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STATE-OF-THE-ART REVIEW

The Cardiohepatic Axis in Metabolic Disease

Liver to Heart

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HIGHLIGHTS

- **There is a strong clinical association between steatotic liver disease and cardiovascular disorders.**
- **Liver-derived secretory factors are an important communication mechanism between the liver and heart.**
- **Bone marrow reprogramming and clonal hematopoiesis of indeterminate potential drive inflammation.**
- **Therapies targeting both organs can bridge the gap between liver and cardiovascular health.**

SUMMARY

Heart and liver metabolic diseases often coexist because of local and systemic disorders that affect both organs via cardiohepatic interactions. Here, we discuss the emerging evidence of organ crosstalk during cardiometabolic disease with an emphasis on the liver-to-heart axis. We highlight potential mechanisms by which metabolic dysfunction-associated steatotic liver disease contributes to cardiovascular complications. Metabolic dysfunction-associated steatotic liver disease, particularly its inflammatory entity, leads to the production of liver-derived secretory factors that regulate cardiac metabolism, inflammation, and remodeling. Thus, secreted hepatic factors represent an important mechanism of communication between the liver and heart during cardiometabolic disease. In addition to the direct crosstalk between organs, we argue that bone marrow reprogramming and clonal hematopoiesis of indeterminate potential are shared mechanisms of systemic inflammation that regulate the heart–liver axis during cardiometabolic disease. Thus, integrated cardiometabolic strategies hold a significant potential to bridge the gap between liver and cardiovascular health to improve patient outcomes.
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The liver and heart engage in a complex, bidirectional crosstalk that is increasingly recognized as a key driver of cardiometabolic disease. The growing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) follows that of obesity, making MASLD a significant cardiometabolic concern.[1] MASLD affects nearly one-third of adults worldwide and is now recognized as a major driver of cardiovascular disease (CVD).[2] The cardiometabolic burden of MASLD is evident given its strong association with several diseases, such as heart failure with preserved

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ABBREVIATIONS AND ACRONYMS

asCVD = atherosclerotic cardiovascular disease

CVD = cardiovascular disease

HFpEF = heart failure with preserved ejection fraction

IL = interleukin

KC = kupffer cell

MASH = metabolic dysfunction-associated steatohepatitis

MASLD = metabolic dysfunction-associated steatotic liver disease

MdM = monocyte-derived macrophage

ejection fraction (HFpEF), atherosclerotic cardiovascular disease (asCVD), and arrhythmias, which independently contribute to elevated mortality.[3] The progression from MASLD to the more severe metabolic dysfunction-associated steatohepatitis (MASH) transitions the liver into an inflammatory organ that amplifies cardiovascular risk.[4] More patients with MASH die of CVD-related events, compared with any other liver-related cause, including hepatic malignancies.[3,5] Although the precise mechanisms are unclear, MASH is now considered an important driver of cardiac diastolic dysfunction. In a mouse model of MASH, administration of a choline-deficient, L-amino acid-defined diet that causes liver damage without weight gain resulted in increased cardiac inflammation, fibrosis, and hypertrophy,[6] raising the possibility that MASH per se is an independent contributing factor of cardiac disease.

HFpEF has emerged as a heterogeneous condition with distinct clinical phenotypes and hallmark heart failure symptoms but preserved left ventricular ejection fraction.[7] Cardiometabolic HFpEF is characterized by systemic metabolic disturbances and chronic inflammation. This form of HFpEF has been described as "MASH of the heart,"[8] considering the shared features such as lipid accumulation, inflammation, oxidative stress, and fibrosis. Notably, there is a heightened risk for HFpEF among patients with MASLD compared with those with heart failure with reduced ejection fraction.[9] For example, one study reported that 37.57% of patients with HFpEF had advanced fibrosis determined by a higher NAFLD fibrosis score.[10] Thus, the degree of liver fibrosis is likely a key predictor of major adverse cardiovascular events in HFpEF patients.[11] Indeed, among heart failure subtypes, a high liver fibrosis index predicted total cardiovascular events in HFpEF.[10,12] This clinical evidence supports the notion that combined heart and liver dysfunctions coexist during cardiometabolic diseases, raising the possibility of direct cardiohepatic interactions.

During cardiometabolic disease, hepatic and cardiac dysfunction promote systemic cardiovascular derangements common to CVD. Emerging evidence indicates that hepatic inflammation and fibrosis directly promote adverse cardiac outcomes in asCVD and arrhythmias. A meta-analysis of over 44,000 individuals revealed a nearly 2-fold increased risk of asCVD in patients with MASLD, independent of conventional risk factors.[13] Similarly, MASLD is strongly linked to atrial fibrillation (AF), the most prevalent form of arrhythmia.[14] Importantly, hepatic fibrosis, and not steatosis, is an important arrhythmogenic factor given that an increase of 1 kPa in liver stiffness correlates with a 9% rise in the risk of AF.[15] These clinical findings suggest that the inflammatory and fibrotic components of MASLD, rather than simple lipid accumulation, are potential mediators of proarrhythmic remodeling. Despite the clinical associations, the mechanistic underpinnings of liver-induced cardiovascular dysfunction remain elusive. In this review, we will discuss the emerging evidence supporting liver-to-heart crosstalk during cardiometabolic disease (**Figure 1**).

