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Immunometabolic Mechanisms of Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is increasing in prevalence worldwide, already accounting for at least half of all heart failure (HF). As most patients with HFpEF are obese with metabolic syndrome, metabolic stress has been implicated in syndrome pathogenesis. Recently, compelling evidence for bidirectional crosstalk between metabolic stress and chronic inflammation has emerged, and alterations in systemic and cardiac immune responses are held to participate in HFpEF pathophysiology. Indeed, based on both preclinical and clinical evidence, comorbidity-driven systemic inflammation, coupled with metabolic stress, have been implicated together in HFpEF pathogenesis. As metabolic alterations impact immune function(s) in HFpEF, major changes in immune cell metabolism are also recognized in HFpEF and in HFpEF-predisposing conditions. Both arms of immunity – innate and adaptive – are implicated in the cardiomyocyte response in HFpEF. Indeed, we submit that crosstalk among adipose tissue, the immune system, and the heart represents a critical component of HFpEF pathobiology. Here, we review recent evidence in support of immunometabolic mechanisms as drivers of HFpEF pathogenesis, discuss pivotal biological mechanisms underlying the syndrome, and highlight questions requiring additional inquiry.

Keywords

HFpEF; immune system; metabolism

Introduction

Recent decades have been marked by robust success in reducing the acutely lethal, typically atherothrombotic, manifestations of cardiovascular disease[1,2]. Clinically impactful therapies and interventions, coupled with public health efforts focusing on primary prevention, have culminated in meaningful improvements in outcomes. Owing to successes seen in much of the world, people are surviving their myocardial infarctions and ventricular tachyarrhythmias, returning to family and society with one of the major manifestations of chronic cardiovascular disease, HF.

Concomitant with these advances, modern society has witnessed dramatic increases in obesity, metabolic dysfunction, diabetes, and hypertension[3]. For example, it is estimated

that over 40% of the US population is obese[3,4] with an increase in obesity prevalence from 30.5% to 42.4% in just the last 8 years. And other parts of the world are not far behind. Strikingly, the incidences of obesity and diabetes stratified by age, sex, or ethnicity are each projected to continue to increase in the next decade[3,5]. It is hard to underestimate the effects of these global changes impacting all manner of cardiovascular health and disease.

As a consequence of these major changes, the clinical syndrome of HF has emerged as an important and growing public health challenge. Prevalence of HF is estimated at >60 million individuals worldwide, including >6 million in the United States alone, contributing in 2017 to 1 in 8 deaths[6–8].

Two major phenotypes of HF are recognized: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF)[9,10]. Importantly, changes in the incidence and prevalence for these two types of HF have differed in recent decades; HFpEF has risen by 10% relative to HFrEF, and this gap is slated to continue to increase in coming years owing to progressive aging of the population and the growing prevalence of conditions predisposing to development of HFpEF, particularly obesity, metabolic syndrome, and diabetes[11,12]. In summary, HFpEF, a syndrome with a 35% two-year rate of hospitalization and 14% two-year mortality, is presently the most common form of HF, and one that is rising progressively, already accounting for the majority of HF worldwide.

Despite similar clinical presentations, increasing evidence supports a model in which HFpEF and HFrEF are mechanistically distinct[13]. Furthermore, the natural histories of HFpEF and HFrEF are dissimilar, as transitioning from HFpEF to HFrEF is rare[11,14]. In support of these observations is the fact that cornerstone neurohumoral therapies effective in HFrEF have failed when repurposed for HFpEF[15,16]. Recent results from EMPEROR-Preserved with empagliflozin, a sodium–glucose cotransporter 2 inhibitor (SGLT2i) that impacts cardiac and global metabolic profiles, are encouraging[17].

Heterogeneity of the clinical manifestations of HFpEF, coupled with the complexities of its pathophysiological mechanisms, stem from the fact that HFpEF is not a disease but rather a clinical syndrome triggered by a variety of diseases; multiple comorbidities differentially contribute to the overall clinical presentation. Indeed, it is possible to distinguish phenotypes within the syndrome of HFpEF that emerge from different predisposing conditions with unique responses to therapy[12,14,18]. These include “cardiometabolic HFpEF”, arguably the most prevalent form of HFpEF and the subject of this review, as well as HFpEF related to auto-immune or inflammatory disease, cardio-renal HFpEF, and more (Figure 1). [It is important to note that other disorders mimic HFpEF, and likely have been included inadvertently in some HFpEF clinical trials; these include cardiac amyloidosis and hypertrophic cardiomyopathy.] As noted above, the global spread of obesity and metabolic syndrome have defined the HFpEF syndrome, with obesity and metabolic syndrome, and often type 2 diabetes, being present in most patients with HFpEF[19,20]. These conditions are now understood to be major drivers of HFpEF pathophysiology shaping the phenotype of what is called cardiometabolic HFpEF.

Heterogeneity in the clinical presentations of HFpEF is reflected in the complexity of preclinical modeling of the syndrome designed to unravel fundamental mechanisms[21]. As elucidation of pathophysiological mechanisms underlying any disease or syndrome relies on the reliability of animal and cellular models, existence of multiple phenotypes of clinical HFpEF requires highly integrated experimental approaches. Here, we discuss basic and translational data focusing on the most common form of HFpEF, cardiometabolic HFpEF. In particular, we emphasize the existence of rapidly emerging evidence pointing to bidirectional crosstalk between metabolic dysregulation triggering immune events – and vice versa – in syndrome pathogenesis.

Cardiometabolic stress and HFpEF

Cardiometabolic stress stemming from obesity is a mechanism contributing to multiple cardiovascular disorders, including both HFrEF and HFpEF[11,22]. And in addition to predisposing to HFpEF more than to HFrEF, obesity in HFpEF is associated with worse clinical outcomes, increased mechanical strain on the heart, insulin resistance, type 2 diabetes, and hypertension. Beyond just the heart, cardiometabolic alterations in HFpEF contribute to dysfunction of the vasculature, skeletal muscle, and other organ systems. As such, HFpEF is a systemic condition[13].

Recent results from the EMPEROR-Preserved trial reveal improvement in HF hospitalization, but not mortality benefit, in HFpEF patients treated with the SGLT2i empagliflozin. Of note, this benefit was greatest in subjects with an EF 40–49%, less in subjects with an EF 50–60%, and absent in those with an EF >60%[17]. Whereas one could interpret these data as lack of benefit of empagliflozin in HFpEF subjects, no significant statistical interaction between the trial primary endpoint (a composite of cardiovascular death and HF hospitalization) and ejection fraction (EF) was found, suggesting that empagliflozin improved the primary endpoint independent of baseline EF. However, a recent examination of the major trial endpoints across the values of EF revealed no protective effects of empagliflozin for EF >62.5% for all the endpoints considered[23]. In aggregate, whereas the results of EMPEROR-Preserved support the use of SGLT2i in HFpEF patients, the cardiovascular benefit of these drugs in patients with EF >50/60% will require further confirmation.

