Emerging Evidence Linking the Liver to the Cardiovascular System: Liver-derived Secretory Factors

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Abstract
Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide. Recently, accumulating evidence has revealed hepatic mediators, termed as liver-derived secretory factors (LDSFs), play an important role in regulating CVDs such as atherosclerosis, coronary artery disease, thrombosis, myocardial infarction, heart failure, metabolic cardiomyopathy, arterial hypertension, and pulmonary hypertension. LDSFs presented here consisted of microbial metabolite, extracellular vesicles, proteins, and microRNA, they are primarily or exclusively synthesized and released by the liver, and have been shown to exert pleiotropic actions on cardiovascular system. LDSFs mainly target vascular endothelial cell, vascular smooth muscle cells, cardiomyocytes, fibroblasts, macrophages and platelets, and further modulate endothelial nitric oxide synthase/nitric oxide, endothelial function, energy metabolism, inflammation, oxidative stress, and dystrophic calcification. Although some LDSFs are known to be detrimental/beneficial, controversial findings were also reported for many. Therefore, more studies are required to further explore the causal relationships between LDSFs and CVDs and uncover the exact mechanisms, which is expected to extend our understanding of the crosstalk between the liver and cardiovascular system and identify potential therapeutic targets. Furthermore, in the case of patients with liver disease, awareness should be given to the implications of these abnormalities in the cardiovascular system. These studies also underline the importance of early recognition and intervention of liver abnormalities in the practice of cardiovascular care, and a multidisciplinary approach combining hepatologists and cardiologists would be more preferable for such patients.


Introduction
Although remarkable advances have been made in clinical and basic research fields, cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality, and impose a significant global health care burden. The prevalence of CVDs cases nearly doubled from 1990 to 2019, with more than 500 million cases being reported in 2019. And the number of CVDs deaths has steadily increased over the same period, reaching 18.6 million in 2019.1 The liver is the largest internal organ and plays a vital role in various physiological and pathophysiological processes by providing essential metabolic, exocrine, and endocrine functions.2 Studies have revealed extensive crosstalk networks within the liver tissue3 and between the liver and other organs/tissues such as gut4 and skeletal muscle.5 The complex interactions between the liver and cardiovascular system have been studied extensively,6 especially in the context of metabolic disorder.7 An example is nonalcoholic fatty liver disease (NAFLD), which has become a serious public health problem affecting up to one-third of the world’s adult population and shown to be significantly associated with a greater risk of CVDs. These in turn, contribute to increased mortality among patients with NAFLD.8 Not only that, a growing body of evidence has...
revealed an essential role of liver-derived secretory factors (LDSFs) in regulating cardiovascular physiology and diseases. In this review, we summarize the current molecular evidence linking the liver to cardiovascular system with a focus on LDSFs, which may extend our understanding of the crosstalk between the liver and cardiovascular system and highlight the importance of these emerging novel mediators as potential biomarkers and therapeutic targets.

Trimethylamine N-oxide

Over the years, the gut microbiota and its metabolites have attracted increasing attention owing to their crucial roles in cardiovascular health and diseases by interacting with the host. Of these, trimethylamine N-oxide (TMAO) is an important and well-studied metabolite. It was reported that dietary phosphatidylcholine, choline and L-carnitine are metabolized by intestinal microbiota into trimethylamine and then further oxidized into TMAO by flavin monoxygenases in the liver. Many clinical investigations have shown that circulating TMAO is an independent risk factor for CVDs such as atherosclerosis, thrombosis, acute coronary syndromes, heart failure (HF) and myocardial infarction (MI). Mechanistically, TMAO was able to accelerate the progression of atherosclerosis by inducing vascular endothelial cells (VECs) pyroptosis through SDHB/ROS pathway, and contribute to endothelial dysfunction by increasing HMGB1 expression and disrupting cell-cell junction proteins, promoting vascular calcification by inducing osteogenic differentiation of vascular smooth muscle cells (VSMCs) via NLRP3 inflammasome and NF-kB pathway, and exacerbate cardiac function and cardiac fibrosis after MI by promoting the transition of fibroblasts into myofibroblasts through TGF-βRI/Smad2 axis. Moreover, it was found that TMAO levels were significantly correlated with the activity of tissue factor in patients with ST-elevation MI, and the activation of NF-κB pathway, and exacerbate cardiac function and cardiac fibrosis after MI by promoting the transition of fibroblasts into myofibroblasts through TGF-βRI/Smad2 axis. Additionally, in the middle-aged/older groups, TMAO was markedly elevated and associated with impaired brachial artery flow-mediated dilation, which could be reversed in mice supplemented with TMAO. Similarly, circulating TMAO levels were found to increase with aging, and further studies demonstrated that TMAO accelerated senescence and vascular aging by reducing SIRT1 expression and enhancing oxidative stress, which caused aging-associated endothelial insufficiency by impairing endothelial nitric oxide synthase (eNOS) and enhancing the production of inflammatory cytokine and superoxide. Increased inflammation and oxidative stress were also responsible for TMAO-induced inhibition of angiogenesis and perfusion recovery after hindlimb ischemia.