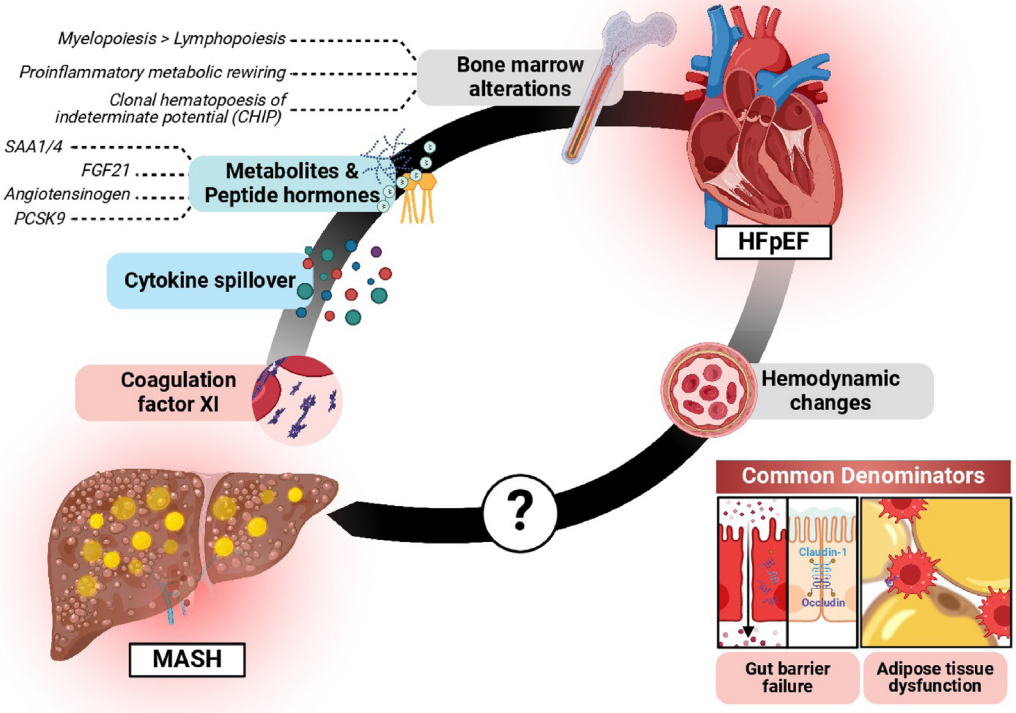
LIVER-HEART ORGAN CROSSTALK DURING CARDIOMETABOLIC DISEASE

ROLE OF LIVER-DERIVED SECRETORY FACTORS IN HFpEF. Intertissue communication via secreted proteins has been established as a vital mechanism to maintain normal organ function. During CVD, recent studies have identified liver-derived secretory factors with an important role in regulating cardiac function.

Coagulation factor XI. Using a system genetics screening approach, the coagulation factor XI (FXI) was recently identified as a liver-derived molecule with a causative role in protecting the heart against diastolic dysfunction.[16] During experimental HFpEF, liver-derived FXI cleaves the extracellular matrix-bound bone morphogenetic protein 7 (BMP7) in the myocardium, activating the BMP7-SMAD signaling pathway, and protecting the heart against key pathological processes in HFpEF.[16] As a result, there is an attenuated infiltration of recruited macrophages and neutrophils, as well as decreased expression of the inflammatory cytokines interleukin (IL)-1β, IL-6, and tumor necrosis factor-α.[16] In humans, lower levels of FXI are associated with worse diastolic function and a higher incidence of AF, suggesting that this pathway is clinically relevant.[17] Together, these findings suggest that FXI regulates myocardial remodeling and systemic metabolic homeostasis during heart failure. To date, this is one of the few direct mechanisms by which a liver-derived factor regulates cardiac remodeling during heart failure. It is worth mentioning that coagulation factors, including FIX, rise in MASLD.[18] Whether this rise would increase the thrombotic risk of afflicted patients or mediate any cardioprotective effects secondary to metabolic benefit is unclear.

Fibroblast growth factor-21. The levels of the hepatokine fibroblast growth factor (FGF)-21 increase in patients with MALSD[19] and HFpEF,[20] suggesting a potential role during cardiometabolic disease.

FIGURE 1 **The Cardiohepatic Axis in Metabolic Disease**



The bidirectional crosstalk between the liver and heart in cardiometabolic disease, highlighting immune and metabolic interactions that drive disease progression. Liver-derived secretory factors and cytokines regulate cardiac remodeling in heart failure with preserved ejection fraction (HFpEF). Bone marrow progenitors are reprogrammed toward increased myelopoiesis, metabolic rewiring, and clonal hematopoiesis of indeterminate potential (CHIP), resulting in immune cells with enhanced inflammatory function. Heart failure can exacerbate liver dysfunction via hemodynamic stress and unknown mechanisms. MASH = metabolic dysfunction-associated steatohepatitis.

Although some reports show that cardiomyocytes express FGF21,[21] their relative contribution is small, and the liver is considered the predominant source.[22] Efruxifermin, a fusion protein mimicking FGF-21, was recently shown to reduce fibrosis of at least 1 stage in biopsy-proven MASH in clinical trials.[23] Mechanistically, FGF-21 improves lipid metabolism and insulin sensitivity, and protects against cellular stress.[24] In the liver, FGF-21 decreases de novo lipogenesis by preventing the nuclear maturation of sterol response element binding protein-1.[25] At the same time, FGF-21 diverts triglyceride-rich lipoproteins to the white and brown adipose tissues by up-regulating CD36 and promoting their catabolism.[26] Hepatic FGF21 production increases during MASH in response to the activation of the endoplasmic reticulum (ER) stress pathway PERK-eIF2α-ATF4, whereas its genetic deletion results in insulin resistance and hepatic lipid accumulation.[27] In addition to its metabolic effects, FGF-21 prevents Kupffer cell death in a mouse model of MASH-induced hepatocellular carcinoma.[23] In the heart, cardiomyocytes express FGF-receptor-1 and its cognate co-receptor beta-Klotho (β-KL) that can recognize liver-derived FGF-21.[22] In mouse diabetic hearts, FGF-21 promotes a proangiogenic and anti-inflammatory environment through the regulation of macrophages.[28] Genetic ablation of FGF21 during experimental diabetes results in cardiac hypertrophy, fibrosis, and mitochondrial dysfunction, supporting a cardioprotective role.[29] However, despite the favorable metabolic effects, increased levels of FGF-21 are associated with a higher risk of asCVD independent of MASLD.[30] Thus, future MASH trials should include secondary endpoints to determine if FGF-21 therapy causes elevated risk for atherosclerotic cardiovascular events.