Mechanisms of SGLT2i-afforded cardioprotection remain elusive. Yet, these agents improve metabolic parameters, lending further credence to the notion of cardiometabolic drivers of HFpEF[24]. Together with EMPEROR-Preserved, another recent US-only trial with the SGLT2i, dapagliflozin, demonstrated improvement in functional capacity of obese HFpEF patients[25]. Interestingly, this is in contrast with other trials in less obese HFpEF populations in which a similar benefit was not observed[26]. In summary, multiple lines of clinical and epidemiological evidence support a model in which cardiometabolic stress functions as a major driver of HFpEF. As such, targeting cardiometabolic stress may emerge as a viable therapeutic objective in the syndrome[22,27].

Obesity, excess total body adipose tissue, commonly tracked as increased body mass index (BMI), is a strong – but modifiable – risk factor for HFpEF. Visceral (abdominal) adipose

tissue accumulation (VAT), measured as waist circumference or waist-to-hip ratio, has the strongest correlation to HFpEF development, hospitalization and mortality[28]. This so-called central obesity is the strongest predictor of increased insulin resistance leading to diabetes, of decreased arterial compliance causing arterial hypertension, and of systemic endothelial dysfunction and inflammation[28], all conditions considered associated with and predisposing to HFpEF. VAT expansion and related metabolic disturbances induce cardiac hypertrophy, fibrosis, and diastolic dysfunction, as VAT is associated with decreased cardiopulmonary performance and impaired left ventricular compliance[28].

VAT is greater in men than women. However, recent data suggest that for a given increase in VAT, there is greater risk for development of cardiometabolic disorders in women compared with men[29] suggesting that the cardiometabolic impact of VAT might exhibit a sex-dependent effect, in line with the slight predilection for women to develop HFpEF[30]. In women with HFpEF, a greater than 30% increase in VAT area has been identified compared with control women with the same BMI. In addition, women with increased VAT manifested a significant reduction in exercise performance with increases in estimated cardiac filling pressures compared with women with normal VAT. Intriguingly, this did not occur in men with or without excess VAT suggesting that accumulation of excess VAT plays a distinct and important role in the pathophysiology of HFpEF preferentially in women[31].

VAT and epicardial adipose tissue (EAT) accumulation can each induce both systemic and local inflammation contributing to oxidative stress, microvascular injury, cardiomyocyte hypertrophy, and myocardial fibrosis. Several adipokines promote microvascular endothelial dysfunction and reduce vascular compliance in obese HFpEF patients[32]. These pro-inflammatory cytokines elicit the infiltration of macrophages, may cause regression (destruction) of microvascular structures, and induce pro-fibrotic pathways[32]. Dysfunctional adipose tissue also triggers secretion of leptin that regulates energy balance and hunger. Leptin also stimulates the secretion of aldosterone and angiotensin II[33] and increases the activity of neprilysin[34], together increasing sodium retention and volume expansion.

For all the reasons stated above, targeting excess body fat might represent a valid therapeutic option in HFpEF. Indeed, multiple trials with anti-diabetic drugs, such as GLP-1 (glucagon-like peptide 1) agonists, with a robust effect on body weight reduction are underway in HFpEF (e.g., STEP-HFpEF, STEP-HFpEF DM, SUMMIT).

Immunometabolic mechanisms of HFpEF

Obesity and metabolic stress elicit a low-grade, systemic inflammatory state, and dysregulation of inflammatory and immune responses are now recognized as culprit mechanisms in HFpEF pathophysiology. Indeed, concomitant with rapidly emerging evidence implicating metabolic stress in HFpEF pathogenesis, a pivotal role of immune mechanisms is also emerging. Indeed, longstanding evidence points to bidirectional crosstalk between metabolic stress and inflammation; adipose tissue, a metabolically active tissue, influences cardiac metabolism and immune activation, all to the detriment of multiple different tissues (Figure 2).

We and others have demonstrated that oxidative and nitrosative stress drive HFpEF[35–39]. Furthermore, inflammatory cells have been detected in endomyocardial biopsies from HFpEF patients[40]. Of note, metabolic alterations promote a pro-inflammatory state as a condition termed metabolic inflammation, or meta-inflammation[22,41,42]. Furthermore, expansion of adipose tissue triggers release of chemokines that initiates recruitment of immune cells[43], and lipids can act as inflammatory molecules, participating in the recruitment of immune cells to HF myocardium[44].

Local cardiac adipose tissue can also contribute to myocardial inflammation. Secretion of cytokines from EAT has been proposed as contributing to meta-inflammation in HFpEF[32], yet mechanisms of EAT-induced myocardial dysfunction in HFpEF remain unknown. The inflammatory state of VAT or EAT induces pro-inflammatory macrophage polarization and recruitment into the heart[45]. Similarly, other myeloid cells, mast cells[46] and neutrophils are also present in obese organs, contributing to tissue damage through elastase secretion, thus promoting macrophage recruitment[47]. Obesity also promotes $CD8^+$ and $CD4^+$ T lymphocyte infiltration together with effector B cells, heightening release of pro-inflammatory factors[48]. In addition, VAT harbors a unique regulatory T cell (Treg) population that specializes in maintaining adipose tissue immune homeostasis and insulin sensitivity[49]. In mouse models of obesity, the number of Treg cells is dramatically reduced in VAT, whereas Treg cell abundances in subcutaneous adipose tissue and spleen remain unaffected[50 51]. Obesity also affects the phenotype and function of VAT Treg cells[51]. Some of these differentially expressed genes are important for maintaining the phenotype and function of VAT Treg cells. For example, the expression of the anti-inflammatory, Treg-produced cytokine IL-10, and the IL-33 receptor ST2, required for VAT Treg cell function, are reduced in VAT Treg cells from obese mice[52]. Similar changes have been reported in obesity in humans[53]. Obesity-induced VAT Treg cell dysfunction has been proposed to contribute to development of chronic inflammation and insulin resistance in metabolic syndrome[49].

In aggregate, these findings highlight HFpEF as a chronic cardiovascular inflammatory syndrome that arises in the setting of multiple pro-inflammatory comorbidities, one in which the role and extent of specific immune cells and mediators of meta-inflammatory pathways remain to be elucidated (Figure 2). Despite evidence implicating inflammation and adipose tissue, drugs that specifically target these inflammatory pathways to treat metabolic syndrome, HFpEF development, and its systemic manifestations are lacking. Future studies are required to investigate whether reduction in this VAT- and EAT-triggered systemic inflammatory dysregulation may afford novel therapeutic targets.

Role of adaptive immunity

Most research on the role of inflammation in HF has focused on HFrEF; much less is known in the context of HFpEF. Experimental models of HFpEF suggest that pro-inflammatory mediators play an important role in the development and progression of the syndrome[44,54,55]. Clinical trials in patients with HF targeting IL-6 or TNFα have manifested no, or even negative, effects on outcomes[54–57]. Therefore, immune modulation in HF remains controversial.