Although there are many studies devoted to revealing the effects of TMAO on CVDs, little information is available about its influence on the liver. It was showed that TMAO at the physiological concentration is able to promote metabolic dysfunction by directly binding the hepatic PERK and thus activating the unfolded protein response. The authors suggested that hepatic TMAO-PERK pathway may represent a therapeutic target for this disorder. In addition, TMAO has been reported to affect the miRNA composition and function of the exosomes secreted from hepatocytes. These studies provided evidence that, although TMAO is generated in the liver, this metabolite can in turn act on the hepatocytes and exert systemic influence. However, liver may differ in its generative capacity and responsiveness for TMAO, particularly across disease state, and future studies should take this into account.

Extracellular vesicles

Extracellular vesicles (EVs) are membrane-bound vesicles secreted by almost all types of cells and include microparticles/microvesicles, exosomes, and apoptotic bodies depending on size, biogenesis, and cargo. EVs have been shown to have a key role in mediating intercellular communication by carrying a variety of bioactive molecules, surface receptors, and genetic information. Evidence of the cardiovascular effects of liver-secreted EVs is growing. A study reported that circulating hepatocyte-derived microparticles were found in patients with cirrhosis but not in healthy controls, and that they contributed to impairment of vasconstrictor responses and reduction of blood pressure (BP). Hepatic EVs derived from mice with NAFLD were shown to augment coronary microvascular permeability by transferring novel miR-7 and regulating the LAMP1/cathepsin B/NLRP3 inflammasome pathway. Jiang and colleagues found that EVs isolated from palmitic acid-supplemented hepatocytes can promote inflammation and atherosclerosis by delivering miR-1 to EVs, thereby inhibiting KLF4 expression and activating NF-κB signaling. In addition, increased arginase activity was detected in the EVs produced by hepatocytes challenged with hepatotoxican, and was responsible for EVs-induced impairment of endothelium-dependent relaxation. Also, among patients with low coronary flow reserve, circulating EVs were found to be remarkably increased in the plasma EVs that supposed to be released by the liver and negatively correlated with coronary flow reserve. EVs isolated from a liver cell line stimulated with TNF-α enhanced ICAM-1 expression in VECs. Additionally, liver-secreted exosomal miR-122 was found to contribute to the development of metabolic cardiomyopathy by inhibiting ARA-2 and affecting cardiac mitochondrial function. Hepatocyte-derived exosomal miR-194 was reported to be involved in hepatopulmonary syndrome by targeting pulmonary microvascular endothelial cells and promoting cell proliferation, migration, and tube formation as well as in vivo angiogenesis. Similarly, exosomes produced by TMAO-activated hepatocytes promoted the expression of inflammatory markers, impaired endothelial function and inhibited angiogenesis, which may have been related to the enriched miRNAs in the exosomes, such as miR-302d-3p, miR-302b-3p, miR-302a-3p, and miR-103-3p. Only that, exosome-based therapy may be a promising approach for CVDs treatment in clinical practice. It was demonstrated that overexpression of Ldlr mRNA in the donor AML12 cells contributed to secretion of exosomes carried Ldlr mRNA, which increased the production of LDLR in the recipient AML12 cells and reduced the number and size of atherosclerotic plaques in Ldlr−/− mice. The above studies provide evidence that EVs may not only be biomarkers of liver damage, but also effectors of the cardiovascular system. Knowledge of the cargo transported by the EVs appears to be decisive for understanding their biological function and molecular mechanism. Based on that, EVs-modifying therapies are emerging as potential treatments for CVDs.