Proprotein convertase subtilisin/kexin type 9. Another hepatokine that is a potential regulator of cardiac disease is the proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 increases in the

circulation of patients with MASLD[31] and those with age-related cardiovascular disease.[32] In MASLD, increased PCSK9 levels correlate with systemic inflammation,[31] whereas its inhibition slows the progression of disease in mice, suggesting a pathological role.[33] In aged mice, increased levels of liver-derived PCSK9 correlate with left ventricular hypertrophy, fibrosis, and impaired diastolic function, whereas its pharmacological inhibition ameliorates liver steatosis and cardiac dysfunction.[32] Mechanistically, PCSK9 inhibition confers antihyperlipidemic effects by preventing the cleavage of the low-density lipoprotein receptor thereby increasing the hepatic uptake of circulating low-density lipoprotein.[34] Another potential mechanism by which PCKS9 promotes cardiac dysfunction is the activation of inflammatory macrophages mediated via the toll-like receptor-4 pathway.[35] However, conflicting data showed that systemic PCSK9 deficiency instigates HFpEF in mice by disrupting cardiac lipid homeostasis and diastolic dysfunction.[36] In the absence of PCSK9, cardiomyocytes increase their lipid uptake within lipid droplets and have dysfunctional mitochondria, suggesting that PCSK9 is required for normal cardiac metabolism.[36] This deleterious effect, however, is not observed clinically as PCSK9 inhibitors show a favorable safety profile.[37]

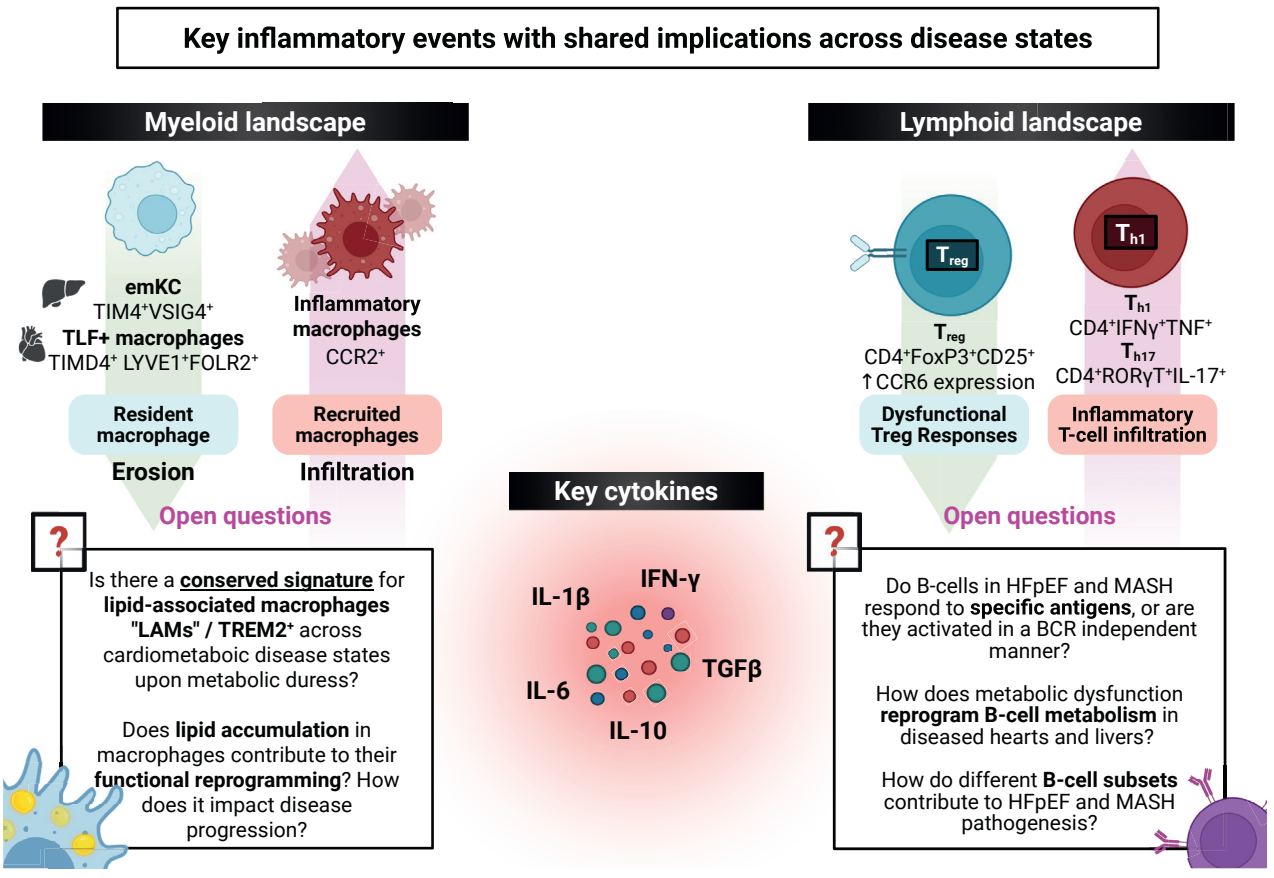
Serum amyloid A. Although causality has not been tested, increased levels of additional secretory factors of hepatic origin correlate with HFpEF progression. For example, serum amyloid A (SAA) levels increase in the circulation of patients with MASLD and HFpEF and mouse models of disease.[38] Increased hepatic SAA, in particular, correlates with a higher expression of extracellular matrix remodeling genes in the heart.[38] In a mouse model of pressure overload, systemic SAA deficiency protects the heart against cardiac fibrosis and down-regulates the inflammatory NF-kB signaling pathway,[39] suggesting a profibrotic role for SAA in cardiac remodeling. Importantly, SAA expression is restricted to the liver and increases during MASH,[40] suggesting that SSA is a potential MASH-induced molecule that promotes cardiac dysfunction. Future research using liver-specific approaches is needed to confirm that SSA of hepatic origin promotes HFpEF pathogenesis.

Angiotensinogen. Angiotensinogen is a hepatic protein and a key component of the renin-angiotensin system, which helps regulate blood pressure and fluid balance. Increased levels of angiotensinogen correlate with worsening left ventricular diastolic function in patients with HFpEF,[41] suggesting a potential role in the liver-heart crosstalk. Furthermore, MASLD is characterized by the activation of the RAAS in humans,[42] and hepatocyte-specific angiotensinogen has been shown to promote hepatic lipid accumulation in a mouse model of MASLD.[43] Despite the initial clinical focus on RAAS antagonists for the treatment of HFpEF,[44] these modalities have resulted in low efficacy. Considering its potential role in MASLD, whether patients with MASLD and HFpEF could benefit from therapies targeting RAAS modulation should be investigated.

