultrastructure, inflammation infiltration, and fibroblast activation.[23,24] In hypertensive fibrosis models, obesity exacerbates myocardial hypertrophy and collagen deposition.[25] In individuals with normal blood pressure and abdominal obesity, ventricular fibrotic cardiac remodeling associated with diastolic dysfunction can be observed, suggesting that obesity exacerbates its impact on the cardiac matrix.[21] One of the primary hemodynamic changes associated with obesity is an increase in left ventricular wall pressure and tension. Among obese patients with normal blood pressure, the increased central blood volume, stroke volume, and CO are the main factors leading to left ventricular dilation and eccentric hypertrophy. Left ventricular eccentric hypertrophy may serve as a compensatory mechanism to heightened wall stress within the left ventricle, potentially culminating in diastolic dysfunction. If the thickening rate of the left ventricular wall does not match the rate of dilation, it may lead to systolic dysfunction. Myocardial fiber thickening serves as a compensatory response to heightened systolic tension. Elevated wall stress during rest or diastole can cause myocardial fiber elongation.[26,27]

Atrial Fibrillation

Atrial fibrillation (AF) is an arrhythmia characterized by irregular and rapid beating of the atria. Once regarded primarily as an electrical disorder, is now understood to be a clinical expression of atrial cardiomyopathy (AtCM), a condition defined by pathological structural, functional, and molecular remodeling of the atria. AtCM is a heterogeneous disease driven by factors such as aging and metabolic dysregulation. The resulting abnormal atrial substrate not only promotes AF initiation but also underlies the increased risk of thromboembolism.[28] Obesity can promote the occurrence of AF through various pathways, including altering the electrophysiological properties of the heart, increasing the load and pressure on the atria, causing changes in cardiac structure, and inducing inflammation and oxidative stress. Obesity-induced cardiac fibrosis contributes to the initiation and persistence of AF. Structural remodeling of the atria mainly includes fibrosis, atrial enlargement, and changes in the ultrastructure of cardiomyocytes.[4,29] Notably, the fibrosis induced by obesity is not limited to the ventricles but also involves the atria, where atrial enlargement is closely associated with fibrosis.[30] In sheep fed a high-fat diet (HFD), obesity is associated with atrial fibrosis and dilation, alongside elevated expression of fibrogenic mediators.[31]

Obesity frequently leads to remodeling of atrial electrical structure, involving alterations in atrial dimensions, conduction properties, histological features, and changes in levels of fibrotic and inflammatory mediators.[31,32] Fibrosis can promote the maintenance of AF through various mechanisms. Fibrotic changes in cardiac tissue lead to irregular and disorganized electrical signal conduction in the atria, laying the groundwork for AF occurrence. Fibrotic atrial tissue may form isolated areas, allowing for the generation and propagation of abnormal electrical signals, thereby increasing the persistence of AF. Simultaneously, the increase in the number of fibroblasts enhances their interaction with cardiomyocytes, resulting in slowed conduction, depolarization of cardiomyocytes, and prolonged action potential duration. Moreover, fibroblasts also affect the electrical activity of cardiomyocytes through the paracrine secretion of bioactive substances.[33,34] Atrial fibrotic remodeling typically originates at the pulmonary vein-left atrial junction and the posterior wall, extending throughout the atria in a regionally heterogeneous yet gradually coalescing pattern. Its progression can be staged from early focal scarring to advanced diffuse fibrosis.[28]

Epicardial adipose tissue (EAT) contains sympathetic and vagal nerve fibers that modulate cardiac autonomic nervous system activity. EAT contributes to AF through mechanisms such as fibrosis, inflammation, oxidative stress, and Ca^{2+} imbalance.[4,35] Clinically, the coexistence of hypertension and AF is prevalent.[36] Statistics indicate that over 60% of atrial AF patients also have hypertension. The Framingham study highlights that hypertension increases the risk of developing AF by 40–50%.[37] Hypertension ultimately impairs myocardial contraction and relaxation functions, leading to elevated left atrial pressure. This pressure increases prompts left atrial dilation, thereby establishing a substrate for AF.[4,38] Circulating fibrocyte levels correlate with both fibrotic burden and AF recurrence, supporting their potential utility as a biomarker. Furthermore, electroanatomical voltage mapping during ablation procedures provides functional correlates of fibrosis, with low-voltage zones increasingly regarded as electrophysiological surrogates of structural remodeling.[39]

In summary, fibrosis is a dynamic and multifaceted process that lies at the core of AtCM pathogenesis and holds important implications for arrhythmia progression and therapeutic intervention.

Heart Failure

The rising prevalence of HF is partly attributed to the increasing rates of overweight and obesity. Existing epidemiological, clinical, and experimental data support the concept of "obesity cardiomyopathy", a cardiac condition that develops independently of coronary artery disease, hypertension, and other cardiac conditions. Obesity-related cardiac pathology manifests with phenotypic heterogeneity, presenting variably as heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF).[27] Long-term obesity may lead to increased cardiac workload, resulting in cardiac enlargement and myocardial hypertrophy, which is a significant mechanism in the development of HF.[40] Left ventricular dilation elevates wall stress, triggering compensatory eccentric hypertrophy. When left ventricular wall thickening matches the degree of dilation, wall stress normalizes, systolic function remains preserved, and HFpEF develops. Conversely, if hypertrophy is insufficient relative to the extent of dilation, wall stress rises substantially, leading to systolic dysfunction. Throughout this pathogenic sequence, obesity is recognized as a central etiological factor in the onset and progression of HFpEF.

Obesity can accelerate cardiac fibrosis by promoting chronic low-grade inflammation and oxidative stress, thereby impairing the normal contraction and relaxation function of the heart. This fibrotic process not only exacerbates HF but also increases the risk of arrhythmias and cardiovascular events. Several studies have indicated a relationship between simple obesity and diastolic dysfunction. Higher BMI and prolonged obesity are often associated with cardiac functional impairments.[41–43] Studies have shown that six months after bariatric surgery, weight loss can improve left ventricular diastolic function and left ventricular morphology in morbidly obese women.[44] Even in healthy overweight individuals, subclinical functional changes have been reported. Tissue Doppler imaging of overweight and mildly obese individuals without clinical heart disease revealed a reduction in both systolic and diastolic function of the ventricles, despite preserved ejection fraction. These functional changes were correlated with fasting insulin levels.[45] Obesity-induced cardiac fibrosis is associated with various diseases, making the development of CVD a significant concern in obesity.

Adipose Tissue and Cardiac Fibrosis

Adipose tissue (AT) is considered an endocrine organ and a "primordial immune organ".[16] Subcutaneous adipose tissue (SAT) is the primary lipid storage depot, which under physiological conditions helps prevent excessive lipid accumulation in peripheral organs such as the liver, heart, and muscles. However, impaired adipogenesis, limited expansion, and functional disturbances of SAT lead to adipocyte hypertrophy and increased fibrosis of AT.[46–48] Lipids can accumulate in visceral adipose tissue (VAT) as well as other tissues with lower fat content, including the liver, skeletal muscles, heart, and pancreas.[49] Some ectopic fat depots, such as vascular adipose tissue, intrahepatic fat, and intramuscular fat, primarily generate systemic effects.[47]

The fat tissue around the heart is divided into two layers based on anatomical location: EAT and paracardial adipose tissue (PAT). EAT refers to the fat tissue located between the visceral layer of the pericardium and the outer surface of the heart, adjacent both anatomically and functionally to the myocardium. Lacking a separating muscular fascia, EAT shares the same microcirculation as the adjacent myocardium. PAT is located outside the visceral layer of the pericardium.[50–52]

Perivascular adipose tissue (PVAT) refers to the fat tissue surrounding blood vessels, playing a crucial role in maintaining vascular function. Adverse local cardiovascular effects are associated with the fat tissue around the heart.[47,53,54]

Obesity leads to a wide range of pathophysiological changes and contributes to the development of cardiac fibrosis. The deposition of fat, especially excessive accumulation in metabolically active VAT and pericardial fat, increases CO and workload, leading to left ventricular enlargement to adapt to the increased energy demand.[13] In obese patients, volume and pressure overload result in hypertension. The increase in systemic blood pressure due to obesity-induced cardiac pressure overload may contribute to left ventricular hypertrophy and increased fibrosis. Additionally, obesity is associated with increased blood volume, leading to volume overload.[55] Pressure overload leads to myocardial hypertrophy, which is associated with increased collagen deposition and diastolic dysfunction. Conversely, volume overload leads to cardiac dilation accompanied by matrix degradation.[56,57]

The expansion of AT includes proliferation or adipogenesis (differentiation of precursor cells into new adipocytes) and hypertrophy (increase in the size of adipocytes).[58] Impaired adipogenesis, along with limited expansion and functional impairment of SAT, leads to hypertrophic hyperplasia of adipocytes and increased fibrosis of AT.[46,59] With the increased secretion of pro-inflammatory adipokines, the dysfunction of PVAT in obesity may lead to increased oxidative stress in blood vessels, resulting in endothelial dysfunction, impaired vasodilation, and vascular stiffness. These changes contribute to vascular dysfunction and CVD.[60,61]