Coordinated innate and adaptive immune responses culminate in sequential immune cell infiltration into the heart contributing to cardiac inflammation and fibrosis. Recent advances in single-cell transcriptomic technologies (scRNA seq) have revealed the variety of immune and non-immune cells in the heart adding many levels of complexity to our understanding of cardiac cell identity[58 59]. With respect to adaptive immunity, T cells have been identified in the inflamed heart in diverse forms of HF in patients[60]. Studies in experimental models of HFrEF support the notion that different T cell subsets play distinct roles in the heart depending on the inflammation-triggering event[61,62]. For example, T cells are involved in the response following myocardial infarction (MI)[63–65]. This may occur in a bi-phasic mode, with an initially beneficial[66] and subsequently a chronic, detrimental phase[64,67]. In age-related HF, T cells have been shown to drive pathology[68,69]. Specifically, cardiac aging is associated with accumulation of a particular $CD4^+$ subpopulation – FoxP3 (forkhead box P3)$^+$ IFN-γ^+ – in heart-draining lymph nodes[68]. Importantly, cardiotropic T cells participate in age-related cardiac inflammation and functional decline suggesting that, at least in part, cardiac aging is mediated by immunological mechanisms[68]. Similar T cell dysregulation occurs in pressure overload-induced HF, in which inhibition or ablation of T cells limits pathology[60,70–72]. Whereas the T cell immune response is dominated by dysfunctional Treg cells that elicit TNF-α in chronic ischemic HF[67], pathogenic T cells polarized toward a type 1 response are central to non-ischemic HF[60,73].

T cell – B cell crosstalk

Meaningful insights have been gleaned regarding the interplay between T cells and B cells in models of HFrEF, but little is known in the context of HFpEF. T cells, in most pathophysiological contexts, are mirrored in function by B cells. Thus, it is not surprising that B cells have been found to contribute to the pathophysiological mechanisms of MI in mice, and antibodies are present in human hearts post-MI[74]. Myocardial B cells express chemokine receptors that could allow them to form tertiary lymph nodes (formations within which adaptive responses initiate) in mice with pressure overload or MI[59,75]. Intriguingly, even though B cell clusters have been observed in human epicardium of coronary artery disease (CAD) patients[76], canonical tertiary lymph node structures have yet to be observed in mammalian heart. T cells, in most of the conditions in which they are found to be activated, are driven by triggering of their antigen receptor. Indeed, T cell-specific activation by cardiac antigens has been reported in experimental HFrEF[77,78]. More specifically, in viral myocarditis, reactivity to viral antigens that mimic cardiac antigens appears to drive disease[79]. Molecular mimicry between microbe-derived antigens and cardiac antigens also promotes myocarditis after a response to a specific commensal bacterial strain[80]. In pressure overload-induced HF, the T cell response is known to involve antigen-specific reactivity[72]. Most recently, the driving antigens in pressure overload were found to include those modified by reactive oxygen species generated by the stress that drives the disease in the first place[77] whereas alpha myosin heavy chain is a dominant cardiac antigen triggering T cell activation in mice post-myocardial infarction.

Ample evidence indicates that T cell recruitment/retention in the heart depends on several factors including differences in T cell responsiveness to specific chemokines in the myocardial environment, as well as differences in the expression of adhesion molecules

in the intramyocardial vasculature[61,81]. These, in turn, regulate T cell-driven cardiac inflammation with consequences in cardiac remodeling and function[62] (Figure 3). Thus, a specific B cell and T cell immune response induced in different types of HFrEF may combine with activation of lymphocyte subsets expressing specific chemokine receptors and adhesion molecules, promoting a unique local cardiac environment with a defined pattern of chemokine ligands and endothelial adhesion molecules to enable recruitment to the heart. As an example, CXCR3 and CCR4 define T cell cardiotropism in certain conditions that induce the cardiac CXCR3 ligands CXCL9 and CXCL10, and c-Met, a hepatocyte growth factor that can be produced in the myocardium[73,81]. Yet, the roles of T cell immunity and cardiotropism in HFpEF remain largely unknown.

In HFrEF, a direct insult to the heart initiates an immune response that promotes cardiac repair or remodeling in an “inside-out” (from the heart to the periphery) manner. In contrast, HFpEF arises from systemic perturbations that may ultimately impact the heart, representing an “outside-in” mechanism of disease that implicates systemic forms of inflammation and metabolic stress that activate T cell immune responses and vascular endothelium systemically. Indeed, the latter is known to involve T cell-mediated effects[51]. Whereas this remains speculative, it is likely that T cells participate in HFpEF pathogenesis, potentially not only as a result of the cardiac stress driving diastolic dysfunction, but also upstream of the cardiac phenotype.

Endomyocardial biopsy data from HFpEF patients reveal a significant increase in cardiac $CD3^+$ cells compared with control patients[82]. Additionally, HFpEF patients have significantly higher levels of circulating T-helper 17 (Th17) cells and significantly lower levels of circulating Treg cells compared with healthy controls[83]. In addition to these data that point to expansion of T cells in HFpEF, there are several lines of evidence suggesting that T cells contribute to adverse cardiac remodeling and systemic inflammation in HFpEF. First, T cells have well-characterized roles in the pathophysiology of several comorbidities that commonly present in HFpEF patients, such as hypertension, obesity, and aging[68,69,84,85]. Second, as noted above, endothelial cell activation and inflammation in the heart are widely recognized hallmarks of HFpEF[86]. Endomyocardial biopsy samples from HFpEF patients reveal significant increases in the expression of VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1), and E-selectin[82,87,88]. Expression of these adhesion molecules is critical for extravasation of T cells, consistent with the premise that myocardial T cell infiltration may be a critical element in the pathophysiology of HFpEF. Preclinical data in multiple animal models of HFpEF corroborate these findings, as ZSF1 rats (obese Zucker diabetic fatty/spontaneously hypertensive hybrids) harbor similar increases in myocardial expression of ICAM and E-selectin[87]. Further studies, particularly using animal models that combine several comorbidities to induce HFpEF, may reveal how the intersection of risk factors affects adaptive immunity and the degrees to which T cells contribute to cardiac pathology in HFpEF.