CYTOKINE SPILLOVER. Chronic inflammation is associated with accelerated development of cardiometabolic diseases, including HFpEF, MASH, and atherosclerosis (**Figure 2**). Cytokines are proteins produced by immune cells that act as signaling molecules to coordinate the interactions between immune and nonimmune cells to regulate immune responses and inflammation. Substantial evidence from animal models and a clinical trial testing a monoclonal antibody against IL-1β[45] suggest that targeting proinflammatory cytokines is a viable strategy to treat cardiometabolic disease. Notably, the liver is a major organ of cytokine production and activity, given that hepatic immune cells such as macrophages and Kupffer cells release cytokines that act locally or spill over into the circulation to reach other organs including the heart. In addition to immune cells, the hepatocytes themselves produce certain cytokines, such as IL-7, -11, and -33, that can reach circulation.[46] Although their precise contribution to cardiac inflammation is unclear, liver-derived cytokines increase during the progression of steatosis to MASH and have been proposed to accelerate cardiometabolic disease.[4]

During MASH, IL-1β is produced in the liver and increases systemically,[47] suggesting that it may contribute to cardiac inflammation. In the inflamed liver, cholesterol crystals and lipotoxicity promote the activation of the NLRP3 inflammasome in macrophages, causing IL-1β secretion and accelerating hepatocyte injury, immune cell infiltration, and fibrosis.[47] As a result, inhibition of IL-1β ameliorates the progression of experimental MASH in murine models.[47] In a mouse model of HFpEF, IL-1β promotes diastolic dysfunction by driving mitochondrial oxidative stress and impairing cardiomyocyte contractility, whereas inhibition of the IL-1β receptor improves diastolic dysfunction without reversing the underlying metabolic stress.[48] This aligns with clinical data from the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial, which demonstrated that IL-1β-targeted therapy reduces cardiovascular mortality by mitigating inflammation independent of lipid-lowering.[45] Notably,

FIGURE 2 **Key Immune and Inflammatory Events Shared Across Cardiometabolic Disease States and Metabolic Tissues**



Alterations in myeloid cells include the dysfunction of resident macrophage populations and the infiltration of inflammatory monocyte-derived macrophages. Among lymphoid cells, cardiometabolic disease is characterized by a loss of T regulatory (Treg) responses and activation of proinflammatory T cells. Immune dysregulation results in the aberrant production of cytokines interleukin (IL)-1β, -6, and -10; interferon (IFN)-γ; and tumor growth factor (TGF)-β, which mediate systemic inflammation and tissue remodeling. Abbreviations as in Figure 1.

neutralization of IL-1β in mice with age-induced MASH improves diastolic cardiac function but fails to attenuate hepatic fibrosis, suggesting a potential role for liver-derived IL-1β in the pathogenesis of cardiometabolic disease.[49] Although this hypothesis has not been experimentally tested, these data suggest that excessive production of IL-1β in the liver can spill over into the circulation and negatively affect the function of the heart during cardiometabolic disease.

In addition to IL-1β, IL-6 plays a central role in the inflammatory processes underlying the pathogenesis of MASH[50] and HFpEF.[51] In patients with HFpEF, elevated IL-6 levels are associated with decreased tolerance to exercise, including reduced peak oxygen consumption, shorter 6-minute walking distance, and increased symptom burden.[51] In a cohort of patients with HFpEF and obesity, IL-6 levels were higher in those with greater BMI,[51] suggesting a relationship between IL-6 and metabolic stress in the setting of HFpEF. IL-6 has a similar role in MASH where circulatory, hepatic,[50] and adipose tissue levels[52] of IL-6 positively correlate with MASH severity in humans. However, a causative role for IL-6 in the pathogenesis of MASH is unclear because studies in mouse models have shown both detrimental[53] and protective[54] roles.

IL-10 is considered an anti-inflammatory cytokine that suppresses excessive immune activation to resolve inflammation. However, in chronic disease settings such as HFpEF and MASH, IL-10 seems to have a more complex role. Plasma from HFpEF patients has been shown to promote monocyte differentiation into IL-10-expressing macrophages,[55] suggesting a compensatory response aimed at mitigating inflammation that later turns harmful.

Although IL-10 plays a protective role in acute cardiac injury,[56] chronic IL-10 production promotes fibroblast activation to drive osteopontin-dependent extracellular matrix deposition and myocardial stiffening in a mouse model of hypertension.[57] In contrast, IL-10 has been found to prevent diet-induced hepatic injury during MASH.[58] Untangling the organ-specific responses to IL-10 and the differential behaviors of cardiac fibroblasts and hepatic stellate cells warrants further investigation.

Interferon-gamma (IFN-γ) is a signature cytokine of Th1-mediated immunity and plays a pivotal role in chronic inflammation associated with both MASH[59] and HFpEF.[60] Elevated IFN-γ levels have been observed in HFpEF patients, with increased infiltration of IFN-γ-producing CD4+ T cells in myocardial tissue.[61-63] This proinflammatory cytokine has been shown to drive cardiac fibroblast activation, leading to excessive extracellular matrix deposition and myocardial stiffening.[64] IFN-γ-expressing T cells accumulate in the MASH livers,[65] where they contribute to hepatocellular injury. The convergence of IFN-γ-mediated inflammation in both cardiac and hepatic tissues highlights its role as a key pathogenic driver linking MASH to HFpEF.