EAT is a specialized visceral adipose tissue situated between the cardiac surface and the visceral pericardium, encompassing adipocytes, inflammatory cells, immune cells, stromal cells, as well as ganglia and nerve fibers. EAT serves as a key player in the development of obesity-related cardiac dysfunction by fostering cardiac inflammation and metabolic disruption (Figure 2). Dysfunctional EAT in obesity exhibits a shifted secretory profile, marked by altered pro-/anti-inflammatory factor balance and chemokine release that promotes macrophage polarization to the M1 phenotype. This process is amplified by local cytokine upregulation, which enhances monocyte recruitment. The infiltrated M1 macrophages subsequently secrete a range of inflammatory mediators, establishing a self-perpetuating inflammatory loop. Ultimately, these mediators drive cardiac disease progression via cross-talk among multiple cardiac cell populations.[62] It acts as a hallmark of cardiac lipotoxicity, directly influencing cardiac structure and function. This includes the promotion of increased left ventricular mass, alterations in right ventricular shape, and impaired diastolic function. The augmented EAT imposes additional mechanical pressure on both ventricles, elevating the heart's workload and resulting in left ventricular hypertrophy. Moreover, its physical hindrance to cardiac filling exacerbates atrial enlargement and ventricular diastolic dysfunction.[63–65] EAT is rich in genes associated with inflammation and endothelial dysfunction in obesity, serving as a local source of pro-inflammatory adipocytokines. Serum levels of inflammatory markers are directly correlated with the large volume of low-density EAT. Pro-inflammatory adipocytokines promote myocardial dysfunction, cardiac fibrosis, and increased myocardial stiffness in obesity.[66,67] Furthermore, in addition to inducing fibroblasts, AT itself can undergo fibrosis.[68] The examination of fibrosis markers can aid in identifying preclinical cardiac fibrosis associated with lipotoxic myocardial injury in patients with EAT-related obesity.[69] The study indicates that in patients with AF, EAT-derived myeloperoxidase and neutrophil extracellular traps are increased before AF develops and are most pronounced in persistent AF, highlighting their potential role in mediating fibrotic remodeling in AF.[70]

Obesity, Cardiac Fibrosis and Cells

Cardiac fibrosis is mediated by interactions between multiple cell types (Figure 3). Although the cellular mechanisms of fibrosis have been widely studied, how obesity and metabolic dysfunction trigger these pathogenic cellular changes is the focus of ongoing research.

Cardiomyocytes

In obesity, a portion of the heightened cardiovascular risk arises from cardiomyocyte death or apoptosis, further worsening myocardial dysfunction. Several studies indicate that the rate of cardiomyocyte apoptosis may increase under conditions of obesity.[71,72] This may contribute to the development of cardiac fibrosis. Factors released by AT, oxidative stress, and other mediators can induce apoptosis in cardiomyocytes, thereby facilitating collagen deposition. In

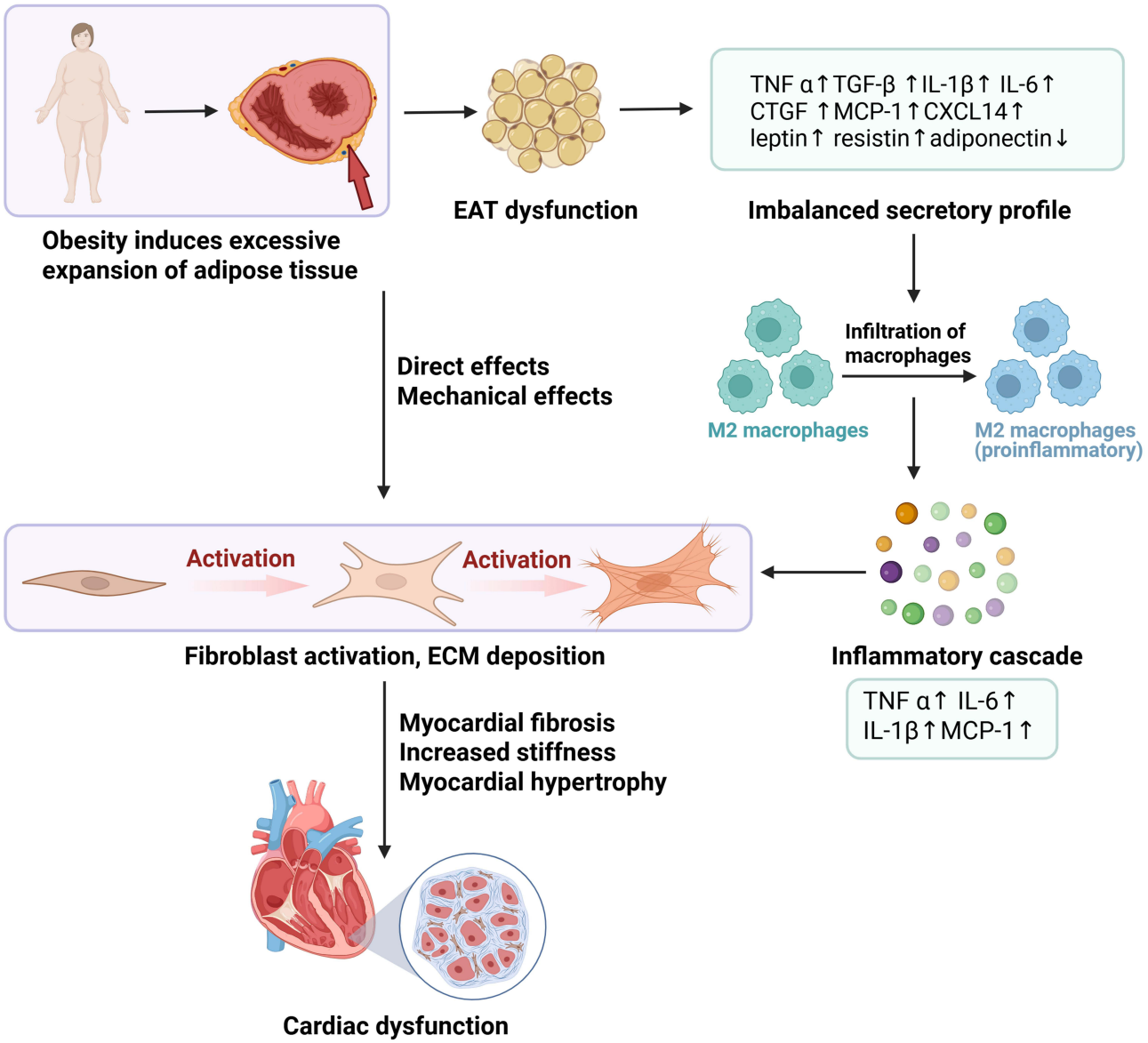

Figure 2 The role of EAT in obesity-induced cardiac fibrosis. Obesity induces the excessive expansion of EAT, leading to its dysfunction. This process results in a dysregulated secretion profile of pro-inflammatory factors, chemokines, and adipokines. This phenomenon promotes macrophage infiltration and their polarization toward a pro-inflammatory M2 phenotype. Concurrently, EAT exerts both direct biochemical and external mechanical effects on the adjacent myocardium. The inflammatory milieu, further amplified by factors such as TNF-α, IL-6, IL-1β, and MCP-1, drives the activation of cardiac fibroblasts. This leads to ECM deposition, myocardial fibrosis, and increased myocardial stiffness. These structural alterations, together with the development of myocardial hypertrophy, ultimately contribute to overall cardiac dysfunction. **Abbreviations**: EAT, epicardial adipose tissue; TNF, tumor necrosis factor; TGF, transforming growth factor; IL, Interleukin; CTGF, connective tissue growth factor; MCP, Monocyte Chemoattractant Protein; CXCL14, chemokine ligand 14, ECM, extracellular matrix. Created with https:BioRender.com.

the process of myocardial remodeling, cardiomyocytes may modulate the fibrotic response by directly interacting with interstitial cells and secreting cytokines and growth factors that influence the phenotype of fibroblasts.[73] Metabolic abnormalities in cardiomyocytes associated with obesity can affect their function. For instance, disruptions in lipid metabolism and insulin resistance (IR) may lead to increased lipid deposition within cardiomyocytes, triggering inflammatory responses and oxidative stress, thereby promoting fibrosis. The excessive accumulation of fatty acids and triglycerides in cardiomyocytes can exert lipotoxic effects, ultimately resulting in cardiac dysfunction and cell death.[74] Cardiomyocytes in obesity may influence the fibrogenic properties of cardiac fibroblasts by releasing pro-inflammatory and pro-fibrotic mediators, thereby contributing to the fibrotic response.[75] Enlarged cardiomyocytes have been shown to produce fibrogenic growth factors and proteases, which are involved in the pathogenesis of cardiac

