Research Advances on Cardiac Macrophages in Heart Failure with Preserved Ejection Fraction Postprint

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a prevalent and highly lethal global disease that accounts for nearly 50% of heart failure patients, necessitating innovative approaches to protect cardiac function and prevent HFpEF progression. Cardiac macrophages (CMs) have emerged as key regulators of HFpEF pathophysiology. CMs constitute a heterogeneous population composed of subpopulations with distinct lineage origins and gene expression profiles. Several critical aspects of HFpEF progression have been demonstrated to be regulated by CMs, including the recruitment of peripheral immune cells, myocardial inflammation, and cardiac electrical conduction. Moreover, CMs play a crucial role in regulating cardiac fibrosis, epicardial adipose tissue dysfunction, and ventricular diastolic dysfunction. Given the multifaceted roles of CMs in HFpEF pathophysiology, targeted modulation of CMs represents a promising therapeutic strategy. Therefore, this review will summarize the research progress on the pathophysiological mechanisms linking CMs and HFpEF from the perspectives of cardiac inflammation and fibrosis, ventricular diastolic dysfunction, epicardial adipose tissue, cardiac electrical conduction, and clinical interventions.

Full Text

Advances in the Study of Cardiac Macrophages in Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a universal and highly fatal global disease, accounting for nearly 50% of patients with heart failure. Innovative methods are needed to protect cardiac function and prevent the progression of HFpEF. Cardiac macrophages (CMs) have emerged as key regulators of the pathophysiology of HFpEF. CMs are a heterogeneous population consisting of subpopulations with distinct lineage origins and gene expression profiles. Several key aspects of HFpEF progression have been shown to be regulated by CMs, including the recruitment of peripheral immune cells, myocardial inflammation, and cardiac electrical conduction. In addition, CMs play a critical role in regulating cardiac fibrosis, epicardial adipose tissue dysfunction, and ventricular diastolic dysfunction. Given the multifaceted roles of CMs in the pathophysiology of HFpEF, targeted regulation of CMs represents a promising therapeutic strategy. Therefore, this article will review the research progress between CMs and the pathophysiological mechanism of HFpEF from the aspects of cardiac inflammation and fibrosis, ventricular diastolic dysfunction, epicardial adipose tissue, cardiac electrical conduction, and clinical intervention.

Key words: Heart failure with preserved ejection fraction; Heart failure; Cardiac macrophages; Epicardial adipose tissues

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In recent years, the incidence of heart failure (HF) has been increasing in China. Heart failure with preserved ejection fraction (HFpEF) represents a common type of HF and has gradually become one of the major challenges in cardiovascular medicine. The primary manifestation of HFpEF is impaired left ventricular diastolic function, accompanied by signs and symptoms of heart failure, with left ventricular ejection fraction (LVEF) $\geq$ 50%. Patients exhibit high heterogeneity and often have multiple comorbidities such as obesity, hypertension, and diabetes. Recent epidemiological studies indicate that the global population of HFpEF patients has reached 32 million, with an annual mortality rate of approximately 15%. In China, HFpEF is characterized by numerous comorbidities and high mortality rates. As molecular biology techniques become increasingly important in understanding HFpEF pathogenesis, attention has turned to how genomics and proteomics influence the pathophysiological processes of HFpEF and their interrelationships. Deciphering the molecular mechanisms of HFpEF and identifying potential targeted therapies have become hot topics and challenging frontiers in HFpEF prevention and treatment research.

Macrophages constitute the largest proportion of immune cell populations in the

heart and play a crucial role in maintaining cardiac homeostasis and modulating cardiac stress responses. Cardiac macrophages (CMs) serve as key regulators in the physiological and pathological mechanisms of HFpEF, influencing cardiac inflammatory responses, ventricular diastolic function, and cardiac electrical conduction. Under normal conditions, CMs remain stable in the myocardium. When myocardial injury occurs, circulating monocytes can migrate into cardiac tissue, generating non-resident macrophages that replace most resident macrophages in the heart, thereby sustaining inflammation in the damaged area. With advancing research, the classification and functions of CMs have been further refined, opening new avenues for clinical treatment of HFpEF. This study provides a comprehensive review of the origins and classification of CMs and their roles in the physiological and pathological processes of HFpEF, aiming to offer novel targets and directions for HFpEF diagnosis and treatment.