Conditions predisposing to dysregulation of adaptive immunity

The notion that dysregulated adaptive immunity contributes to HFpEF pathogenesis is underpinned by emerging observations demonstrating that adaptive immunity is profoundly affected by systemic dysmetabolism. For example, dendritic cells (DCs) are instrumental in the initiation of the adaptive immune response and promote pro-inflammatory adaptive immunity during metabolic overload[89] (Figure 3). VAT is now considered an immune site harboring an array of innate and adaptive immune cells with a direct role in immune surveillance and host defense. In homeostatic conditions, conventional DCs in VAT display a tolerogenic phenotype through upregulation of Wnt/β-catenin and the PPARγ pathways[89]. Upon conditions of long-term over-nutrition, however, VAT accumulates and systemic inflammation ensues. This can be attributed to adipocyte alterations reducing β-catenin and PPARγ activation[89]. Systemic dysmetabolism also promotes pro-inflammatory differentiation of T cells[41]. Specifically, obesity-induced low-grade systemic inflammation promotes recruitment of effector T cells in adipose tissue, heart, and vasculature leading to a variety of cardiovascular complications[46]. Metabolic stress also affects differentiation and trafficking patterns of T cells[90]. Memory T cells primed by overfeeding migrate preferentially to non-lymphoid, inflammatory sites due to biased T cell differentiation into effector-like T cells. A similar phenotype skew was observed in obese subjects in a general population cohort[90]. Mechanistically, this effect is mediated by direct exposure of CD4+ T cells to palmitate, leading to increased activation of a PI3K p110δ-Akt-dependent pathway upon priming[90,91].

What about the other cardinal sign of HFpEF, *viz.* hypertension? Since the seminal paper by Guzik et al[92] reporting that T cell-deficient mice do not develop hypertension, T cells have been known to play a major role not only in the pathogenesis of, but also the progression of, hypertensive HF. Compelling recent evidence indicates that hemodynamic overload-induced HF also involves immune dysregulation as a major etiological factor[60,71,72,93]. In summary, the presence of systemic DC activation, such as significantly increased CD80 (required for T-cell co-stimulation), in HF promotes the triggering of systemic T cells[77,93]. Under certain conditions, these activated T cells may target the heart in an autoimmune response-type manner, promoting development of hypertrophy, cardiac fibrosis, remodeling, and failure, as has been proposed recently[56]. We could speculate, by analogy to the generation of antigen-specific T cell responses in HFrEF, that the multi-system stress that HFpEF drivers impose on adipose tissue and the vasculature, among other tissues, could generate or modify antigens recognized by T cells, activating the T cells and thus contributing to disease (Figure 3). In aggregate, the presence of T cell alterations in humans with HFpEF justifies detailed mechanistic investigation of adaptive T cell immune responses with basic and translational studies in preclinical models that allow for elucidation of the effects of T cells in diastolic dysfunction and specific aspects of cardiac remodeling in HFpEF.

Contributions of myeloid cells

Inflammatory myeloid cells and innate macrophages have been implicated in development of diastolic dysfunction[94], yet our understanding of how risk factors that predispose to HFpEF regulate myeloid mobilization and function pales, yet again, in comparison to

our understanding of macrophages in HFrEF. This includes our limited understanding of how HFpEF risk factors affect the activation and differentiation of macrophage precursors such as peripheral monocytes. For example, previous studies have shown that metabolic stress can promote a “priming” of monocytes that in turn enhances monocyte adhesion and chemotaxis[95]. In addition, monocyte lipid metabolism is distinct from that of macrophages and is critical in the differentiation of monocytes into phagocytic macrophages[96].

Tissue macrophages are conventionally associated with homeostatic clearance of dying cells, immunosurveillance, and tissue repair. Interestingly, macrophages have been linked more recently to diastolic dysfunction, such as that occurring in the context of increased salt consumption, unilateral nephrectomy, or aldosterone infusion[94]. However, the role of cardiac macrophages in HFpEF-associated diastolic dysfunction with an integrated metabolic contribution (i.e., obesity) remains unclear, as reviewed[97]. This is important given the common association of metabolic syndrome with HFpEF[11]. Multiple studies have examined the individual effects of hyperlipidemia on macrophage function[98], yet little is known regarding how combinatorial “hits” rewire functional macrophage proinflammatory functions, including in the heart (Figure 4).

As mentioned above, in contrast to myocardial “damage from within,” which often initiates HFrEF, HFpEF develops from peripheral “damage from without”[86]. This injury from the periphery may be fueled by the bone marrow or extramedullary myelopoiesis[99]. Interestingly, recent studies highlight the impact of dyslipidemia on pro-inflammatory monocyte production by the bone marrow in humans[100]. Specifically, $CD34^+$ bone marrow hematopoietic stem and progenitor cells (HSPCs) of patients with familial hypercholesterolemia manifest increased gene expression in pathways involved in HSPC migration and myelomonocytic skewing. These findings are consistent with prior studies in animals demonstrating that cholesterol augments proinflammatory monocyte production[101]. Increased proliferation of hematopoietic stem cell clones – clonal hematopoiesis – has been associated with increased cardiovascular risk[102]. In addition, a causal relationship between the increase in hematopoietic stem cell division and atherosclerosis has been reported recently[103]. In summary, studies of cardiac myeloid-cardiomyocyte crosstalk may lead to novel insights regarding the interplay between myocardial metabolism and cardiac function (Figure 4).

As noted, the HFpEF population is characterized by multiple, usually interrelated pro-inflammatory co-morbidities such as advanced age, obesity, type 2 diabetes mellitus, kidney disease, chronic obstructive pulmonary disease, and autoimmune diseases[104]. Chronic cardiac and systemic inflammation is associated with capillary regression and endothelial dysfunction, cardiomyocyte hypertrophy and interstitial fibrosis. Importantly, the presence and severity of these co-morbidities correlate with poor outcome in HFpEF, with greater impact on clinical outcome than parameters of left ventricular diastolic function or brain natriuretic peptide levels[105].

Whereas it is generally accepted that inflammation plays a role in HFpEF initiation and progression, the prevailing paradigm is that systemic inflammation leads to left ventricular diastolic dysfunction and myocardial hypertrophy via coronary endothelial microvascular

inflammation[86] that results in myocardial infiltration by activated macrophages[87] and elicitation of interstitial fibrosis[82]; this model, however, ignores the possible role of resident macrophages. Activation of the resident macrophage population occurs much earlier than systemic inflammation and therefore may represent a crucial first step aiming to protect the heart against these inflammatory co-morbidities (Figure 4). Furthermore, within activated macrophages, remodelling of the tricarboxylic acid cycle can generate metabolites that shift the balance between inflammation activation versus inflammation resolution. For example, exogenous administration of itaconate, a metabolite significantly induced in activated macrophages, has been shown to limit cardiac inflammation and injury[106], yet its role or therapeutic potential in HFpEF is currently unknown.