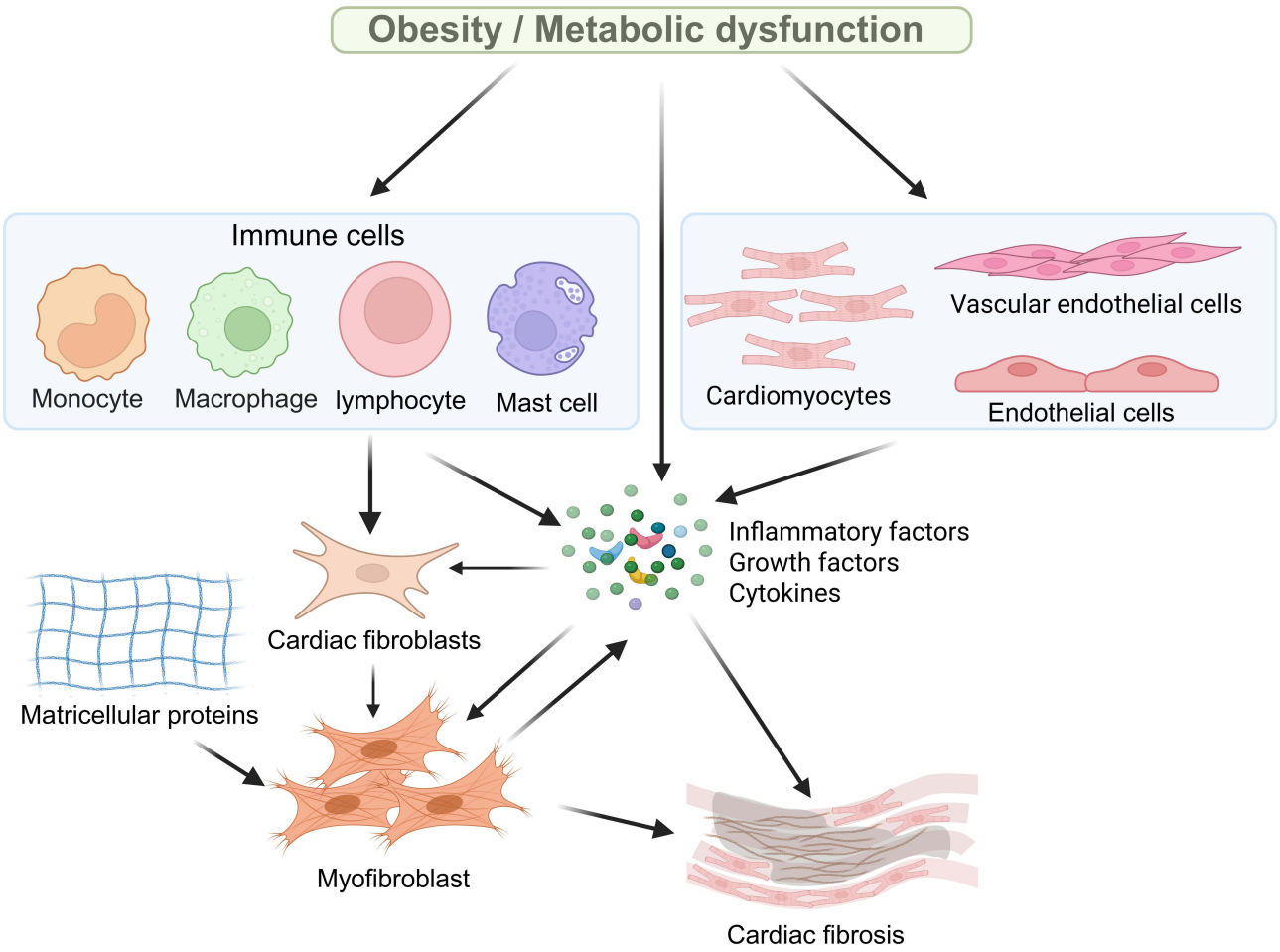

Figure 3 Cellular Mechanisms of Cardiac Fibrosis in Obesity and Metabolic Dysfunction. Cardiac fibroblasts are the primary effector cells responsible for the deposition of extracellular matrix in cardiac fibrosis. These cells can be directly activated or indirectly modulated by a multitude of other cardiac cell types, including cardiomyocytes, endothelial cells, vascular cells, and immune cells (eg, macrophages, monocytes, lymphocytes, mast cells). These diverse cells collectively contribute to obesity-associated fibrosis by releasing soluble paracrine factors or through contact-dependent mechanisms. Created with BioRender.com.

fibrosis in models of myocardial infarction (MI), cardiac pressure overload, and cytokine overexpression.[76–78] The role of mast cells in obesity-related cardiac fibrosis remains unclear. Overall, cardiomyocytes play a significant role in obesity-induced cardiac fibrosis, participating in both the initiation and progression of fibrosis.

Fibroblasts

As the primary matrix-producing cells in the cardiac interstitium, fibroblasts are integral to all cardiac fibrotic disorders. Their function and activity are regulated by various factors, and they participate in multiple cellular signaling pathways, such as TGF-β and Wnt/β-catenin, which are crucial for the occurrence and progression of cardiac fibrosis. During the fibrotic process, fibroblast proliferation and migration are essential steps. They proliferate and migrate to damaged areas, contributing to the formation and expansion of fibrotic plaques. Fibroblasts are the main collagen-producing cells in the heart. Following cardiac injury, fibroblasts undergo differentiation into myofibroblasts, expressing contractile proteins such as α-smooth muscle actin (α-SMA), and forming stress fibers.[79,80]

In obesity, fibroblasts may become activated, promoting the synthesis and deposition of collagen. This leads to an excessive collagen accumulation in cardiac tissues, thereby initiating the fibrotic process. Activated fibroblasts may release inflammatory factors, further promoting inflammation and fibrosis.[81,82] Fibroblasts participate in cardiac tissue remodeling by regulating the synthesis and degradation of the extracellular matrix (ECM). They secrete enzymes such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases to degrade and remodel the ECM.

Fibroblasts isolated from db/db mice exhibit a matrix-retaining phenotype, characterized by increased expression of collagen and proteinase inhibitors such as plasminogen activator inhibitor (PAI)-1.[83] Descriptive studies suggest that obesity is associated with phenotypic changes in cardiac fibroblasts. For instance, cardiac fibroblasts isolated from Zucker rats exhibit enhanced contractile gel capacity and increased expression of α-SMA, consistent with a myofibroblast phenotype.[84] Additionally, research indicates that leptin-induced production of collagen, TGF-β, monocyte chemoattractant protein-1 (MCP-1), connective tissue growth factor (CTGF), and reactive oxygen species (ROS) involves of lysyl oxidase (LOX), an ECM-modifying enzyme primarily expressed in cardiac fibroblasts. Inhibiting LOX activity can significantly alleviate cardiac fibrosis.[85] Studies using single-cell transcriptomics have identified key markers of obesity-induced cardiac fibrosis. Transcriptomic data from non-cardiomyocyte cells indicate that the primary cell types include fibroblasts, immune cells, and endothelial cells. Functional enrichment analysis shows that differentially expressed genes are closely associated with collagen and ECM. Col1a1 and Col1a2 may serve as important markers of obesity-induced cardiac fibrosis, with fibroblasts playing a crucial role in this process.[86]

Metabolic changes associated with obesity may activate cardiac interstitial fibroblasts. Factors such as elevated blood glucose levels, activation of the renin-angiotensin-aldosterone system (RAAS), and the involvement of cytokines and growth factors can regulate the phenotype of cardiac fibroblasts, leading to their proliferation and inducing pathways for matrix synthesis and retention. In ischemic fibrosis models, the recruitment of precursor cells to fibroblasts aids in the remodeling of fibrotic myocardium.[87] Fibroblasts play a key role in obesity-induced cardiac fibrosis, and changes in their activity and function directly impact the structure and function of the heart, ultimately leading to the occurrence and progression of cardiac fibrosis.

Vascular Cells

In obesity-induced cardiac fibrosis, vascular cells play a crucial role, impacting the structure and function of cardiac tissue and contributing to the occurrence and progression of fibrosis. The heart contains abundant endothelial cells, vascular smooth muscle cells (VSMCs) and pericytes. Endothelial cells may experience functional abnormalities in obesity, leading to endothelial dysfunction. This dysfunction can result in an imbalance of vascular tone and increased vascular wall permeability, thereby promoting inflammation and fibrosis. Endothelial cells may contribute to cardiac fibrosis by producing various pro-fibrotic mediators, such as endothelin-1 (ET-1), TGF-β, and several pro-inflammatory cytokines and chemokine.[88–90] Additionally, endothelial cells may promote cardiac fibrosis by providing a new source of activated fibroblasts through endothelial to mesenchymal transition (EndMT). In experimental models of chronic pressure overload, MI, and diabetes, EndMT has been closely associated with the pathogenesis of cardiac fibrosis.[91,92] Experimental studies have shown that EndMT is involved in the expansion of cardiac interstitial fibroblasts in type 1 diabetes models.[93]

In the obese state, VSMCs may undergo hypertrophy and functional abnormalities, leading to changes in vascular wall structure and function. This may promote fibrosis by stimulating cell proliferation and the synthesis of collagen and other matrix components. Additionally, immune cells surrounding blood vessels, such as macrophages and lymphocytes, may undergo inflammatory reactions and release inflammatory factors that promote endothelial damage and fibrosis. Vascular neogenesis may also be affected in obesity-induced cardiac fibrosis. The formation of new blood vessels is regulated by various factors, including inflammatory factors, growth factors, and cytokines, which may directly or indirectly influence the process of cardiac fibrosis.[94] In obesity, increased vascular permeability can lead to the infiltration of inflammatory cells and mediators such as proteins into the vascular wall and surrounding tissues, thereby promoting the occurrence and progression of fibrosis. However, the exact role of vascular cells in obesity and cardiac fibrosis remains unclear.