CONSEQUENCES OF CARDIAC DYSFUNCTION ON LIVER PATHOLOGY

Compared with the liver-to-heart axis, the pathological mechanisms causing liver injury secondary to cardiac insults are poorly understood. Clinical data show that cardiovascular disease accelerates fibrosis progression in MASLD, suggesting the possibility of direct heart-to-liver crosstalk or that cardiac dysfunction establishes a systemic environment conducive to liver disease.[66] Cardiogenic liver injury, defined as hepatic dysfunction caused by the inability of a failing heart to meet the metabolic and circulatory demands of the liver, has been attributed to passive venous congestion and impaired perfusion.[67] However, emerging evidence shows that the effects of cardiac injury are mediated by inflammation. In a model of cardiogenic liver disease induced by inferior vena cava ligation, macrophage recruitment into the liver is mediated by C-C chemokine receptor type 2-dependent signaling, suggesting that liver congestion is not merely a passive manifestation of increased central venous pressure, but is also an inflammatory process.[68] In this study, the authors found increased expression of macrophage-derived lipocalin-2 in the liver of patients with heart failure, suggesting a potential mechanism of cross-organ communication.[68] A cardiac-derived factor that regulates liver function under homeostatic conditions is phospholipase A2 (sPLA2), whose expression is negatively regulated by matrix metalloproteinase-2.[69] In the absence of matrix metalloproteinase-2, the level of sPLA2 increases leading to hepatic inflammation and metabolic disturbances, suggesting that cardiac sPLA2 regulates normal hepatic function.[69]

During myocardial infarction (MI), the liver presents with evidence of tissue injury in mouse models, highlighting the potential role of myocardial pathology as a driver of hepatic disease.[66] Following MI, Ly6C^{hi} monocytes infiltrate the liver where they promote inflammation and fibrosis, suggesting that the mobilization and infiltration of proinflammatory myeloid cells is an important mechanism of MI-induced liver disease.[66] In parallel, MI drives the production of periostin by the injured myocardium, which acts on hepatocytes and hepatic stellate cells to promote lipid accumulation and fibrosis.[66,70] Notably, periostin is a potent chemoattractant that exacerbates macrophage infiltration and perpetuates inflammation.[13] The consequences of MI on liver function are amplified by the activation of the hepatocyte mineralocorticoid receptor by IL-6 signaling in a process that promotes hepatic inflammation and fibrosis, reinforcing a maladaptive loop between the 2 organs.[71] Collectively, these findings challenge the conventional view of cardiogenic liver injury as a passive consequence of circulatory failure and highlight the central role of inflammation.

COMMON REGULATORS OF HEPATIC AND CARDIAC DYSFUNCTION DURING CARDIOMETABOLIC DISEASE

HEMATOPOIESIS. Hematopoietic stem cells (HSCs) have the ability of self-renewal and differentiation into several lineages to continuously replenish the hematopoietic system with committed progenitor cells and differentiated immune cells. While bone marrow is the main site for hematopoiesis in adults, the spleen has an important role in the maintenance and differentiation of HSCs.[72] Emerging evidence suggests that cardiometabolic disease can remodel the bone marrow, leading to an overproduction of inflammatory leukocytes that potentially exacerbate the disease. Under metabolic stress, HSCs undergo transcriptional reprogramming resulting in increased myelopoiesis driven by the NLRP3 inflammasome activation.[73] As a result, HSPCs produce an increased number of Ly6C^{high} monocytes, which are epigenetically and metabolically equipped for heightened inflammatory responses.[73] Notably, even short-term

exposure to a Western diet results in a durable increase in myelopoiesis, which persists after the removal of dietary intervention.[74] The infiltration of inflammatory monocyte-derived macrophages into the heart and liver is an important pathological mechanism in the pathogenesis of both MASH and HFpEF.[75,76] Thus, although the manifestation of the disease is tissue-specific, the inflammatory immune response can be partially explained by the reprogramming of the bone marrow.[77] Interestingly, a recent study showed that maladaptive myeloid fatty acid metabolism promotes hematopoietic activation in the spleen and increased monocyte mobilization that exacerbates HFpEF.[78] Mechanistically, enhanced mitochondrial fatty acid oxidation in macrophages drives an increased expression of adhesion molecules that promotes a proinflammatory hematopoietic niche.[78] In contrast to cardiometabolic disease, lifestyle interventions such as exercise counteract the effects of diet-induced metabolic disease on myelopoiesis, although the underlying mechanisms are unclear.[79] Overall, inflammation associated with cardiometabolic disease disrupts the homeostasis of HSPCs in the bone marrow, leading to the production of proinflammatory myeloid cells that can infiltrate the heart and liver to exacerbate disease.

CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL. Clonal hematopoiesis of indeterminate potential (CHIP) is a state in which HSCs acquire somatic alterations, conferring a selective survival advantage.[80] Although it was initially considered a precursor to hematologic malignancies,[80] recent work has shown that CHIP is a risk factor for cardiometabolic diseases given that patients with CHIP exhibit increased all-cause mortality caused by cardiovascular events.[81] The most frequently CHIP-associated alterations include *TET2, DNMT3A,* and *ASXL1*.[81] In HFpEF, CHIP is associated with worse diastolic function and increased cardiovascular-related hospitalization.[81] In a cohort of patients with HFpEF, those with TET2 alterations had exacerbated cardiac hypertrophy, worsened diastolic dysfunction, and interstitial fibrosis.[81] Mechanistically, deficiency of TET2 in bone marrow–derived cells enhances the inflammatory potential of circulating monocytes, leading to increased fibroblast activation and myocardial stiffness in the heart.[81] Patients with CHIP, particularly those with TET2 alterations, exhibit an approximately 2-fold increased risk of developing MASH.[82] In mouse models of disease, TET2-deficient macrophages accumulate in the liver and produce higher levels of IL-1β, promoting a maladaptive fibrotic response.[82]