1.1 Origins and Classification of CMs

Tissue macrophages primarily originate from circulating monocytes, which can be further subdivided into classically activated macrophages (M1) and alternatively activated macrophages (M2). However, the M1/M2 concept was derived from in vitro studies and may not fully capture the more nuanced phenotypes observed in vivo. The structure of CMs in the body is relatively complex and highly heterogeneous. CM phenotypes persist in both physiological and pathological states, rather than representing merely two polarized cell types.

By examining the expression of chemokine receptor 2 (CCR2) on the cell surface, different CMs can be distinguished. Genetic fate mapping has revealed two distinct origins of CMs. The first class forms during embryonic and fetal developmental stages, capable of self-maintenance and regeneration. These CMs express CCR2-, originate from yolk sac and fetal monocyte progenitors, and persist into adulthood. The second class expresses CCR2+, originates from circulating monocytes, and develops when monocytes from peripheral blood infiltrate and differentiate in the heart under the influence of chemokines and inflammatory factors during developmental stages. Consequently, two types of macrophages can be observed in the heart: tissue-resident macrophages and monocyte-derived macrophages. Furthermore, based on the expression of major histocompatibility complex II (MHC II) and CCR2, cardiac macrophages can be divided into three distinct categories: MHC II^{low} CCR2-, MHC II^{high} CCR2-, and MHC II^{high} CCR2+.

1.2 Functions of CMs

As a core component of immune cells, CMs play important roles in the cardiovascular system. Initially, scientists classified activated macrophages into M1 pro-inflammatory macrophages and M2 reparative macrophages based on cell surface markers and inflammatory status. The balance between M1 and M2 macrophages is critical for maintaining cardiac growth, function, and electrical homeostasis, while macrophage phenotype imbalance may trigger ventricular

remodeling and various cardiac diseases. Through in-depth studies of CM phenotypes, numerous similarities with M1/M2 macrophages have been identified. Cardiac non-resident macrophages derived from monocytes (CCR2+ CMs) are primarily associated with inflammatory responses and myocardial injury. In contrast, cardiac resident macrophages derived from the yolk sac embryo (CCR2- CMs) not only possess cardioprotective functions but also play crucial roles in cardiac repair.

When inflammation occurs, monocytes infiltrate the heart and transform into non-resident macrophages, replacing the original resident macrophages. With aging, resident macrophages derived from the yolk sac in adult hearts are gradually replaced by non-resident macrophages derived from monocytes. Prospective cohort experiments in mice have shown that elderly patients have higher probabilities of cardiovascular complications and mortality compared to young patients, suggesting that the risk of cardiac diseases increases with age and is associated with the accumulation of non-resident macrophages. Systemic inflammation is central to HFpEF-related comorbidities, and CMs, as immunomodulators, play key roles in the inflammatory process following cardiac injury. CCR2+ CMs can induce fibroblast production of extracellular matrix and tissue remodeling, which exacerbates myocardial inflammation and fibrosis in HFpEF. Conversely, CCR2- CMs secrete anti-inflammatory cytokines to maintain the normal function of surrounding tissues and the heart.

CMs have been identified as dominant factors in HFpEF pathogenesis and are therefore considered potential intervention targets. Notably, CCR2- CMs demonstrate stronger proliferative potential compared to CCR2+ CMs, indicating that most proliferative macrophages are primarily resident reparative macrophages, while most non-proliferative macrophages are pro-inflammatory macrophages generated from monocyte infiltration. In a healthy heart system, CMs are predominantly controlled by embryonic-derived CCR2- CMs, which are responsible for clearing apoptotic cells and debris, thereby participating in the maintenance of cardiac homeostasis. When the heart suffers damage, CCR2+ CMs derived from monocytes accumulate in cardiac tissue. These cardiac macrophages undergo metabolic reprogramming, transforming into pro-inflammatory M1 macrophages that participate in pathological ventricular remodeling by releasing inflammatory cytokines and chemokines under pathological conditions. When inflammatory or environmental stress signals diminish, inflammatory M1 macrophages transition to anti-inflammatory M2 macrophages, facilitating cardiac repair. In summary, CMs play a vital role in maintaining cardiac health.