Studies in mice and recently in humans[107] have provided evidence that resident macrophages represent a heterogeneous population of cells, serving to protect the heart against pathological stimuli such as diabetes, hypertension, and inflammation, common co-morbidities and drivers of HFpEF. These resident cardiac macrophages derive from different embryonic lineages, are long-lived, and persist independent of blood monocyte input[108]. Also, their behaviour is different from that of blood-derived macrophages or mononuclear cells isolated from spleen and brain, suggesting a unique phenotype of cardiac macrophages[109]. Recent data indicate that those resident macrophages mainly proliferate in response to external pathological stimuli to promote cardiomyocyte survival and physiological hypertrophy, prevent adverse monocyte recruitment, and stimulate vascular expansion[107,110]. As such, those resident macrophages may serve to protect the heart from the metabolic stress of diabetes and hypertension. Invading cardiac monocytes, on the other hand, are required to “heal” the diseased myocardium, but they also promote pathology by stimulating fibrosis, pathological hypertrophy, and vessel regression, thereby contributing to HF. Whereas evidence exists for a role of resident macrophages in preventing cardiac systolic failure upon ischemic injury, a possible role of resident macrophages in HFpEF is unclear. Importantly, myocyte injury[111] and microvascular dysfunction[112 113] with the capacity to contribute to myocardial ischemia and injury, have been implicated in HFpEF.

Future studies are required to determine whether stimulation of resident macrophages – tissue resident CCR2-negative versus invading CCR2-positive cardiac macrophages – antagonizes progression to HFpEF by reducing pathological hypertrophy, capillary regression and fibrosis, in the setting of diabetes, obesity, hypertension and ageing.

Immunometabolic crosstalk

Whereas direct damage to the myocardium mediated by infiltrating effector immune cells has been investigated extensively, metabolic crosstalk between inflammatory cells and the cardiac muscle itself is less well understood. The systemic increase of circulating cytokines in metabolic syndrome, a major HFpEF comorbidity, induces production of chemokines and expression of adhesion molecules by cardiomyocytes, fibroblasts, and endothelial cells leading to myocardial recruitment and retention of immune cells such as monocytes and lymphocytes[114]. Whereas the impact of systemic inflammation on cardiac function and remodeling in HFrEF has been well documented[114,115], few studies have examined the impact of pro-inflammatory stimuli on cardiac metabolism. Even though the mutual

influence of immune/parenchymal cell metabolic crosstalk in HFpEF hearts, and consequent impact on adverse remodeling, remain to be resolved, it is tempting to propose hypotheses based on parallel analysis of metabolic changes in failing (mostly HFrEF) hearts and inflammatory cell infiltrates.

Quiescent T cells rely predominantly on oxidative metabolism and consume small amounts of glucose, amino acids, or fatty acids to meet basic energetic demands. T cell activation by T cell receptor (TCR) triggering and concomitant co-stimulation via the CD28 receptor induce a dramatic shift to aerobic glycolysis to support rapid growth and differentiation into effector T cells (T_{eff})[116]. T_{eff} cells include cytolytic T cells, secreting granzyme B, perforin, interferon-γ (IFN-γ), and helper T cells (Th) such as type-1 (Th1), type-2 (Th2), and type-17 (Th17) producing characteristic cytokines, and finally regulatory T cells (T_{reg})[117]. Each T cell subset is characterized by signaling pathways and metabolic signatures that define its fate and function[118]. Once activated, T_{eff} cells infiltrate inflamed tissue, adapting to the local microenvironment (oxygen tension, acidification, and the presence of metabolites) by undergoing further metabolic reprogramming. For example, immune cells respond quickly to a decrease in oxygen availability – typical of sites of inflammation – by stabilizing the transcription factor HIF1α (hypoxia-inducible factor 1α) which, in turn, induces transcription of anabolic genes for glycolysis and mitochondrial metabolism in T cells[119] and macrophages[120].

Cardiac macrophages also play important roles in maintaining myocardial homeostasis. A recent study demonstrated that macrophages within the heart engulf decaying mitochondria released from cardiomyocytes[121]. This process requires cardiomyocyte autophagy. Furthermore, depletion of cardiac macrophages, or deficiency of macrophage phagocytic receptors, such as MerTK, lead to increases in functionally impaired mitochondria in cardiomyocytes and, in turn, reduced production of ATP. These hearts also exhibit impaired cardiac filling similar to that seen in HFpEF. Given that the extracellular domain of MerTK can be cleaved from cardiac macrophages and released into the serum as a biomarker[122], it may be of interest to determine whether solubilized MerTK is a biomarker of clinical HFpEF. Mononuclear phagocytes specialize in sampling the tissue microenvironment and mediating crosstalk with neighboring cells, thus bridging innate and adaptive immunity. After stimulation, DCs undergo a burst of oxidative phosphorylation which is rapidly replaced by full engagement of aerobic glycolysis[123]. Macrophages undergo similar metabolic reprogramming after activation. Inflammatory macrophages manifest reduced TCA cycle activity which allows for accumulation of succinate that promotes inflammation[124] via mitochondrial ROS production, HIF1α stabilization, and persistent activation of glycolysis. In contrast, anti-inflammatory M2-like macrophages rely on the TCA cycle to meet their metabolic demands[125].

We propose that direct and indirect crosstalk between metabolic events and inflammatory immune cells, occurring via both nutrient and oxygen competition as well as direct signals from cytokines and metabolites, contribute to the development of HFpEF (Figures 3, 4). If correct, this hypothesis would justify therapeutic targeting of aberrant metabolic pathways in cardiac inflammatory disease. Reviews of recent trials targeting inflammation in CAD have argued that immunometabolic correction with statins is superior and less prone to

severe side effects as seen with direct immunomodulation[126]. We have also proposed that modulation of systemic and cellular metabolism might be an attractive strategy to reduce organ inflammation[42].

Cardio-immune metabolites

Under normoxic conditions, >95% of ATP generated in the heart is derived from oxidative phosphorylation in mitochondria, mainly fueled by free fatty acid oxidation. The remaining 5% derives largely from glycolysis[127]. There is general agreement that development of overt cardiac dysfunction is accompanied by reduced FFA oxidation[127 128]. HF is also characterized by alterations in glucose metabolism. Specifically, whereas glucose uptake and glycolytic rates are increased, this is not accompanied by a concomitant rise in glucose oxidation[128]. The profound defect in oxidative phosphorylation in the failing heart is reflected by overt mitochondrial dysfunction, with altered size and number of mitochondria, disorganized cristae, reduced density, membrane disruption, and aggregation[44]. Excessive ROS production from dysfunctional mitochondrial electron transport chain ATP synthesis also contributes to oxidative damage and ultimately to cardiomyocyte loss[44].

Overall, both immune cells and cardiac parenchyma contribute to shaping the microenvironment in cardiac inflammation. Next, we focus on two key metabolites likely to participate in metabolic crosstalk in the failing heart.

Lactate.

Lactate is produced by highly glycolytic, activated immune cells[129]. Extracellular lactate, when enriched in the cytosol following uptake by lactate transporters, can signal directly to immune cells themselves and tissue parenchymal cells via lactate receptors as well as by affecting metabolic pathways.