Immune Cells

Immune cells such as macrophages and lymphocytes, recruited to AT after activation, transform into an active inflammatory phenotype, releasing inflammatory mediators that promote inflammation and fibrosis in cardiac tissue. The AT of obese individuals is typically infiltrated by many activated macrophages, reflecting a systemic inflammatory state. The degree of macrophage infiltration is directly proportional to an individual's body weight. When weight is

reduced, both the number of infiltrating macrophages and the levels of inflammatory factors decrease. Compared to lean animals, db/db mice show increased accumulation of macrophages in the cardiac interstitium.[95,96] In a pig model, obesity related to metabolic dysfunction led to increased infiltration of pro-inflammatory M1 macrophages, exacerbating cardiac fibrosis in the narrowed coronary artery perfusion area.[97] Adipose tissue macrophages (ATMs) can be classified into two main phenotypes: M1 (classically activated macrophages) and M2 (alternatively activated macrophages).[98] In lean mice, ATMs typically exhibit an M2 anti-inflammatory phenotype, whereas in obese mice, ATMs predominantly display an M1 phenotype. Generally, M2 macrophages produce anti-inflammatory adipokines, contributing to maintaining AT homeostasis by participating in processes such as phagocytosis of necrotic or apoptotic cells, tissue remodeling, and damage-induced cardiac fibrosis.[99,100] In contrast, obesity leads to an increase in M1 macrophages in AT, which is associated with AT inflammation and IR triggered by pro-inflammatory cytokines.[46,101]

EAT is a major source of M1 macrophages in the heart and may be a primary factor contributing to obesity-related cardiac abnormalities. Both systemic and cardiac inflammation, which are associated with obesity and pathological cardiac remodeling, are predominantly mediated by M1 macrophages.[102] Macrophages contribute to obesity-induced cardiac hypertrophy and dysfunction, mediating left ventricular inflammation and remodeling through multiple mechanisms. Firstly, macrophages promote pathological hypertrophy and impair cardiac contractile and diastolic function by releasing pro-inflammatory cytokines. Additionally, macrophages degrade the ECM by secreting MMPs and phagocytosing dead cardiomyocytes. They also drive myocardial stiffness by activating fibroblasts, promoting collagen deposition, and secreting ECM proteins, indirectly affecting myocardial relaxation.[102,103]

Macrophages represent a promising therapeutic target for the prevention and alleviation of obesity-induced cardiomyopathy. Ezetimibe, an effective cholesterol absorption inhibitor, has been shown to ameliorate macrophage infiltration in the hearts of db/db mice, thereby reducing the extent of interstitial fibrosis and coronary artery thickening.[96] Additionally, the use of low-dose spironolactone to inhibit the mineralocorticoid receptor (MR) has been shown to selectively increase M2 macrophages, leading to reduced cardiac inflammation, restoration of diastolic function, and alleviation of cardiac fibrosis.[104] Besides macrophages, other immune cells are also significant contributors to the inflammatory response that can impact overall energy metabolism. For instance, monocytes and lymphocyte subpopulations are involved in the pathogenesis of cardiac fibrosis in models of MI and cardiac remodeling due to pressure overload.[80,105] Within the Helper T cell (Th) subset, Th2 cells are important drivers of cardiac fibrosis, primarily through the production of Interleukin-4 (IL-4) and IL-13, which are potent inducers of M2 macrophages.[106–108] Th17 cells have been shown to drive fibrotic responses through the secretion of fibrosis-related cytokine IL-17 under pathological conditions such as chronic pressure overload and diabetes.[109,110] Although the accumulation and activation of immune cells in obesity have been extensively studied, the exact mechanisms by which these inflammatory changes trigger and exacerbate cardiac fibrosis remain not fully understood.

Cardiac Fibrosis and Extracellular Matrix

Normal cardiac structure and contractility rely on a complex ECM primarily composed of fibrillar collagen. Normal cardiac structure and contractility rely on a complex ECM primarily composed of fibrillar collagen. Type I collagen forms thick fibers that provide tensile strength, while type III collagen forms thin fibers that maintain elasticity. In addition to these collagens, the interstitial cardiac ECM contains glycosaminoglycans, glycoproteins, and proteoglycans. The cardiac ECM interacts with numerous proteinases and growth factors, playing a crucial role in cardiac remodeling. Cardiomyocytes and interstitial cells, including fibroblasts, vascular cells, and immune cells, integrate into the collagenous matrix, interact with it, and respond to changes in the microenvironment.[111] Obesity induces alterations in the cardiac ECM, characterized by heightened deposition of collagen. Collagen, a principal constituent of the ECM, demonstrates varied concentrations of its degradation products in heart diseases.[112] These ECM modifications profoundly impact cardiac structure and function. Factors such as lipid metabolites, ECM-regulating molecules, and the TGF-β signaling pathway can directly or indirectly influence cardiac fibrosis in obesity. Fibrosis, a predominant pathological alteration observed in obese animal models, may augment myocardial stiffness, consequently precipitating cardiac dysfunction.[113]

Obesity-Induced Cardiac Fibrosis: Molecular Signaling Pathways

In the context of obesity, dysfunctional AT mediates the development of cardiac fibrosis through multiple pathways (Figure 4). Chronic inflammation is a hallmark feature of obesity, which is a progressive pathological process typically associated with IR and Type 2 diabetes mellitus (T2MD). This inflammatory cascade activates both adipocytes and immune cells, leading to the release of an array of secretory factors. Inflammation within the cardiac tissue may contribute to myocardial fibrosis. Both animal studies and clinical observations in human subjects demonstrate a close correlation between obesity and systemic inflammatory responses. Given the intimate association between inflammatory pathways and the pathogenesis of fibrosis and cardiac remodeling, the activation of inflammatory signals observed in obese individuals may precipitate fibrosis and cardiac hypertrophy.[67,80,114–116] In general, adipokines comprise hormones, metabolites, exosomes, microRNAs (miRNAs), cytokines, and chemokines secreted by AT and transmitted to other organs. These include adiponectin, leptin, resistin, TGF-β, interleukins, free fatty acids, and others.[117,118] A hallmark of obesity is the dysregulation of adipokine secretion, marked by a reduction in anti-inflammatory adipokines and an increase in pro-inflammatory ones. This shift exerts multifaceted effects on physiological processes, including appetite

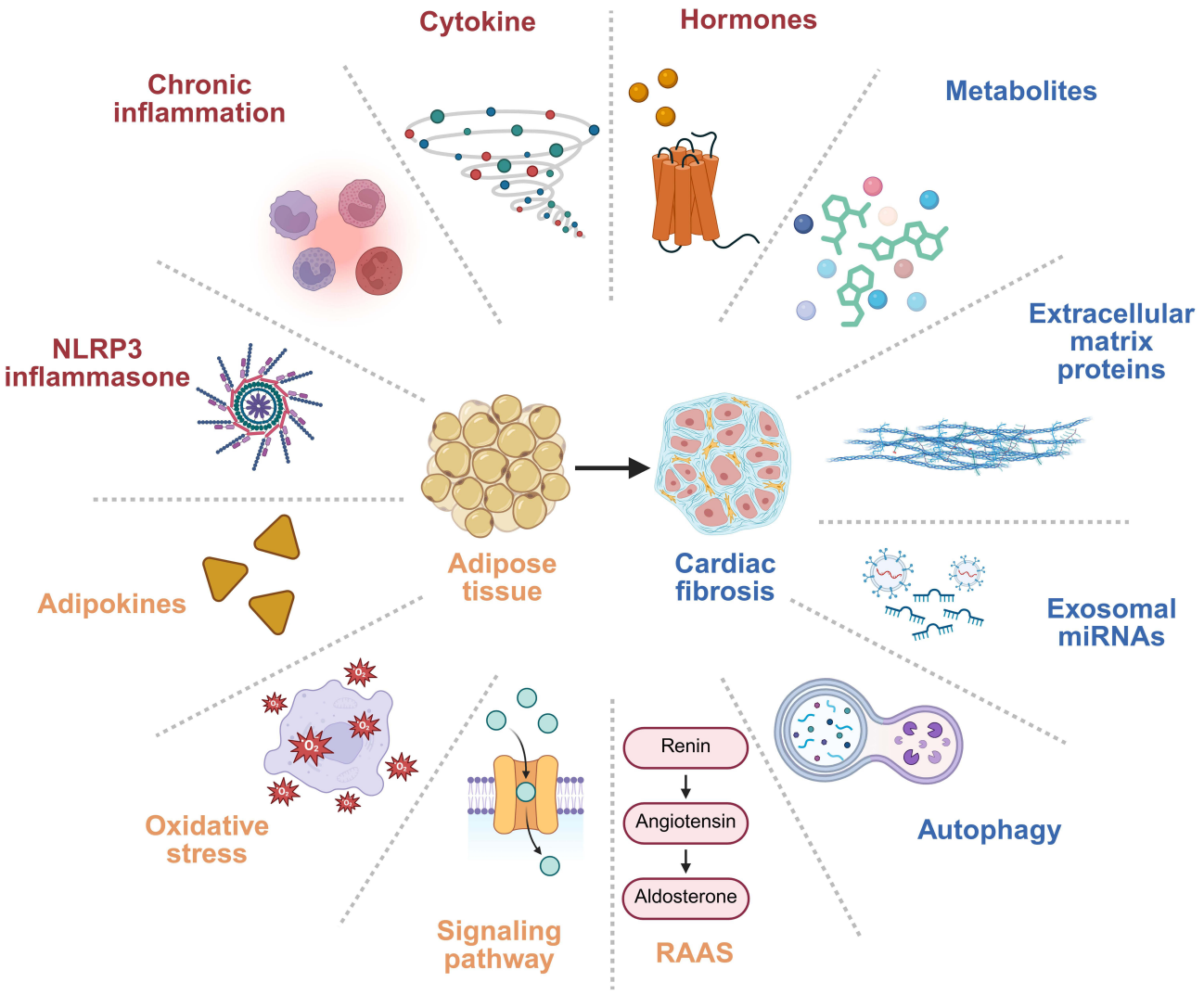

Figure 4 Adipose tissue dysfunction in obesity mediates cardiac fibrosis through multiple pathways. In the context of obesity, dysfunctional adipose tissue contributes to the development of cardiac fibrosis through multiple biological processes. These include chronic inflammation and NLRP3 inflammasome activation, oxidative stress, autophagy, altered secretion of cytokines, metabolites and hormones, activation of the RAAS, dysregulation of specific signaling pathways, modifications in extracellular matrix proteins, and the release of exosomal miRNAs. Created with BioRender.com.