2 CMs and HF

Regardless of the primary disease underlying HF, inflammation and immune cell infiltration, particularly macrophage infiltration, play important roles in HF pathogenesis. CMs are protective immune cells in the heart that become extensively infiltrated in HF hearts, primarily depending on local macrophage pro-

liferation and monocyte infiltration from hematopoietic progenitor cells in bone marrow and spleen. These monocytes enter the remote myocardium through the classical CCL2/CCR2 pathway, leading to the release of inflammatory factors that further aggravate myocardial inflammation and fibrosis.

CMs also influence the formation and progression of adaptive cardiac remodeling. Specifically, CCR2- CMs can regulate adaptive growth of cardiomyocytes through insulin-like growth factor expression. When CCR2- CMs are depleted, adaptive cardiac growth is abolished, potentially leading to adverse remodeling, cardiac dilation, and severe cardiac dysfunction, further demonstrating that CCR2- CMs are important protective factors. Conversely, CCR2+ CMs can release or generate inflammatory cytokines that cause cardiomyocyte injury, cell death, and cardiac fibrosis, triggering pathological ventricular remodeling and cardiac dysfunction. Therefore, CMs have become central mediators in regulating adaptive cardiac remodeling.

As an important phenotype of HF, increased CM infiltration has been observed in HFpEF animal models. In HFpEF mice, the number of CMs doubled, associated with increased CCR2+ monocytes in bone marrow and spleen, leading to CCR2+ CM-dependent migration to the heart and exacerbation of HFpEF symptoms. Overall, CCR2- CMs play an irreplaceable role in balancing cardiac structural remodeling and slowing HF progression. Maintaining or enhancing CCR2- CM function may offer innovative options for current HF treatments.

3.1 CMs and Cardiac Inflammation and Fibrosis

The increased levels of pro-inflammatory cytokines in HFpEF patients are significantly associated with poor clinical outcomes, indicating that inflammation accompanies the entire development and progression of HFpEF. Currently, anti-inflammatory therapy is considered an effective method for preventing and treating HFpEF. Researchers have begun exploring interventions targeting the NO-cGMP-PKG signaling pathway using sGC activators, phosphodiesterase-5 inhibitors, and NO inducers. These interventions have shown positive effects in enhancing cardiomyocyte function, reducing inflammation and oxidative stress, and augmenting sGC-PKG signal transduction, suggesting they may represent potential therapeutic options for HFpEF patients.

Single-cell sequencing methods have revealed that multiple cell types in HFpEF, particularly CMs, undergo significant changes in both quantity and transcriptional characteristics. Following cardiac injury, cells release numerous damage-associated molecular patterns (DAMPs) that utilize specific receptors such as RAGE, TLR2, and TLR4 to signal and rapidly recruit CMs, which undergo remarkable phenotypic and functional changes. Approximately 30 minutes later, Ly6C^{high} monocytes infiltrate the heart through CCL2/CCR2 signaling and further differentiate into macrophages. These substances trigger a cascade of robust sterile inflammatory responses and generate various inflammation-related factors, thereby exacerbating myocardial inflammation. Additionally, CCR2+

CMs are enriched with NLRP3 inflammasomes that secrete large amounts of IL-1β through NLRP3, further worsening cardiac inflammation. Zhang Ning et al. observed significantly increased CXC chemokine receptor type 4 (CXCR4) in HFpEF patients with hypertension, and further confirmed that CXCR4 deficiency could effectively inhibit CCR2+ CM infiltration and inflammatory responses in HFpEF mice, thereby improving cardiac function.

In the later stages of cardiac injury, macrophages gradually transition from Ly6C^{high} to Ly6C^{low}. During this phase, large amounts of transforming growth factor-$ $1(TGF-1)aregenerated, promotingthetransformationofcardiacfibroblastsintomyofibrobla$\kappa Bsignalingpathway, includingTNF-, MCP-1, andIL-1$ $. MCP-1 binds to the CCR2 receptor on monocyte membranes, causing their infiltration into the heart and differentiation into CCR2+ CMs. On one hand, CCR2- CMs are replaced by CCR2+ CMs; on the other hand, cardiac fibroblasts are activated, transforming into myofibroblasts that generate massive collagen fibers, causing cardiac fibrosis. Therefore, inhibiting CCR2+ CM infiltration while promoting CCR2- CM proliferation and activation represents a key strategy for preventing excessive cardiac fibrosis, resolving adverse cardiac remodeling, and improving HFpEF.