In immune cells, lactate mainly signals via the surface-expressed G-protein-coupled receptor GPR81[130], eliciting signals that are strong inhibitors of immune effector functions[41]. However, extracellular sodium lactate and lactic acid inhibit the motility of $CD4^+$ and $CD8^+$ T cells, respectively, entrapping T cells at the inflammatory site and preventing the resolution of inflammation[131]. Impairment of T cell motility is mediated by uptake via subtype-specific transporters (Slc5a12 and Slc16a1) expressed by $CD4^+$ and $CD8^+$ cells, respectively, by interference with glycolysis triggered by chemokine receptors. Importantly, sodium lactate also induces a switch toward the Th17 cell subset, promoting robust biosynthesis of the proinflammatory cytokine IL-17, enhancing fatty acid synthesis[132].

Lactate accounts for a minimal component of energy production in the healthy heart at rest[133], but this fraction can increase substantially during exercise or in the setting of various pathophysiological conditions. Lactate production in the cardiomyocyte cytosol is balanced by oxidation of pyruvate in mitochondria (reviewed in[134]). Of note, down-regulation of the mitochondrial pyruvate carrier (MCP), which transports pyruvate generated in the cytosol in the failing human heart, has been recently reported[135,136]. Excess extracellular lactate resulting from protracted inflammation has been linked to cardiomyocyte apoptosis in human end-stage HF[137]. Under inflammatory conditions, elevated concentrations of

intracellular lactate promote ROS generation[132]. High levels of ROS, in turn, can trigger mitochondrial damage and activation of mitochondria-dependent apoptosis. Accordingly, a significant association has been identified between the lactate signaling cascade and HF and other conditions[132,138,139].

Excess extracellular lactate in the heart is a metabolic indicator of ischemia. A key feature of HFpEF is endothelial dysfunction, which may contribute to chronic oxygen deficiency in the failing myocardium. Lactate has been linked to cardiomyocyte apoptosis in several experimental models of cardiovascular disease, including end-stage HF[137]. Despite these associations, a recent study comparing metabolomics of blood from artery, coronary sinus, and femoral vein in patients with or without HF (including patients with EF>50%) reported that the failing heart almost doubles lactate consumption[133]. Therefore, the overall contribution of lactate to HFpEF remains to be established.

Succinate.

Succinate accumulation is also a hallmark of the ischemic heart, where it fuels ROS production[140]. In addition, elevation of blood succinate has been reported in rodent models of hypertension and metabolic syndrome[141]. Extracellular succinate is a powerful pro-inflammatory stimulus. In the context of metabolic syndrome, exposure of adipocytes to hypoxia and hyperglycemia (such as during obesity) induces succinate release from adipose tissue in mice[142] leading to macrophage infiltration and inflammation[142]. In DCs, exposure to succinate increases TNFα and IL-1β expression[143] and the capacity of DCs to initiate adaptive immunity. In macrophages, TLR engagement by lipopolysaccharide increases intracellular succinate levels and cell surface expression of the succinate receptor SUCNR1[144]. Released succinate can act in an autocrine and paracrine manner to enhance pro-inflammatory cytokine production by the same cells or by nearby SUCNR1-expressing cells. Production of IL-1β further enhances SUCNR1 expression fueling this pro-inflammatory cycle. Collectively, these observations point to succinate as a likely candidate in the induction and maintenance of inflammation and adverse remodeling in HFpEF.

Therapeutic approaches in cardiometabolic HFpEF

We propose that targeting metabolic and inflammatory pathways in HFpEF is a therapeutic strategy with promise. However, targeting inflammation directly has been a longstanding challenge in cardiovascular medicine. Canonical anti-inflammatory therapies, such as anti-TNFα therapeutics, to treat HFrEF have been abandoned[27]. However, results from the CANTOS trial provided the first evidence that targeted anti-inflammatory approaches in cardiovascular disease have merit[145]. In that trial, inhibition of interleukin-1 (IL-1ß) resulted in reduced rates of recurrent cardiovascular events independent of lipid lowering[145]. More recently, the COLCOT trial reported that colchicine, an inexpensive, orally administered, potent, anti-inflammatory drug, led to a significantly lower risk of ischemic cardiovascular events than placebo in patients with a recent myocardial infarction[146]. In aggregate, the results of recent clinical trials aiming to reduce the inflammatory burden in cardiovascular disease have shown promising results, setting the stage for renewed interest in inflammation-targeting strategies in cardiovascular disease. Of note, it is important to recognize that the

clinical trials mentioned above targeted conditions predisposing more often to HFrEF (e.g. atherosclerosis, CAD) than HFpEF. Hence, the validity of these therapeutic strategies in HFpEF remains to be tested.

We have reported activation of the inflammatory molecule iNOS (inducible nitric oxide synthase) in both preclinical and clinical HFpEF contributing importantly to nitrosative stress[22]. Furthermore, we reported that pharmacological inhibition or genetic silencing of iNOS ameliorated the HFpEF phenotype. Based on this, we suggest that the availability of clinically approved iNOS inhibitors heralds therapeutic promise in HFpEF[22]. Going forward, additional investigation into molecular mechanisms of immune/inflammatory activation in HFpEF will likely reveal additional targets with potential clinical efficacy.

Given the long-established crosstalk between metabolic and inflammatory mechanisms, it is conceivable that a two-pronged attack on HFpEF, combining strategies that target both metabolism and inflammation, is warranted. We and others have shown that a key metabolic alteration observed in HFpEF (and HF in general) is reduced bioavailability of NAD^+ (nicotinamide adenine dinucleotide), a cofactor required for cellular respiration and sirtuin activity. We reported that reduced mitochondrial fatty acid oxidation in HFpEF is dependent, at least in part, on hyperacetylation of key mitochondrial enzymes stemming from NAD^+ deficiency-derived suppression of sirtuin activity[147,148]. Separately, NAD^+ precursors can enhance anti-inflammatory innate immune functions, including potentially in the heart[149]. As oral supplementation with the NAD^+ precursor NR (nicotinamide riboside) increases tissue NAD^+ levels in humans[150], and ameliorates the HFpEF phenotype in rodents[147], the prospect of pharmacologically boosting cardiac NAD^+ levels emerges with the potential for rapid translation to patients.

Conclusions and perspectives

Emerging evidence implicates bidirectional crosstalk between metabolic stress and inflammation in the pathogenesis of cardiometabolic HFpEF; inflammation rewires cellular metabolism, and systemic and local metabolic perturbations dictate immune cell behavior. Given the well-established heterogeneity among HFpEF phenotypes, coupled with the robust complexity and intertwined interactions between metabolic events and inflammation, a comprehensive program of investigation will be required. That HFpEF is a systemic disorder, not simply a cardiac disorder, amplifies this complexity yet further. Nevertheless, work to unravel meta-inflammatory mechanisms contributing to HFpEF pathophysiology holds the potential to benefit millions of individuals around the globe.

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We regret that we were unable to recognize all pertinent research in this field and contributions from all investigators owing to journal space limitations.