IMMUNE RESPONSES. Recent studies have revealed a substantial heterogeneity in the subsets, origin, and function of immune cells in the liver and heart.[76,83] During MASH, there is a robust accumulation of innate immune cells in the liver, where they release molecules that cause local and systemic inflammation.[84] Tissue-resident macrophages are ontogenically distinct from their monocyte-derived macrophages (MdMs) counterparts and exhibit remarkable heterogeneity in their transcriptional programs, metabolic adaptations, and reparative functions.[76,83] At a steady state, resident macrophages derived from the yolk sac and fetal liver progenitors known as Kupffer cells (KCs) maintain tissue homeostasis through specialized effector functions. Sinusoidal KCs provide antimicrobial defense by clearing gut-derived bacteria and associated toxins from portal circulation.[85] Another important function of KCs is the surveillance of hepatic injury by recognizing danger-associated molecular patterns or pathogen-associated molecular patterns.[85] Under normal conditions, lipoproteins are endocytosed by KCs into lysosomes, followed by transport to the cytoplasm for intracellular metabolism or excretion from the cell by efflux mechanisms.[86] KCs might also play an important role in xenobiotic-induced hepatotoxicity as they express several enzymes capable of their metabolism.[87] During MASH, however, liver-resident KCs decline and are replaced by monocyte-derived macrophage subpopulations.[76,88] Thus, in addition to the regulation of hepatic remodeling, the loss of KCs during MASH can undermine the liver's capacity for pathogen surveillance, xenobiotic detoxification, and lipoprotein regulation.[85] MASH-induced KC loss is accompanied by an influx of monocytes, primarily from the bone marrow and, to a lesser extent, the spleen.[57,89] This infiltration of monocytes into the liver is a critical event in the progression of MASH, because these cells are skewed toward inflammatory and profibrotic activation states, characterized by enhanced secretion of TGF-β, IL-1β, and osteopontin, but diminished phagocytic and tolerogenic function.[88] Consequently, pharmacological inhibition of MdM recruitment leads to improved insulin resistance, hepatic inflammation, and fibrosis in a mouse model of MASH.[90] Importantly, the inflammatory mediators derived from the liver MdMs could potentiate endothelial dysfunction, promote coronary microvascular rarefaction, and prime cardiac fibroblasts toward profibrotic activation during cardiometabolic disease.[91]

Once in the liver, the infiltrating monocytes differentiate into MdMs with distinct fates, becoming either monocyte-derived KCs that occupy the original

KC niche or lipid-associated macrophages (LAMs),[92] a novel population that expresses a unique lipid- and lysosomal-associated signature, including the triggering receptor expressed on myeloid cells-2 (TREM2).[93] Although most LAMs originate from MdM, recent work has shown that a subset of resident KCs can also adopt a LAM-like phenotype during MASH.[94] In MASH, TREM2-expressing LAMs are induced by lipid exposure and localize to steatotic and fibrotic regions[95] where they promote hepatocyte fatty acid oxidation, lipid handling, extracellular matrix remodeling, and clearance of apoptotic cells.[96,97] Interestingly, the expression of TREM2 in cardiac macrophages increases during HFpEF in mice, whereas its deficiency exacerbates cardiac hypertrophy, capillary rarefaction, and inflammatory cytokine production, suggesting a cardioprotective role.[75] Given their similar role in HFpEF and MASH, TREM2$^+$ macrophages may share common regulatory pathways and effector functions in the liver and heart that can be exploited therapeutically. Indeed, molecules that activate the TREM2 active domain or block its shedding are being tested in neurodegenerative diseases,[98] with potential applications in CVD.

In HFpEF, T cells infiltrate the myocardium of humans[62] and mice[99] where they promote inflammation and fibrosis. Patients with HFpEF have increased circulatory tumor necrosis factor-α– and IFNγ-expressing CD4 T cells, compared with those with HFrEF.[63] This shift toward a proinflammatory state is facilitated by a loss of regulatory T cells (Tregs) and expansion of Th17 cells, similar to the inflammatory process typical of metabolic disease.[100] In a separate study, increased circulating levels of the Th17 cytokine IL-17 were observed in children with diastolic dysfunction and diabetic acidosis.[101] Patients with HFpEF have a higher expression of vascular cell adhesion molecule-1,[62] intercellular adhesion molecule-1, and e-selectin,[102] which are required for T-cell infiltration and recruitment. Notably, a subpopulation of CCR6$^+$ Tregs that can suppress Treg normal function expands during HFpEF, suggesting a potential mechanism by which these cells become inefficient at controlling inflammation.[63] A similar Treg/Th17 imbalance is observed in MASLD, which is often used to determine the severity of inflammation in the liver.[103] In the inflamed liver, pathogenic Th17 and Th1 cells secrete effector cytokines, contributing to inflammatory tissue milieu.[104] Furthermore, CD8$^+$ T cells accumulate in the liver during MASH where they become exhausted and promote hepatic inflammation, fibrosis, and antigen-independent cell death of hepatocytes.[105] One of the possible mechanisms leading to T-cell accumulation in MASH is clonal expansion and differentiation in response to antigen-specific T-cell receptor activation.[106] In contrast, cardiac T-cell activation is not restricted to antigens during HFpEF, but is rather driven by an impaired unfolded protein response.[99] Thus, T-cell recruitment into the heart during cardiometabolic disease is likely the result of inflammatory activation and not an adaptive immune response.

Unlike T cells, less is known about the contribution of B cells to cardiometabolic disease, but there is limited evidence that B cells are an important factor in the development of HFpEF. Patients with diastolic dysfunction have elevated circulatory B cells[63] while depleting them improves cardiac diastolic function in mouse models[107] and humans.[108] In a murine model of hypertension-induced myocardial hypertrophy and fibrosis, B-cell depletion ameliorated heart failure by reducing cardiac hypertrophy and collagen deposition.[109] Although causality was not tested, the pathological role of B cells was attributed to decreased IgG deposition in the myocardium. In MASH, B cells accumulate in the liver and adopt a proinflammatory phenotype, aggravating liver inflammation and fibrosis via both innate and adaptive immune signaling.[110] However, the triggers of B-cell activation in MASH remain elusive. The gut-liver axis is a key source of antigens for B-cell responses in MASH.[110] Yet, the specific microbiota-derived signals and their downstream effects on B cells require further elucidation. In cardiometabolic disease, an unresolved question is whether B-cell activation occurs in response to self-antigens, pathogen-derived stimuli, or simply metabolic stress and inflammatory cues. Furthermore, the relative contributions of the distinct B-cell subsets such as regulatory B cells remain unclear. Understanding these mechanisms is crucial for the development of targeted immunomodulatory therapies aimed at mitigating B-cell–mediated inflammation.