3.2 CMs and Ventricular Diastolic Dysfunction

Myocardial inflammation may impair endothelial function of coronary microvessels and increase adhesion molecule expression, facilitating macrophage infiltration into the myocardium and collagen accumulation. Furthermore, inflammation can interfere with the bioavailability of nitric oxide and cyclic guanosine monophosphate, triggering cardiomyocyte hypertrophy and stiffness. Stiff cardiomyocytes, combined with macrophage-mediated interstitial fibrosis, impair ventricular diastolic function, which manifests primarily as abnormal active relaxation and rigid wall motion. Invasive hemodynamic studies have revealed that HFpEF patients often exhibit severely impaired diastolic function and relatively high wall tension. Single-cell RNA sequencing analysis of HFpEF animal models to assess the relationship between CMs and diastolic dysfunction has revealed that the main immune cell types affecting the heart include four subpopulations of resident and monocyte-derived macrophages. Metabolic dysregulation directly activates inflammatory genes in CMs, further impacting biological pathways such as hypertrophy, fibrosis, and autophagy, thereby causing ventricular diastolic dysfunction.

CMs, as key immune cells in the heart, play an indispensable role in regulating ventricular diastolic function. Zhu Si-Meng et al. found that high-fat diet feeding in mice leads to metabolic dysregulation and obesity, causing severe fibrosis and diastolic dysfunction. Analysis of mouse hearts revealed significant changes in inflammatory pathways in CMs and triggered metabolic dysfunction, indicating that metabolic dysregulation is intertwined with CMs in HFpEF. Further studies have shown that specific knockout of the pro-fibrotic molecule interleukin-10 in macrophages of a preclinical HFpEF model significantly improved diastolic

dysfunction and reduced fibrosis. Myeloid-specific CXCR4 deficiency hindered CM infiltration and inflammatory responses in HFpEF mice, thereby improving cardiac fibrosis and diastolic function. Isoproterenol injection-induced sympathetic stress can cause stress cardiomyopathy, with the main mechanism being sympathetic overstimulation-induced CM activation and myocardial inflammation, leading to NADPH oxidase 4-dependent reactive oxygen species-mediated fibrosis and impaired diastolic function. These data reveal that CM expansion and phenotypic changes may represent primary targets for treating cardiac fibrosis and diastolic function impairment.

3.3 CMs and Epicardial Adipose Tissue

Epidemiological data reveal that up to 80% of HFpEF patients are concurrently obese, and metabolic dysregulation of glucose and lipids in these patients can lead to chronic metabolic inflammation. Epicardial adipose tissue (EAT) is located between the myocardium and pericardium, sharing a microcirculation system with the myocardium. In HFpEF patients, EAT thickness increases significantly, impairing cardiac contractile, diastolic, and metabolic functions. EAT metabolic dysfunction releases large amounts of pro-inflammatory adipokines that enter myocardial tissue through paracrine and autocrine mechanisms. Through recruitment and induction of CCR2, monocytes undergo phenotypic changes and release inflammatory factors, thereby increasing myocardial inflammation and causing cell hypertrophy and fibrosis.

Based on clinical and evidence-based medicine, domestic and international guidelines recommend using glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors to treat HFpEF. Both drugs can reverse EAT metabolic dysfunction by reducing EAT volume, thereby inhibiting the release of pro-inflammatory adipokines and effectively alleviating inflammation and fibrosis in HFpEF. In the process of dysfunctional EAT inducing HFpEF, the recruitment and phenotypic switching of CCR2+ CMs are critical steps. Studies have found that when EAT thickness is excessive, it releases numerous adipose inflammatory factors that attract monocytes. Under the influence of CCR2, these cells undergo phenotypic transformation, enhancing inflammatory responses in resident CCR2+ CMs in the myocardium and exacerbating myocardial inflammation and accelerating the fibrosis process.