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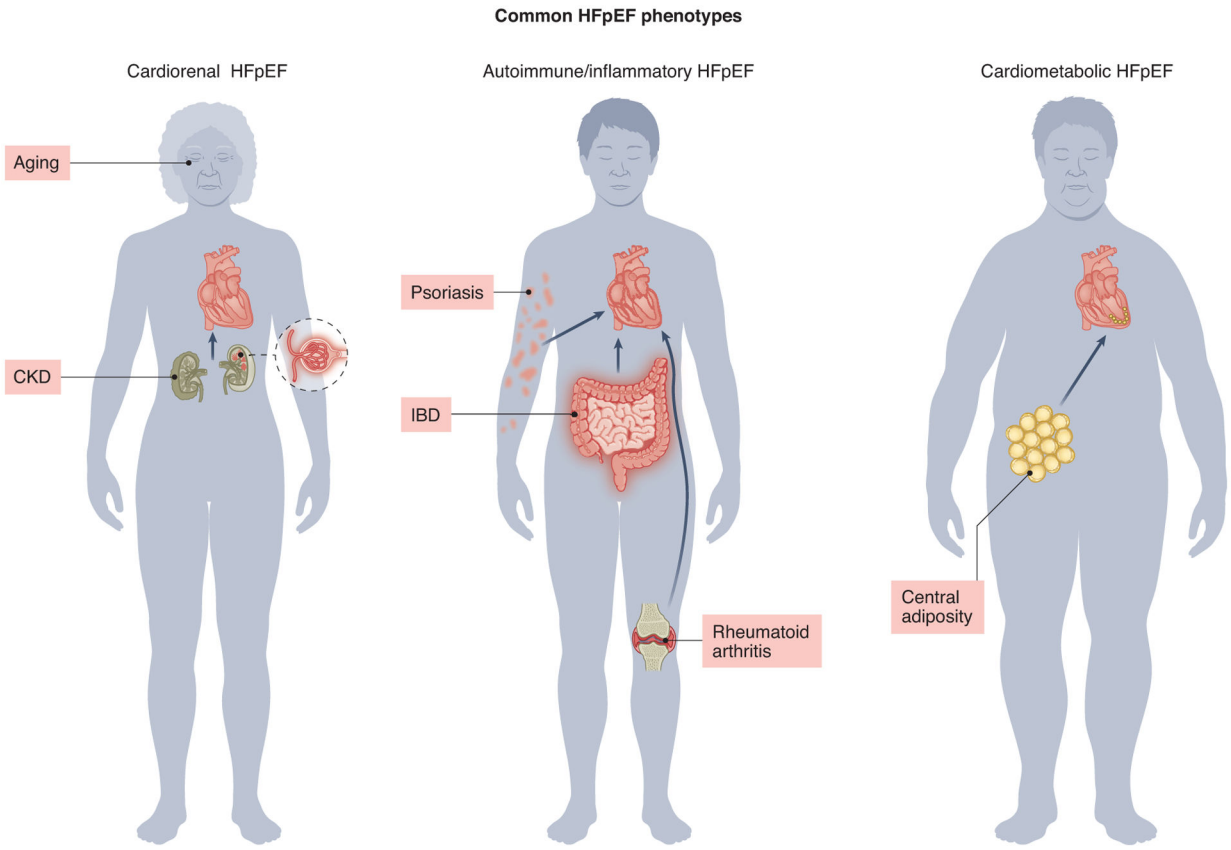

Figure 1.

Schematic overview of common HFpEF phenotypes.

CKD: chronic kidney disease

IBD: inflammatory bowel disease

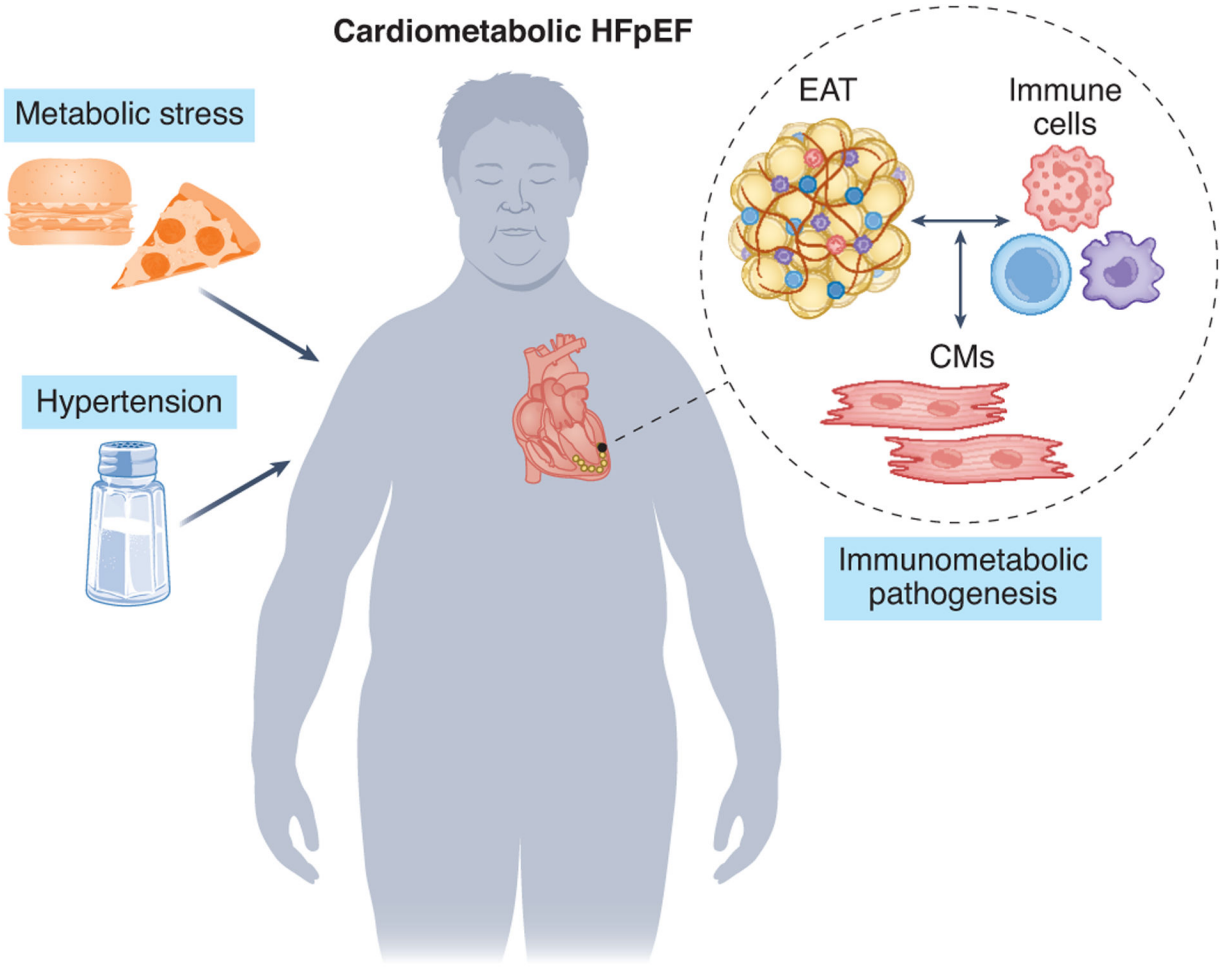

Figure 2.