METABOLIC DYSREGULATION. A substantial proportion of patients with HFpEF are overweight or obese, and increased adiposity is associated with a worsening of cardiovascular structure, function, exercise capacity, and reserve.[111] However, the mechanisms underlying obesity-induced metabolic alterations in HFpEF are incompletely understood. In the heart, adult cardiac myocytes rely predominantly on fatty acid oxidation for energy production, requiring a high degree of metabolic flexibility. However, this metabolic flexibility is severely impaired in HFpEF because of systemic disturbances in metabolism.[112] Indeed, treating patients with

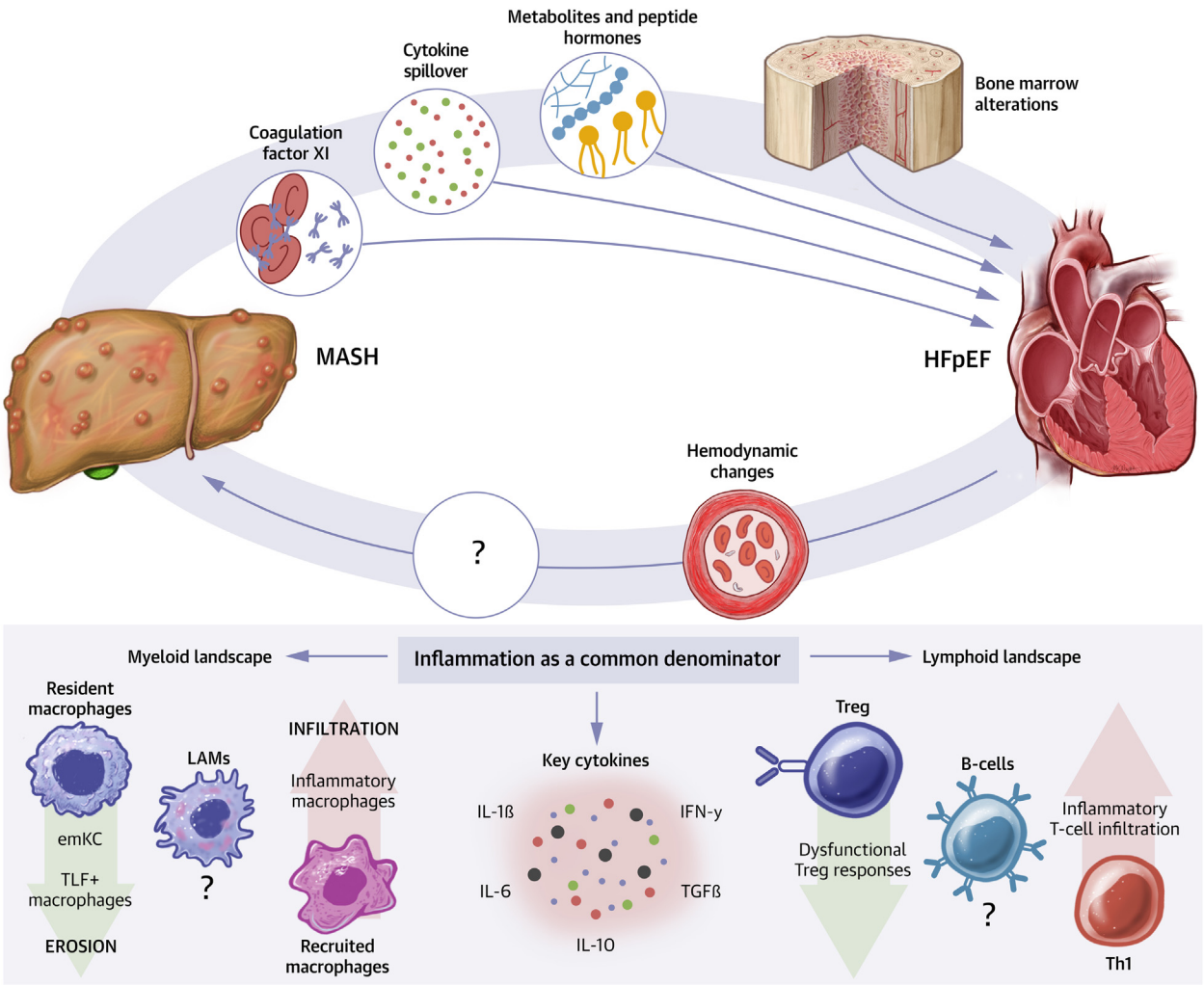
HFpEF with antidiabetic sodium-glucose cotransporter-2 inhibitors results in improved endothelial and cardiomyocyte function.[113] During cardiometabolic disease, fatty acids and lipid intermediates overwhelm cardiomyocyte mitochondria, increasing oxidative stress, disrupting ATP production, and promoting reactive oxygen species accumulation,[114] resulting in a self-perpetuating cycle of mitochondrial damage and impaired cardiac function. Particularly, reactive oxygen species-driven mitochondrial dysfunction compromises ATP synthesis, damages mitochondrial DNA, and destabilizes membrane potential, exacerbating HFpEF.[115] Notably, these metabolic disarrangements can result in local and systemic inflammation that can affect myocardial remodeling and function in the heart. For example, mitochondrial protein hyperacetylation activates the NLRP3 inflammasome inducing IL-1β and -18 secretion, as well as myocardial stiffening.[116] Lipotoxic conditions in MASH could also impair mitochondrial quality control mechanisms systemically, aggravating HFpEF progression.[117-119] Epigenetic regulation via sirtuin-6 (SIRT6) is central to maintaining mitochondrial integrity and energy homeostasis. In HFpEF, endothelial expression of SIRT6 is reduced, while its experimental restoration enhances mitophagy and mitochondrial biogenesis and ameliorates HFpEF in mice with diabetes.[120] Similarly, SIRT6 has a hepatoprotective role in diet-induced MASH.[121] Together, these findings highlight mitochondrial epigenetic regulators as potential therapeutic targets to treat both hepatic and cardiac metabolic dysfunction.