Abbreviations: NLRP3, NOD-like receptor thermal protein domain associated protein 3; RAAS, renin-angiotensin-aldosterone system.

regulation, energy homeostasis, endothelial function, and immune response. It fosters the onset of chronic systemic inflammation and IR, recognized as central mechanisms in obesity-related CVD.[27,119] These bioactive molecules exert direct or indirect influence on myocardial fibrosis by activating inflammation responses, oxidative stress, or other signaling pathways.

Oxidative Stress

The accumulation of oxidative stress in AT is an early event in obesity.[120] Compared to non-obese subjects, oxidative stress significantly increases in both obese animals and human WAT.[121] Furthermore, the increase in body weight in children and adolescents is positively correlated with elevated levels of oxidative stress.[122,123] Extensive research indicates that oxidative stress exacerbates in obesity models.[85,124,125] The hallmark of oxidative stress is the excessive generation or impaired clearance of highly reactive molecules, particularly ROS. Obesity-induced oxidative stress plays a significant role in myocardial fibrosis. This oxidative stress contributes to cardiac fibrosis either by directly affecting cardiac fibroblasts or by participating in fibrogenic processes. ROS are involved alongside other fibrosis-promoting factors such as TGF-β, ET-1, Angiotensin (Ang) II, and aldosterone.[126,127] Reduction of body weight and fat accumulation can decrease the formation of ceruloplasmin, thereby reducing the production of reactive oxygen metabolites and α-dicarbonyl compounds, and lowering oxidative stress indicators such as ROS, nitric oxide, and malondialdehyde.[4]

In obesity, excessive fatty acid oxidation and mitochondrial dysfunction may lead to oxidative stress. Moreover, the inflammatory process itself may activate oxidative stress responses associated with inflammatory pathways, creating a vicious cycle where oxidative stress and inflammation interact.[128,129] Studies have demonstrated the in vivo role of oxidative stress in obesity-related cardiac fibrosis through drug interventions. Research indicates that the use of antioxidants can slow down or reverse myocardial fibrosis in obese patients.[130] Administration of antioxidants such as MitoQ and vitamin E effectively inhibits oxidative stress, reduces cardiac fibrosis, and improve cardiac dysfunction in HFD-induced obese rodents, thereby supporting the involvement of oxidative stress in obesity-related cardiac fibrosis.[131,132] Mitochondrial ROS scavengers have been shown to reduce cardiac fibrosis in obese rats fed a HFD.[133] Additionally, treatment of mice fed a high-fat, high-sugar diet with polyphenols such as resveratrol and S17834 (a synthetic flavonoid derivative) lowers oxidative modification levels and prevents cardiac hypertrophy, interstitial fibrosis, and diastolic dysfunction.[19] Supplementation with the dietary antioxidant coenzyme Q10 for 10 weeks in db/db mice resulted in reduced superoxide production, improved diastolic dysfunction, and alleviated cardiomyocyte hypertrophy and fibrosis.[134]

Research has found that in the myocardium of db/db mice, the production of mitochondrial ROS significantly increases, and the degree of lipid and protein peroxidation also rises.[135] Additionally, non-mitochondrial mechanisms may contribute to the exacerbation of cardiac oxidative stress in obese animal models.[136] Hyperglycemia and IR may directly increase the generation of myocardial ROS in metabolically dysfunctional obese animals. Furthermore, defects in free radical clearance may also cause the observed increase in oxidative stress levels in obese animals. For example, rats fed a HFD and Zucker rats with genetic obesity exhibit diminished activation of myocardial antioxidant enzymes such as manganese superoxide dismutase and glutathione peroxidase-1.[137,138] Moreover, ROS stimulate the proliferation of atrial fibroblasts and promote the expression of inflammatory and fibrotic factors such as MMP-9, p38, and c-Jun.[139]

RAAS

RAAS is an crucial hormone system involved in regulating blood pressure and fluid balance, and it is also implicated in the development of CVD. The activation of RAAS persists throughout the progression of cardiac fibrosis.[140] Activation of RAAS has been reported in animal models of obesity and T2MD.[111] Levels of Ang II are elevated in db/db mice, and plasma activity of angiotensin-converting enzyme (ACE) is also significantly increased.[141] Additionally, crossing Dahl and Zucker rats to produce obese Dahl salt-sensitive rats results in elevated levels of ACE and Ang II receptors 1 (AT1Rs) in the myocardium.[142] Activation of the RAAS is evident in fibrotic myocardium. Increasing evidence suggests that each component of RAAS is closely associated with the pathogenesis of obesity-related cardiac fibrosis. In vivo administration of RAAS inhibitors can attenuate interstitial fibrosis in experimental models of MI and pressure overload-induced cardiac remodeling.[143–145] Therefore, RAAS inhibitors such as ACE inhibitors (ACEIs), Ang II receptor

blockers (ARBs), and aldosterone receptor antagonists are widely used in the treatment of CVD, including cardiac fibrosis. These drugs can reduce levels of Ang II and aldosterone, thereby reducing cardiac load, decreasing activation of cardiomyocytes and fibroblasts, and thus delaying or reversing the progression of cardiac fibrosis.

Renin serves as the initiating enzyme of the RAAS, directly or indirectly triggering cardiac fibrosis, playing a crucial role in the generation of Ang II. RAAS directly influences the occurrence and development of cardiac fibrosis by regulating the activity of Ang II and aldosterone. Research has demonstrated that renin can induce a profibrotic response in cardiac fibroblasts, while renin inhibitors significantly improve cardiac fibrosis and diastolic dysfunction in obese db/db mice.[146,147] Ang II is a classic profibrotic molecule whose production depends on the key enzyme ACE and activates cardiac fibroblasts, proliferation, and collagen synthesis through the AT1R, either dependent on or independent of TGF-β signaling.[148] ACEIs or ARBs have been reported to reduce collagen deposition in the myocardium of genetically and HFD-induced obese rats.[149,150] In addition to preclinical evidence, some clinical studies have shown that the use of ACEIs and ARBs can reduce the risk of all-cause mortality and hospitalization and improve the prognosis of patients with HFpEF, indicating that pharmacological intervention targeting Ang II may be beneficial in alleviating cardiac fibrosis and diastolic dysfunction in HFpEF.[151–153]

A high-glucose environment can increase levels of renin and Ang II in cardiac fibroblasts, and Ang II signaling activation is closely associated with the synthesis of matrix proteins and TGF-β induced by high glucose.[154] In obese Zucker rat models, treatment with perindopril to inhibit ACE can reduce collagen synthesis in the myocardium and decrease levels of PAI-1 and TGF-β.[149] Treatment with ACEIs or ARBs in ob/ob and db/db mice can effectively reduce the degree of fibrosis around coronary arteries.[155,156] Additionally, it was found that the use of ACEIs in db/db mice can reduce the generation of superoxide in the myocardium, indicating that angiotensin signaling may promote myocardial oxidative stress through pathways independent of TGF-β signaling.[157] Activation of AT1R in IR rats promotes the production of myocardial ROS, thereby facilitating the transmission of inflammatory signals.[158] The use of captopril not only normalizes myocardial insulin signaling and insulin-regulated metabolic processes but also alleviates autonomic dysfunction in ob/ob mice.[159,160]

Aldosterone can directly stimulate the proliferation, migration, and collagen production of cardiac fibroblasts. It induces macrophages and T cells to adopt profibrotic phenotypes and activates fibrotic signals derived from cardiomyocytes and endothelial cells by interacting with MR expressed in these cells.[140] In rodent models of obesity, administration of the MR antagonist spironolactone significantly alleviates cardiac fibrosis and diastolic dysfunction.[104,161] Similarly, in obese human subjects with or without other comorbidities, aldosterone antagonists can improve left ventricular function and myocardial acoustic characteristics, and reduce circulating levels of fibrosis biomarkers.[162,163] Besides causing sodium retention, excess aldosterone may also promote inflammation in EAT, leading to microvascular rarefaction and fibrosis in the myocardium. Perivisceral AT can transform into a proinflammatory phenotype through a MR-dependent pathway.[164]

NLR Family Pyrin Domain Containing 3 (NLRP3)