Immunometabolic mechanisms involving crosstalk between inflammatory and metabolic events contribute to the pathogenesis of cardiometabolic HFpEF.

EAT: epicardial adipose tissue

CMs: cardiomyocytes

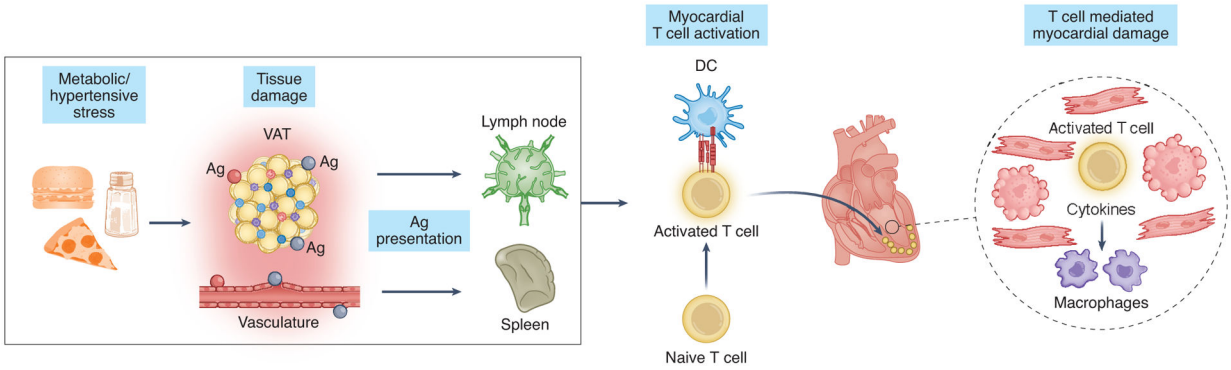

Figure 3.

Cardiometabolic stress triggers alterations in adaptive immunity in HFpEF. Metabolic stress activates T cells in peripheral organs that, in turn, promote recruitment of other immune cells to the heart and consequent myocardial damage.

VAT: visceral adipose tissue

Ag: antigen

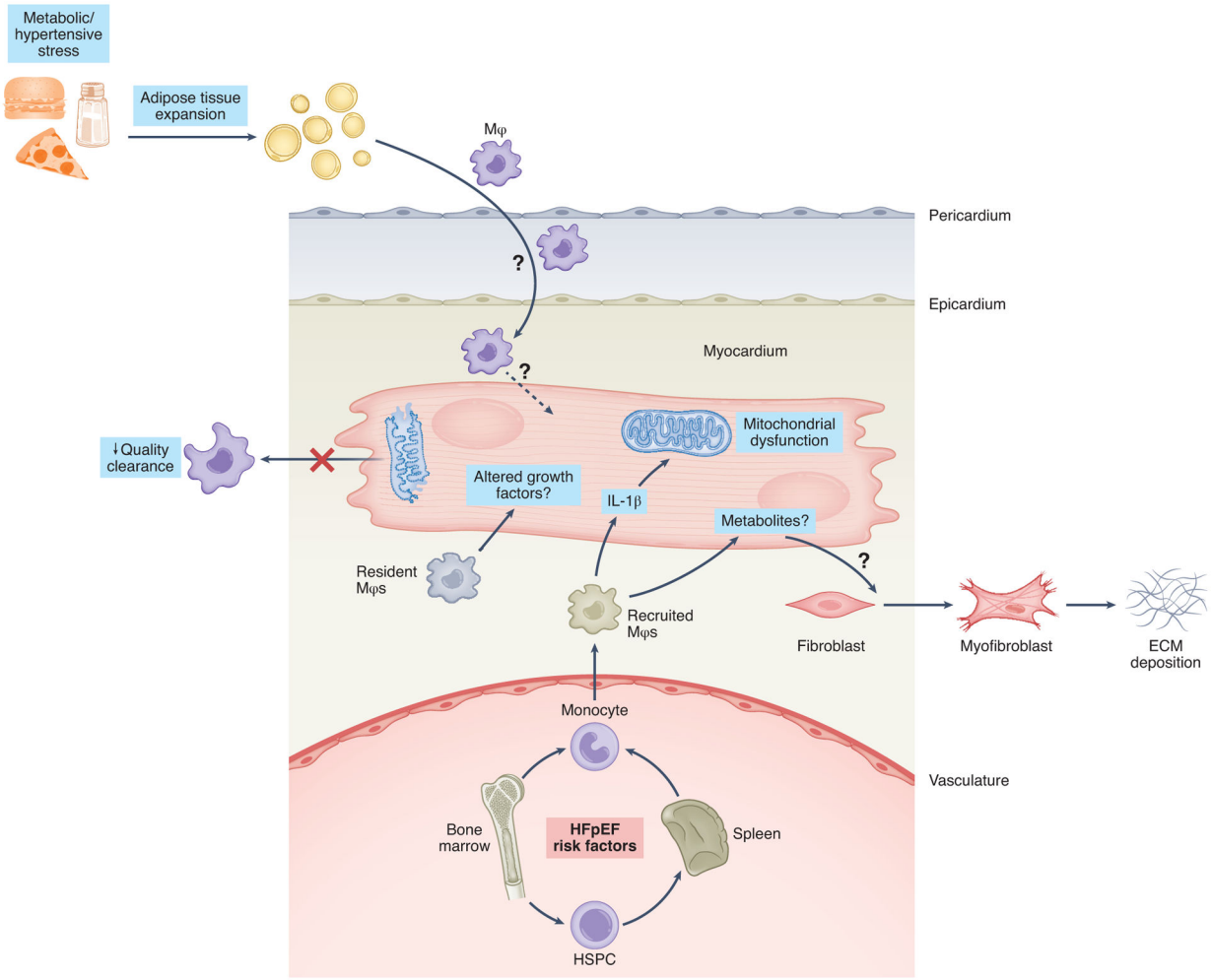

Figure 4.

Potential contributions of innate immunity to the pathogenesis of cardiometabolic HFpEF. Depicted is a working model in which cardiometabolic risk factors, including visceral adiposity and hypertension, fuel immunometabolic mobilization of innate immune cell subsets. This immune cell mobilization, in turn, activates intercellular crosstalk that also regulates myocardial metabolic pathways.

HSPC: hematopoietic stem/progenitor cell

Mϕ: macrophages

IL-1β: interleukin 1β