Increasing evidence has shown a causative and consequential role for ER stress in the etiology of obesity, MASLD, HFpEF, and CVD that results in a vicious cycle under these comorbidities.[122,123] Chronic lipotoxicity in MASLD leads to sustained ER stress, activating the unfolded protein response (UPR) through IRE1α, PERK, and ATF6 signaling pathways.[124] Although initially adaptive, prolonged UPR activation exacerbates inflammation, oxidative stress, and hepatocyte apoptosis, accelerating liver dysfunction.[124] In HFpEF, chronic lipid overload leads to UPR activation to initially enhance protein-folding capacity and mitigate proteotoxic stress. However, sustained metabolic challenge overwhelms this compensatory mechanism, shifting UPR signaling toward maladaptive pathways.[125] Lipid overload and nitrosative stress disrupt ER homeostasis via the X-box binding protein 1 (Xbp1), which undergoes splicing and regulates protein folding and lipid metabolism.[125] In MASLD, chronic metabolic overload also impairs Xbp1 activity, promoting persistent ER stress and hepatocyte dysfunction.[126] Increased hepatic Xbp1 expression and transcriptional activity are associated with hepatic lipid accumulation and insulin resistance.[127] Collectively, these findings underscore mitochondrial and ER dysfunction as a mechanistic bridge between MASLD/MASH and HFpEF. Impaired calcium homeostasis is another common feature of metabolic damage observed in both MASLD and HFpEF. In MASH, dysregulated calcium homeostasis results in mitochondrial and ER dysfunction, exacerbating energy deficits.[128] Lipid-induced calcium overload precipitates mitochondrial permeability transition pore opening, leading to membrane potential collapse and ATP depletion.[129] In HFpEF, calcium dysregulation impairs oxidative capacity and disrupts sarcoplasmic reticulum calcium handling, worsening diastolic dysfunction.[129] Therefore, targeting mitochondrial metabolic reprogramming, epigenetic regulators, and ER proteostasis is a promising avenue for cardiometabolic disease.

AF CONVERGING MASH AND HFpEF

AF has been long recognized as a driver of cardiovascular morbidity but has recently emerged as a critical link between MASH with HFpEF.[130] Epidemiological studies show that patients with MASLD, particularly MASH, have a significantly increased prevalence of AF, independent of traditional cardiovascular risk factors.[131] However, the mechanisms underlying how hepatic disease drives atrial arrhythmogenesis are unknown. A recent prospective population-based proteomic study found that increased liver stiffness, an established marker of progressive fibrosis in MASH, is independently associated with AF risk.[132] This study provided a proteomic inflammatory signature involving the chemokine CXCL10 as a potential factor driving atrial remodeling. Multiple additional pathways have been proposed, including systemic inflammation, insulin resistance, and RAAS activation.[133] Inflammatory cytokines released in MASH have been proposed as potential effector molecules that cause atrial remodeling, fibrosis, conduction abnormalities, and autonomic dysfunction during AF.[133] However, studies demonstrating a causative role for MASH-associated cytokines in atrial arrhythmogenicity are needed.[134] Similarly, metabolic disturbances associated with obesity are clinically associated with AF,[134] but whether there is a direct liver-to-heart crosstalk is unknown. HFpEF and AF are increasingly recognized as interwoven pathophysiological entities as nearly 43% of patients with HFpEF develop AF.[135] Diastolic dysfunction and left atrial hypertension in HFpEF

CENTRAL ILLUSTRATION **The Bidirectional Crosstalk Between the Liver and Heart in Cardiometabolic Disease**



Hakeem A, et al. JACC Basic Transl Sci. 2025;10(7):101309.

create an electrophysiological substrate conducive to AF, while AF itself exacerbates hemodynamic congestion, perpetuating myocardial stiffening and diastolic impairment.[134] Whether MASH accelerates this cycle remains an open question, although proteomic evidence suggests key inflammatory mediators in liver fibrosis may simultaneously prime both hepatic and atrial tissues for fibrotic remodeling.[132]

CONCLUSIONS AND PERSPECTIVES

Interorgan communication is crucial for homeostasis, but dysfunction of the liver-to-heart axis plays an important role in the pathogenesis of cardiometabolic disease (Central Illustration). Beyond sharing common inflammatory and metabolic disorders, emerging evidence has shown that several liver-derived factors such as FXI directly regulate cardiac disease. Considering that the liver is an endocrine organ that produces a wide variety of hepatokines and other factors, future research must identify the liver-derived molecules that regulate cardiac function. Importantly, these studies should use gain or loss of function experiments to investigate a causative role for these molecules and their effector mechanisms.

It is well-established that common cardiovascular risk factors considerably alter hematopoietic processes.[136] However, future studies are needed to investigate the hematopoietic niche factors, the timing of cell fate decisions, and the differentiation trajectories and relative contributions to mature immune cells that originate in the bone marrow and

spleen and populate the liver and heart during cardiometabolic disease. Notably, chronic inflammation is not confined to 1 organ during cardiometabolic disease, but it is a multiorgan and systemic process affecting both the liver and heart. We argue that MASLD should be considered a systemic inflammatory process that expands to other organs including the heart. Future research should investigate how the immune-metabolic crosstalk that underlies both conditions rewires metabolism in the liver and the heart. Conversely, how systemic and local metabolic disturbances regulate immune cell-driven inflammation also requires further investigation. Although chronic inflammation has emerged as a unifying pathological mechanism in CVD, some aspects of inflammation may be part of an adaptive response to metabolic stress as shown in the adipose tissue where obese adipocytes require innate immune signaling for tissue remodeling.[137] Thus, this possibility should be explored in the context of cardiometabolic disease.

Although the role of the liver-to-heart axis in cardiometabolic disease is an emerging area of research in the field, we are still far from understanding the underlying mechanisms and targeting it therapeutically. Given the heterogeneity of HFpEF and its systemic nature, targeted interventions addressing shared inflammatory and metabolic pathways are promising. However, future work needs to determine the therapeutic actions of HFpEF drugs on other metabolic active organs such as the liver. Therapeutic strategies modulating whole-body metabolism such as SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists may confer dual benefits by restoring metabolic homeostasis and dampening inflammation. Overall, improving our understanding of the meta-inflammatory mechanisms driving MASLD and HFpEF holds the potential to transform therapeutic strategies and improve outcomes for cardiometabolic patients.

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