NLRP3 inflammasome is a multiprotein complex that acts as innate immune sensors, recognizing "danger signals" and triggering the activation of caspase-1, which leads to the release of IL-1β and IL-18. Once activated, the NLRP3 inflammasome initiates an inflammatory response, thereby influencing immune system function and the body's inflammatory state. Its activation has been associated with both inflammation and fibrosis.[165,166]

In obesity, the activation of the NLRP3 inflammasome appears to contribute to the development of myocardial fibrosis. Both caloric restriction and exercise have shown efficacy in reducing NLRP3 levels in AT, thereby suppressing inflammation and improve insulin sensitivity in obese individuals. The NLRP3 inflammasome promotes intracellular neuroinflammation by activating caspase-1 in macrophages and adipocytes, consequently elevating intracellular ceramide levels.[27] Studies have demonstrated the activation of NLRP3 inflammasomes in the heart and other organs with increasing body weight in patients, sheep, and mice.[167,168] Inhibition of NLRP3 in the heart has been found to mitigate atrial arrhythmias induced by a HFD, highlighting the significant role of NLRP3 inflammasomes in obesity-related arrhythmias.[167,169] Furthermore, NLRP3 deficiency has been associated with delayed systemic inflammation, left ventricular concentric remodeling, and diastolic dysfunction resulting from obesity.[168] Additionally, research suggests

that activation of the NLRP3 inflammasome contributes to cardiac inflammation and hypertrophy under pressure overload conditions,[170] and its signaling pathway is implicated in cardiac fibrosis in obese hypertensive rats.[171]

NLRP3 may interact with various signaling pathways, potentially exacerbating the progression of cardiac fibrosis. For instance, NLRP3 might crosstalk with the TGF-β signaling pathway, collectively affecting the fibrotic process.[172] In a study conducted by Che et al, inhibition of NLRP3 inflammasomes alongside TGF-β1/Smads notably ameliorated cardiac function and reduced collagen production in diabetic mice.[173] Evidence suggests that activation of NLRP3 could escalate oxidative stress levels, consequently eliciting a cascade of pathological responses, including inflammation and fibrosis.[174] IL-1β, a potent inflammatory cytokine, exhibits significant elevation in CVD and cardiac fibrosis, thereby contributing to fibrotic progression.[175]

Obesity-Associated Molecules in TGF-β-Mediated Cardiac Fibrosis

Under obesity conditions, multiple inflammatory factors produced by AT are released into the circulatory system, thereby affecting distant organs including the heart. Within this process, TGF-β serves as the central regulator of fibrotic mechanisms.

TGF-β

TGF-β stands as a pivotal cytokine with a significant role in cardiac fibrosis. It exerts pleiotropic effects on cardiovascular cells, regulating cell growth, fibrosis, and inflammation. Obesity may trigger the activation of TGF-β, consequently promoting collagen synthesis and myocardial fibrosis. Moreover, TGF-β effectively induces cardiac hypertrophy and sustains the ECM phenotype in cardiac fibroblasts.[176,177] Primarily, TGF-β mediates its fibrotic effects through the Smad signaling pathway. Experimental evidence from obesity studies reveals heightened expression of TGF-β in the myocardium, correlating with cardiac fibrosis. In obesity-related cardiomyopathy, the upregulation of TGF-β may be induced by Ang II signaling,[31,149] as well as directly stimulated by high glucose and leptin levels, thereby activating transcription and activation pathways.[178,179] Comparative analysis between lean and obese rabbits demonstrates significantly elevated levels of TGF-β1 in the left ventricle of obese subjects, potentially contributing to increased collagen deposition.[180] Inhibition of TGF-β has shown promise in reducing cardiac fibrosis, while Ang II can activate the Smad pathway independently of TGF-β, sharing many numerous signaling pathways associated with fibrosis.[94]

Tumor Necrosis Factor α (TNF α)

TNF-α, acting as an upstream signaling molecule of TGF-β, is a key inflammatory cytokine involved in cardiac structural remodeling. TNF-α can modulate the expression of connexin-40 in mice and promote myofibroblast activation by triggering the TGF-β signaling pathway, thereby initiating atrial fibrosis.[181,182] Furthermore, TNF-α can induce the expression of MMP-2 and MMP-9, disrupting the distribution of connexin-43 in atrial tissue and promoting myocardial remodeling.[182] Elevated plasma levels of TNF-α are associated with obesity. Inhibition of TNF-α in HFD-fed rats can suppress cardiac fibrosis.[183] In a study involving 110 obese males, it was found that the serum levels of TNF-α and IL-6 were significantly elevated in subjects with an epicardial fat thickness ≥ 7 mm, whereas the levels of leptin and adiponectin were decreased compared with those in the control group.[69]

Interleukin

IL-6, a multifunctional cytokine intricately involved in immune responses and inflammation, emerges as another inflammatory factor associated with obesity and implicated in cardiac fibrosis.[184] Deficiency in IL-6 may exacerbate insulin resistance, cardiac lipid accumulation, interstitial fibrosis, and obesity-related inflammation resulting from a HFD.[185] IL-6 likely contributes to the progression of myocardial fibrosis by activating fibrotic pathways such as TGF-β and also promotes AF by influencing atrial electrical remodeling and fibrosis.[186] IL-6 induces early atrial fibrosis and enhances the expression of α-SMA, type I collagen, and type III collagen by inhibiting regulatory T cells (Tregs) function.[187,188]

Thrombospondin-1 (TSP-1)

TSP-1 is a key platelet response protein and the most common ECM protein involved in obesity, diabetes, and metabolic disorders.[189] Clinical studies have shown that abnormal expression of TSP-1 is positively correlated with obesity, fatty liver, and diabetes.[190] In obese patients and animal models, the expression of TSP-1 is upregulated, which promotes adipocyte proliferation and activates inflammatory signaling pathways.[191,192] Additionally, the hexosamine pathway has been found to upregulate TSP-1 in vascular cells in response to high glucose levels.[193] TSP-1 may regulate fibrotic responses in MI and pressure overload-induced cardiac remodeling by activating TGF-β and inhibiting MMP activity.[194,195] TSP-1 influences ECM synthesis and degradation, affecting matrix remodeling and fibrosis, thereby modulating the structure and function of cardiac tissue. It also induces the TGF-β/Smad2 signaling axis, promoting a fibroblast phenotype that preserves the matrix and provides mechanical support to the myocardium, preventing chamber dilation and adverse remodeling.[196] Increased expression of TSP-1 in the cardiac interstitium of diabetic mice is associated with collagen deposition and fibrosis. Knockout of TSP-1 in db/db mice reduces collagen deposition, increases chamber size, and may mediate capillary rarefaction through upregulation of angiopoietin-2.[197] TSP-1 may also regulate inflammatory responses,[198] indirectly promoting cardiac fibrosis.

CTGF

CTGF is another ECM protein, a key downstream effector molecule of TGF-β, is primarily secreted by cardiomyocytes and cardiac fibroblasts. Through paracrine/autocrine actions, it directly promotes the proliferation, differentiation of cardiac fibroblasts and the synthesis of ECM.[199–201] Monoclonal antibody inhibition of CTGF has been reported to attenuate MI and pressure overload-induced cardiac fibrosis, underscoring the crucial role of CTGF in the development of cardiac fibrosis.[202,203] Obese rats induced by a HFD often exhibit significantly increased left ventricular CTGF expression, along with aggravated ventricular fibrosis, stiffness, and diastolic dysfunction. Additionally, leptin can stimulate CTGF synthesis in adult rat cardiac fibroblasts, suggesting that CTGF may serve as a terminal effector of leptin-induced ECM production.[85,204,205] Clinical studies have shown that human epicardial adipose tissue CTGF expression levels are positively correlated with the degree of atrial fibrosis and may be an independent risk factor for AF.[206]

ET-1

ET-1 is a potent vasoactive peptide secreted by endothelial cells, acting as a powerful fibrotic mediator through downstream signaling pathways of TGF-β and Ang II.[207] ET-1 interacts with various growth factors and cytokines such as NF-κB and TGF-β, to promote cardiac fibrosis.[208,209] ET-1 increases the expression of tissue fibronectin mRNA in diabetic hearts[210] and enhances the synthesis of collagen (types I and III) in adult rat cardiac fibroblasts, as well as the proliferation of cardiac fibroblasts.[211] Experimental data suggest that in obesity-related cardiomyopathy, the expression of ET-1 may be regulated by leptin.[212] The elevation of ET-1 levels in the myocardium of db/db mice is associated with increased expression of ECM proteins.[213] In streptozotocin-induced diabetic mice, endothelial cell-specific deletion of ET-1 mitigates myocardial fibrosis.[93]

Galectin (Gal)-3

Gal-3 is a member of the β-galactoside-binding lectin family, and a recently identified biomarker for cardiac fibrosis. Substantial evidence indicates that Gal-3 stimulates the proliferation of cardiac fibroblasts and the production of collagen and ROS.[214,215] Additionally, Gal-3 induces macrophage polarization toward a pro-fibrotic/M2 phenotype.[216] Its plasma concentration is closely associated with the degree of diastolic dysfunction and prognosis in HFpEF patients, particularly in obese individuals.[217–219] Elevated plasma Gal-3 levels have been observed in both obese humans and rodents,[220,221] and it is considered an independent predictor of diastolic dysfunction in morbidly obese patients.[221] Genetic deletion or pharmacological inhibition of Gal-3 has been shown to improve cardiac function and mitigate adverse fibrotic remodeling under various pathological conditions.[222–224] These findings suggest that Gal-3 may represent a promising new therapeutic target for obesity-related cardiac fibrosis.