The close connection between EAT biology and cardiomyocyte function supports EAT-targeted therapy to prevent HFpEF development. First, direct surgical removal of EAT in obese rats was found to enhance myocardial contractility after myocardial infarction, and clinical case reports have also shown significant improvement in diastolic function after EAT removal in humans. Weight loss induced by diet or endurance training reduces EAT volume and further improves cardiac metabolic characteristics. In addition to direct EAT removal, optimizing adipokine secretion from EAT can also reduce myocardial inflammation induced by CCR2+ CMs. In 2003, Yang and colleagues identified omentin-1 in a human omental fat cDNA library. Omentin-1 is highly expressed in EAT and is

a recently discovered cardioprotective adipokine. EAT-secreted omentin-1 can stimulate phosphorylation of AMP-activated protein kinase in CMs, thereby inhibiting inflammatory cytokine expression and macrophage infiltration within atherosclerotic plaques. Moreover, omentin-1 is reduced in HFpEF patients and is considered a valuable biomarker for HFpEF development in elderly patients. Thus, EAT metabolic and functional dysfunction leads to changes in secreted adipokines, subsequently inducing CCR2+ CM infiltration, aggravating cardiomyocyte inflammatory responses and fibrosis, and ultimately causing HFpEF onset and progression.

3.4 CMs and Cardiac Electrical Conduction

The generation and conduction of action potentials are essential cardiac characteristics. When the myocardium is damaged or ischemic, it can cause a series of pathophysiological changes including slowed ventricular rate, tachycardia, and arrhythmias. Cardiac electrical conduction activity is influenced by multiple factors. Large numbers of CMs exist in the atrioventricular node of both mice and humans, and CMs enhance communication between cardiomyocytes through gap junctions with atrioventricular nodal cells, playing a key role in electrical conduction regulation that is crucial for cardiac function recovery after HFpEF.

Recent studies have revealed that in the cardiac atrioventricular node, macrophages are not only numerous but also highly consistent with cardiomyocyte action potentials, as cardiomyocyte depolarization induces macrophage depolarization. Conversely, macrophage electrical activity significantly affects cardiomyocyte action potentials by reducing the negative amplitude of resting potential, shortening action potential duration and refractory period, thereby enhancing cardiomyocyte conductivity. Hulsmans and colleagues have confirmed that numerous CMs in the atrioventricular node are connected to cardiomyocytes through gap junctions containing connexin 43 (Cx43) and contribute to cardiac electrical conduction. When Cx43 is absent in macrophages, it disrupts electrical interactions and communication between macrophages and cardiomyocytes, subsequently causing increased intracardiac pressure and reduced myocardial contractility. Amphiregulin produced by CMs plays a crucial role in regulating Cx43 phosphorylation and translocation processes in cardiomyocytes. Deficiency of amphiregulin in CMs triggers gap junction disarray, which may lead to fatal arrhythmias during acute stress phases. Additionally, when macrophages are activated, released pro-inflammatory cytokines can affect cardiac electrical activity and cause remodeling of cardiac electrical structure. These studies demonstrate that maintaining normal cardiac electrical conduction in HFpEF requires CMs.

4 CMs in Clinical Therapeutic Intervention for HFpEF

Current clinical trials for HFpEF immunotherapy primarily target inflammatory cytokines, including IL-1, IL-6, CCL2, and other factors. These cytokines are considered key biomarkers of CCR2+ CMs. Some anti-inflammatory drugs

or antibodies that inhibit or block these inflammatory cytokines have been developed for HFpEF treatment. A clinical trial showed that using the IL-1α receptor antagonist anakinra could improve arterial stiffness and microvascular inflammation in rheumatoid arthritis patients, thereby inhibiting myocardial deformation and preventing progression to HFpEF. Additionally, in two small clinical studies of HFpEF patients, anakinra treatment effectively alleviated inflammatory responses and diastolic dysfunction. IL-6 has the ability to regulate cardiomyocytes and macrophages and plays a key role in HFpEF pathogenesis. A randomized controlled clinical trial demonstrated that statins can reduce IL-6 expression levels, thereby helping to improve prognosis in HFpEF patients. Clinical trials conducted by the National Institutes of Health also support that inhibiting IL-6 in HFpEF patients can effectively improve their clinical condition. Colchicine is a broad-spectrum anti-inflammatory drug that can inhibit the production of IL-1, IL-6, and CCL2, showing certain clinical application and therapeutic prospects in HFpEF treatment. One clinical trial found that colchicine treatment could reduce systemic inflammatory responses and improve left ventricular diastolic function in HFpEF patients.