Hepatokines

Hepatokines are a diverse family of cytokines secreted by the liver, and have been shown to exert autocrine, paracrine, and endocrine functions in metabolic disorders. Accumulating evidence shows that many of them are important to CVDs.

Adropin

Adropin is a peptide hormone secreted primarily by the liver and has been shown to have a significant role in regulating...
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glucose and lipid homeostasis. Notably, the impact of adropin on cardiovascular physiology and disease has recently gained increasing attention. Adropin levels were found to be significantly lower in obese adolescents and adults and markedly increased following aerobic exercise, and its concentration had negative correlation with arterial stiffness and abdominal visceral fat and positive correlation with plasma nitrite/nitrate content, cardiorespiratory fitness as well as vascular reactive hyperemia indexes. Among individuals with type 2 diabetes mellitus (DM) and metabolic syndrome, the blood concentration of adropin was significantly declined and inversely associated with the coronary angiographic severity, and even lower values were found in the endothelial dysfunction group and had a positive correlation with the flow-mediated dilatation values. Additionally, serum adropin was reduced in patients with coronary artery disease (CHD), and lower levels were associated with hyperhomocysteinemia and more severe coronary disease and poor coronary collateral circulation. Also, in patients who underwent drug-eluting stent implantation, serum adropin concentrations were significantly decreased among the in-stent restenosis (ISR) group, and by levels were inversely correlated with the neointimal volume in both groups. Moreover, plasma adropin concentrations were significantly decreased in hypertensive patients compared with normotensive subjects, and showed a negative correlation with endothelin-1, an indicator for endothelial dysfunction. However, another study reported opposite results regarding the association between adropin levels and BP variables.

Mechanically, adropin has been confirmed to regulate mitochondrial energy metabolism through GPR19-p44/42-PDK4 pathway, activate cardiac insulin signaling and improve cardiac efficiency, enhance cardiac glucose oxidation under high fat diet conditions and improve diastolic function by alleviating myocardial fibrosis in diabetic cardiomyopathy rats. Although short-term administration of adropin may fail to exert a protective effect on cardiac function in obese animals. Besides, adropin could promote eNOS activation and perfusion recovery after hindlimb ischemia by upregulating VEGFR2, suppress proliferation and phenotypic modulation of VSMCs induced by angiotensin II via AMPK/ACC signaling, and attenuate vascular calcification by repressing VSMCs osteogenic differentiation through JAK2/STAT3 signaling, as well as inhibit TNF-α-induced THP1 monocyte adhesion to VECs, prevent macrophages from polarizing into a pro-inflammatory phenotype and reduce the formation of atherosclerotic lesions in apoE/−/− mice. Additionally, exposure to cell-free hemoglobin resulted in decreased expressions of adropin and increased paracellular permeability of VECs, and treatment with adropin was able to protect against the hyperpermeability and suppress macrophage trans-endothelial migration.

In contrast, another study demonstrated that adropin levels were increased in serum from patients with Kawasaki disease and even higher in those with coronary artery lesions, and showed positive correlation with inflammatory markers and D-dimer. And among patients with HF, circulating adropin levels were significantly increased with the progressive deterioration in cardiac function, which could be effectively decreased by HF treatment.

Fibroblast growth factor 21

Fibroblast growth factor 21 (FGF21), a peptide hormone synthesized primarily in the liver, adipose tissue, pancreas, and heart, has been found to exert pleiotropic functions, depending upon which organ is implicated. Liver was believed to be the major endocrine source of plasma FGF21 during bacterial inflammation, and elevated FGF21 was required for survival by contributing to the maintenance of thermogenesis and cardiac function. And the releases of FGF21 from hepatic cells and adipocytes were showed to be increased in mice after myocardial ischemia/reperfusion (I/R) injury, thus reducing cell death and MI as well as improving myocardial function through FGF1/β-Klotho-P13K-Akt1-BAD signaling. Also, Pan et al. demonstrated that liver may be the primary site for the production of circulating FGF21 in angiotensin II-induced hypertension, and increased expression of FGF21 could counteract angiotensin II-induced hypertension and vascular dysfunction by enhancing the generation of angiotensin-converting enzyme 2. FGF21 deficiency resulted in aggravation of atherosclerosis and premature death in apoE/−/− mice, and FGF21 supplement could attenuate vascular inflammation and atherosclerotic plaque formation.