Adipokines

Adiponectin

Adiponectin is a hormone secreted by adipocytes with anti-inflammatory, anti-atherosclerotic, and cardioprotective properties, and it may also be involved in the regulation of fibrotic responses.[225,226] In individuals with obesity, plasma levels of adiponectin typically decline. Adiponectin may exert cardioprotective effects by inhibiting inflammation and regulating metabolic pathways.[227,228] Some studies suggest that the decreased levels of adiponectin may be associated with the development of myocardial fibrosis in obese patients, while adiponectin inhibits myocardial hypertrophy by activating the AMPK signaling pathway.[229,230] Notably, in a study involving 933 middle-aged individuals, low plasma adiponectin levels were independently associated with increased left ventricular hypertrophy.[231] Moreover, in an angiotensin-induced cardiac remodeling model, adiponectin exhibited anti-fibrotic effects, possibly mediated through peroxisome proliferator-activated receptor-α activation.[232]

Under physiological conditions, adiponectin exerts cardioprotective effects by attenuating myocardial oxidative stress and fibrosis. However, its expression is downregulated in pathological contexts such as T2DM and obesity. Furthermore, adiponectin receptors (AdipoR1 and AdipoR2) are also suppressed in these conditions, collectively leading to impaired adiponectin signaling in the heart and a consequent reduction in cardioprotection.[233] In vitro studies suggest that adiponectin has both fibrogenic and antifibrotic effects on fibroblasts.[234,235] Tectorigenin protects diabetic mice from cardiac fibrosis by activating the AMPK pathway mediated by adiponectin receptor 1.[236] Additionally, Shibata et al demonstrated that exogenous adiponectin attenuates hypertrophic signaling in db/db mice.[229] Adiponectin deficiency may accelerate the transition from myocardial hypertrophy to HF under pressure overload by disrupting the AMPK-dependent vascular growth regulatory axis.[237]

Leptin

Leptin exerts complex and debated effects on the myocardium. Acute leptin exposure inhibits cardiomyocyte fatty acid oxidation and promotes glucose utilization, thereby improving energy production efficiency while reducing myocardial oxygen demand and lipid accumulation—effects that may offer cardioprotection under ischemic stress. In contrast, chronic leptin exposure is detrimental to cardiovascular health, likely due to the development of tissue resistance to its initial protective actions.[62] Leptin, a hormone produced by adipocytes, plays a crucial role in regulating appetite and weight, and is encoded by the ob gene as a 16 kDa peptide.[238] Leptin typically transmits signals from AT to the hypothalamus, indicating sufficient energy reserves and promoting satiety.[27] Elevated leptin levels are associated with obesity, and in the rat heart, leptin binds to short-form leptin receptors, with levels increasing during obesity, which is consistent with cardiac hypertrophy.[239] Leptin deficiency can polarize macrophages into an anti-inflammatory phenotype, thereby mitigating diet-induced and pre-existing obesity. In contrast, hyperleptinemia is often associated with an increased incidence of IR, T2MD, and CVD.[240,241] Additionally, the adiponectin/leptin ratio, which reflects AT status, is negatively correlated with mild chronic inflammation.[242]

Besides established role as a regulator of satiety, leptin significantly influences cardiac function and is associated with mechanisms of cardiac remodeling due to obesity and metabolic dysfunction.[243] Elevated leptin levels in the blood of obese patients have been found to be associated with left ventricular hypertrophy.[244] Evidence suggests that db/db mice may be more prone to fibrosis because peripheral cells, including fibroblasts, transmit complete leptin signaling through the short form of the leptin receptor. These leptin-mediated effects may contribute to a pro-fibrotic environment.[245,246] Obese Zucker rats with hyperinsulinemia also exhibit perivascular cardiac fibrosis, which is associated with cardiac hypertrophy and diastolic dysfunction.[247,248] While some studies suggest that degradation of leptin may lead to promoting cardiac hypertrophy,[249] substantial evidence indicates that leptin can directly induce hypertrophy in cardiomyocytes.[239] Moreover, leptin regulates the phenotype of fibroblasts, thereby activating fibrogenesis.[250] Leptin can also activate the RAAS through multiple pathways, further promoting cardiac fibrosis.[126] Sharma et al demonstrated that the involvement of leptin in Ang II–induced atrial fibrosis and AF.[250] Administration of exogenous leptin to ob/ob mice significantly increased collagen content in the myocardium, thereby promoting matrix protection.[243] In vitro experiments have shown that leptin can directly influence myocardial matrix metabolism.[251] Leptin increases oxidative stress by activating mTOR pathway, which results in Gal-3 production and TGF-β-induced collagen synthesis, ultimately

leading to cardiac fibrosis.[204] Additionally, leptin stimulates ET-1 synthesis, which directly induces hypertrophic and profibrotic responses in cardiomyocytes and cardiac fibroblasts—a process further amplified by leptin-dependent ROS generation. Finally, leptin stimulates secretion of pro-inflammatory cytokines such as TNF-α and IL-6, thereby exacerbating their adverse impact on cardiac function.[62]

Advanced Glycation End Products (AGEs)

AGEs are complex compounds formed through non-enzymatic reactions between reducing sugars and proteins, resulting from prolonged exposure to aldoses. They accumulate during metabolic disorders, diabetes, and aging, and may mediate the development of diabetic complications. AGEs can accumulate in both intracellular and extracellular environments, profoundly impacting the structure and composition of cardiac stroma. First, AGE-mediated crosslinking of ECM proteins (such as collagen and laminin) can increase cardiac stiffness, triggering diastolic dysfunction. Second, AGEs may activate interstitial fibroblasts through signaling triggered by the receptor for advanced glycation end products (RAGE). The binding of AGEs to RAGE can activate multiple signaling pathways, leading to the release of inflammatory factors and increased oxidative stress, promoting matrix protein synthesis, and directly or indirectly advancing the process of cardiac fibrosis. Third, the fibrotic action of RAGE may be partly mediated through the TGF-β and AT-1 cascades. Fourth, AGEs may regulate macrophage phenotype, inducing profibrotic programs.[111,252] Animal experiments have shown that blocking RAGE in db/db mice can alleviate diastolic dysfunction and reduce myocardial collagen synthesis.[253] Thus, AGEs are involved in the occurrence and development of cardiac fibrosis through various mechanisms. Therefore, blocking the formation of AGEs or their interaction with RAGE may be a viable strategy for preventing and treating cardiac fibrosis. High glucose levels stimulate multiple fibrotic pathways, generate ROS, stimulate neurohumoral responses, activate growth factor cascades (such as TGF-β/Smad3 and platelet derived growth factor), induce pro-inflammatory cytokines and chemokines, produce AGEs, and stimulate the AGE-RAGE axis. This upregulates fibrotic matrix proteins in fibroblast cells, thereby promoting cardiac fibrosis.[254] Evogliptin, a dipeptidyl peptidase-4 inhibitor and antidiabetic drug used to treat T2DM, has been shown to improve cardiac systolic/diastolic function, hypertrophy, and fibrosis in db/db mice following intervention.[255]

Osteopontin (OPN)

OPN is a glycoprotein and another pro-inflammatory cytokine involved in diverse in physiological and pathological processes, including bone formation, immune regulation, and inflammation. Its expression levels significantly increase in the AT of obese individuals, where OPN plays a crucial role in fostering macrophage proliferation within the local AT environment.[256,257] Additionally, OPN exhibits significance in cardiac pathologies, notably cardiac fibrosis. Studies suggest that the expression of OPN may increase during the process of cardiac fibrosis. OPN accelerates collagen deposition and fibrous tissue formation by promoting fibroblasts proliferation and migration through binding to cell surface receptors.[258] OPN emerges as a pivotal regulatory factor in inflammation and insulin resistance-induced obesity.[259] Physiologically, OPN, acting as both a cell-intrinsic protein and a soluble cytokine, modulates tissue remodeling and immune infiltration within cardiac AT. Conversely, heightened OPN expression is associated with the severity of obesity-related cardiovascular outcomes.[260]

Unique Mechanisms of Obesity-Induced Cardiac Fibrosis

Chemokine Ligand 14 (CXCL14)

CXCL14 is a chemokine secreted by brown adipose tissue that plays a role in various physiological and pathological processes, including immune response, inflammation, and cancer.[261] It mediates communication between BAT and macrophages during thermogenesis.[262] Some studies suggest that CXCL14 may have anti-fibrotic effects.[263,264] CXCL14 may influence the fibrotic process by modulating the activation state of cardiac fibroblasts and other relevant cells. However, research on CXCL14 is currently limited, and further studies are needed to elucidate its exact role in cardiac fibrosis and its potential therapeutic applications in clinical settings.