Furthermore, a clinical trial targeting macrophage migration inhibitory factor (MIF) demonstrated that MIF can improve the inflammatory status of HFpEF patients and reduce mortality. Taken together, cytokines and chemokines play key roles in CM phenotypic switching. In HFpEF, CCR2+ CMs exacerbate myocardial inflammation and fibrosis. Inhibiting the expression of CCR2+ CM-related biomarkers has potential clinical significance in HFpEF treatment and may open new avenues for managing this disease. By targeting these factors, it is possible to effectively intervene in CM phenotypic transformation, alleviate changes in cardiac structure and function, and provide more effective treatment strategies.

5 Summary and Outlook

Given the important experimental and clinical research findings in the HFpEF field, targeting CMs as a therapeutic strategy for HFpEF warrants further investigation. This article summarizes current research on CMs in HFpEF from six aspects: CM classification and function, CMs and cardiac inflammation/fibrosis, CMs and ventricular diastolic dysfunction, CMs and epicardial adipose tissue, CMs and cardiac electrical conduction, and the role of CMs in clinical therapeutic intervention for HFpEF.

Although significant progress has been made in the CM field, several limitations and challenges remain. First, there are currently no specific biomarkers to distinguish beneficial from detrimental macrophage phenotypes. Existing biomarkers are primarily based on cytokines and chemokines secreted by macrophages, with CCR2 being the most commonly used biomarker to differentiate non-resident from resident cardiac macrophages, but it is not an ideal molecular marker for distinguishing beneficial from harmful macrophages. Second, although methods targeting pathological cardiac macrophages or modulating their function hold

great therapeutic promise, there is currently a lack of effective drug delivery systems specifically targeting tissue or organ macrophages, particularly cardiac macrophages. Finally, current in vitro and in vivo experimental models for cardiac macrophages are overly simplified and cannot accurately simulate the complex pathological environment of heterogeneity and plasticity seen in patient cardiac macrophages, making it difficult to translate experimental results into clinical applications. Overcoming these challenges will be central to future cardiac macrophage research.

Therefore, a deeper understanding of biomarkers, effective drug delivery systems, and cardiac macrophage plasticity in the processes of cardiac tissue injury and repair will help enhance cardiac tissue repair capacity and improve outcomes for HFpEF patients. By intervening in CM phenotypic switching, novel therapeutic approaches for HFpEF prevention and treatment may emerge.

Note: HFpEF = heart failure with preserved ejection fraction, IL-1β = interleukin-1β, TNF-α = tumor necrosis factor-α, MCP-1 = monocyte chemoattractant protein-1.

Figure 1 [**Figure 1: see original paper**] Schematic diagram of the mechanism of action of cardiac macrophages in HFpEF

Table 1 Effects of cardiac macrophages on the pathophysiological processes of HFpEF

	Cardiac Resident Macrophages	Cardiac Non-resident Macrophages
Myocardial Inflammation	Release anti-inflammatory cytokines, alleviate myocardial inflammation	Release pro-inflammatory cytokines, exacerbate myocardial inflammation
Myocardial Fibrosis	Inhibit cardiac fibrosis, resolve adverse cardiac remodeling	Promote cardiac fibrosis, cause adverse cardiac remodeling
Ventricular Diastolic Function	Improve ventricular diastolic function and reduce cardiomyocyte stiffness	Exacerbate ventricular diastolic dysfunction and cardiomyocyte stiffness
Epicardial Adipose Tissue	Improve epicardial adipose tissue metabolism and dysfunction	Exacerbate epicardial adipose tissue metabolism and dysfunction
Cardiac Electrical Conduction	Maintain normal cardiac electrical conduction	Cause abnormal cardiac electrical conduction

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