Autophagy

Autophagy is a highly conserved evolutionary process in which autophagosomes engulf cellular cargo and organelles, subsequently fusing with lysosomes to form autolysosomes, leading to the production of ATP and macromolecules. In metabolic diseases such as obesity, interactions between genetic factors, the environment, and energy imbalance can result in either upregulation or downregulation of autophagy.[265–267] Obesity, dyslipidemia, hypertension, and insulin resistance/hyperglycemia are major risk factors for dysregulated autophagic responses. Dysregulation of autophagy, particularly autophagic loss, may exacerbate metabolic disorders, IR, and obesity. Mice are more prone to obesity when autophagy-related proteins are absent from from the whole or specific tissues.[268] Activating autophagy can ameliorate obesity-induced cardiac dysfunction and remodeling.[269] Autophagy primarily regulates the pathological sequelae of obesity by accumulating autophagic substrates, including protein aggregates, lipid droplets, and damaged mitochondria.[268,270]

In the context of cardiac fibrosis, autophagy plays a complex and dual role. It protects cardiomyocytes from oxidative stress and other damage by eliminating damaged mitochondria and other harmful cellular components, thereby reducing cell death and limiting secondary fibrotic responses. Proper autophagic activity can suppress the excessive activation and proliferation of fibroblasts, which is a key factor in the development of cardiac fibrosis. However, if autophagic activity is excessive or uncontrolled, it may lead to extensive cardiomyocytes death, exacerbating cardiac injury and fibrosis. Under certain conditions, autophagy may support the survival and activation of fibroblasts, thereby promoting the deposition of collagen and the progression of fibrosis.[271]

Substantial evidence suggests that employing autophagy inducers or activating autophagy through transcription factor EB, the master regulator of lysosomal function, holds promise in effectively restoring cardiac protein quality control, mitigating cardiac structural remodeling, and enhancing cardiac contractile function across various pathological conditions.[272–275] Recent studies have demonstrated that oral probiotics exhibit potential in ameliorating myocardial fibrosis, myocardial hypertrophy, and myocardial autophagy signaling pathways in obese rats.[276] Assessment of lipid storage can be achieved through lipophagy, a selective autophagic process targeting lipid droplets, thus facilitating breakdown into free fatty acids and glycerol.[275] Altered cardiac lipophagy patterns observed in obesity mouse models suggest its involvement in heightened myocardial lipid accumulation.[277] Additionally, research has highlighted that impaired fibroblast growth factor21-mediated promotion of autophagy/lipophagy exacerbates lipid accumulation and structural disturbances in the hearts of obese mice.[278]

MicroRNAs

MiRNAs are short non-coding RNAs that function as regulators of gene expression and participate in nearly all cellular responses. Accumulating evidence suggests that miRNAs play a pivotal role in cardiac fibrosis.[279] For instance, IL-6-miR-210 has been demonstrated to promote atrial fibrosis,[188] while MiR-21 regulates the activation of metalloproteinase 2 or TGF-β receptor, thereby inducing cardiac fibrosis.[280,281] Additionally, studies have indicated the association of miR-20 with the development of cardiomyocytes hypertrophy and fibrosis, serving as a response to cellular stress.[282] Notably, cardiac macrophages express elevated levels of miR-155, the inhibition of which significantly mitigates cardiac inflammation, hypertrophy, and dysfunction following pressure overload.[283] Numerous studies have underscored the critical involvement of miRNAs in cardiac fibrosis induced by pressure overload or MI.[284,285] However, evidence regarding specific miRNAs implicated in obesity-related cardiac fibrosis remains limited.

In the context of obesity, the expression profile of miRNAs in cardiac tissue may undergo changes. Studies have investigated the myocardial miRNA landscape in type 1 diabetes mice models.[286,287] MiRNAs associated with diabetic cardiac fibrosis demonstrate upregulation of miR-125b and miR-199a, alongside downregulation of miR-150, miR-29b, and miR-30a. Furthermore, dysregulation of fibrosis-related miRNAs persists even in animals receiving insulin treatment.[286] MiR-29 directly targets numerous ECM proteins and has been implicated in cardiac fibrosis. It is expressed at reduced levels under cardiac stress conditions and may enhance ECM production by "derepression" of genes encoding collagens, elastin, or fibrillin, thereby contributing to fibrosis development.[284,288] Exercise training has been shown to prevent the downregulation of miR-29 after MI in rats, resulting in decreased expression of ECM genes and improved ventricular function.[289] Inhibiting miR-543 can reduce the transformation of myocardial fibroblasts and

collagen expression under IR conditions.[290] MiR-133 can regulate collagen I chain and CTGF, and its overexpression in the heart can mitigate myocardial fibrosis.[279] The downregulation of of miR-133 may be associated with fibrotic remodeling of the diabetic heart. In type 1 diabetes models, cardiac fibrosis is linked to inhibition of myocardial miR-133 expression, and overexpression of miR-133 attenuates fibrotic responses by inhibiting extracellular regulated kinase and Smad activation.[291] In the treatment strategies for myocardial fibrosis in obese patients, miRNAs represent potential targets.

Obesity Management Strategies: Surgical and Pharmacological Approaches

According to WHO guidelines, obesity management relies on healthy diet, regular physical activity, and when indicated, medical or surgical interventions. Current approaches include (1) weight loss and metabolic surgery and (2) pharmacotherapy, as summarized below.

Weight Loss and Metabolic Surgery

Approximately 480,000 bariatric procedures were performed globally between 2021 and 2022. Sleeve gastrectomy accounted for about 60% and Roux-en-Y gastric bypass for 30%. Endoscopic bariatric and metabolic therapies are increasingly used as less invasive alternatives.[62]

Pharmacological Therapy

Pharmacotherapy is indicated for patients with BMI $\geq$30 kg/m^2 or BMI $\geq$27 kg/m^2 with weight related complications insufficiently controlled by lifestyle measures. Several agents are now approved for obesity.[62,292]

For obese patients presenting with significant fibrosis, anti-fibrotic therapeutic strategies may include RAAS inhibitors, among which direct renin inhibition represents a promising anti-fibrotic approach. The oral renin inhibitor aliskiren has been reported to modulate collagen metabolism in cardiac fibroblasts. ACEIs, which prevent the conversion of inactive Ang I to active Ang II, have been effectively utilized in various human diseases. Lisinopril alleviates myocardial fibrosis and improves left ventricular diastolic function, whereas enalapril antagonizes the activation of the TGF-β signaling pathway.[157,293] Aldosterone plays a crucial role in regulating blood pressure and plasma sodium levels. Under obese conditions, overactivation of the RAAS coupled with hyperleptinemia promotes excessive aldosterone production and sodium retention. Notably, adipocytes are also capable of directly synthesizing aldosterone. Beyond inducing water and sodium retention, hyperaldosteronism exacerbates inflammation in the EAT, which subsequently contributes to myocardial microvascular rarefaction and fibrosis.[294]

Besides RAAS blockade, sodium-glucose linked transporter (SGLT) 2 inhibitors, which are now cornerstone drugs in heart failure, exhibit pleiotropic cardioprotective effects. SGLT2 inhibitors constitute a recently introduced class of glucose-lowering therapeutics. Recent evidence indicates they increase energy expenditure, attenuate inflammation (via M2 macrophage polarization in AT and liver), and improve obesity related insulin resistance, thereby offering indirect cardiovascular benefits.[164] Mechanistically, SGLT2 inhibitors promote lipolysis, ketone body formation, mitochondrial biogenesis, and autophagic flux, while concurrently attenuating the renin–angiotensin–aldosterone system, de novo lipogenesis, endoplasmic reticulum stress, oxidative stress, apoptotic signaling, and fibrotic processes.[295]

Glucagon-like peptide −1 receptor agonists (GLP-1RA) exert direct anti fibrotic effects by modulating cardiac fibroblast activity via GLP-1R signaling, suppressing key mediators such as TGF-β and CTGF, and limiting ECM deposition. They also attenuate fibrotic remodeling by reducing macrophage infiltration and cytokine expression, improving myocardial glucose/lipid metabolism, and enhancing antioxidant defenses. Indirectly, they may alleviate fibrosis by reducing cardiac hypertrophy and wall stress. Liraglutide, semaglutide, and tirzepatide are FDA and EMA approved for obesity. Recent studies support the efficacy and safety of semaglutide in obesity related HFpEF, regardless of T2MD.[164,292] These pharmacologic agents may synergistically target multiple profibrotic pathways, ameliorating obesity induced cardiac fibrosis.

Conclusions

Myocardial fibrosis represents a prominent pathological hallmark of CVD in obese patients, and its progression is orchestrated by a complex interplay of multiple cell types and molecular signaling pathways. This review systematically delineates the pathophysiological links between obesity and myocardial fibrosis. In the setting of obesity, activation of cardiac cells, adipose tissue, and the ECM triggers a cascade of biological processes including oxidative stress, activation of the RAAS, NLRP3 inflammasome, dysregulated secretion of inflammatory cytokines and adipokines, altered chemokine signaling, and impaired autophagic function. These alterations act synergistically through multiple signaling pathways to accelerate myocardial fibrogenesis, thereby inducing structural and functional cardiac impairment. This ultimately manifests clinically as HF, AF, and cardiomyopathy, significantly elevating the risk of adverse cardiovascular events. Beyond metabolic surgery, current potential pharmacotherapeutic strategies for obesity-related cardiomyopathy include RAAS inhibitors, SGLT2 inhibitors, and GLP-1RA. Nevertheless, more comprehensive and in-depth research is warranted to elucidate their mechanisms of action and identify novel therapeutic targets, thereby advancing more effective strategies for the prevention and treatment of obesity-associated myocardial fibrosis.

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