Similar results were found in a study of atherosclerotic rats, in which FGF21 was able to alleviate inflammation and oxidative stress by activating the Nrf1-ARE pathway. FGF21 has also been shown to exert a protective effect in part through the activation of the AMPK-PON1 signaling and cardiac hypertrophy and fibrosis during hypertension, as well as suppress lipid- or diabetes-stimulated cardiac apoptosis via ERK1/2-p38 MAPK-AMPK pathway. Additionally, FGF21 could alleviate doxorubicin-induced cardiac insults by inhibiting inflammatory stress, oxidative and apoptosis via SIRT1/LKB1/AMPK pathway. However, it was reported that, in the mouse model of myocardial hypertrophy, FGF21 levels were increased in cardiac tissue but remained unchanged in the circulation, suggesting that FGF21 may inhibit cardiac hypertrophy predominantly through its autocrine effects. Indeed, there is evidence suggesting that FGF21 can be expressed and secreted by the heart following cardiac damages such as cardiac hypertrophy, oxidative stress and MI, and exerts its diverse cardioprotective functions in an autocrine manner. Therefore, tissue-specific knock-out of FGF21 is necessary to elucidate its autocrine, paracrine, and endocrine effects, which may vary depending on the context.

Selenoprotein P

Selenoprotein P is a transport protein that is mainly synthesized and released by the liver, and plays an essential role in delivering selenium from the liver to other tissues. The population with lowest plasma concentrations of selenoprotein P have a higher risk of cardiovascular morbidity and mortality, and among patients with CVDs, circulating selenoprotein P levels were significantly lower in individuals with metabolic syndrome. And another study has suggested that plasma selenoprotein P can bind to proteoglycans on the vascular endothelium and form a protective layer against oxidants. Further, selenoprotein P was showed to protect low density lipids (LDLs) from oxidation and prevent tert-butylhydroperoxide-induced oxidative injury and loss of cellular membrane integrity by restoring the enzymatic activity of glutathione peroxidase in human endothelial cells. However, the influence of selenoprotein P on the cardiovascular system remains controversial, with opposed results in different studies. Elevation of selenoprotein P was observed in patients with HF, and its levels were associated with adverse cardiac outcomes. And inhibition of selenoprotein P protected the heart from I/R injury by activating RISK pathway. It was also found that the serum concentrations of selenoprotein P were significantly increased in patients with pulmonary hypertension and its levels were...
able to predict all-cause death and lung transplantation. Furthermore, the absolute changes in selenoprotein P after initial therapy were correlated with the hemodynamic changes and prognosis. Of note, however, it was demonstrated that selenoprotein P produced by pulmonary artery smooth muscle cells, but not by the liver, promoted the development of pulmonary arterial hypertension. Thus, further research is needed to clarify the sources of selenoprotein P and its roles in the pathogenesis of CVDs.

**Fetuin-A**

Fetuin-A is a multifunctional glycoprotein secreted by the liver, and has been shown to be an important inhibitor of mitral annular calcification in persons with CHD and without severe kidney disease and valvular calcification in patients with end-stage renal disease. In patients on dialysis, low serum fetuin-A was reported to increase the risk of all-cause and cardiovascular mortality. Data from patients with type 2 DM and without renal dysfunction further suggested that fetuin-A may suppresses the calcification of atherosclerotic plaques independently of the dialysis conditions. Moreover, fetuin-A-deficient mice spontaneously developed significant myocardial calcification, characterized by myocardial stiffness, cardiac remodeling and fibrosis, and diastolic dysfunction. In addition to acting as a calcification inhibitor, however, it may also act as an atherogenic factor. In a case-cohort study, significantly increased risks of MI and ischemic stroke were found in subjects with higher plasma fetuin-A levels. Fetuin-A also influenced the expression of proinflammatory and angiogenic proteins associated with atherosclerosis. These inconsistent behaviors raise the important questions about the potential protective or exacerbating role of fetuin-A in CVDs, which may be complicated by its multiple functionalities, and more research are therefore definitely needed to elucidate these aspects.

**Fetuin-B**

Fetuin-B, a liver-derived secretory protein, has been reported to have an adverse effect on the cardiovascular system. It was found that serum fetuin-B concentrations were independently associated with the presence of CHD and acute coronary syndromes, and urinary fetuin-B levels were higher in individuals with cardiovascular risk factors than healthy subjects. A recent study showed that plasma fetuin-B levels were significantly elevated in patients with ISR compared with non-ISR patients and healthy controls. Also, circulating fetuin-B levels were increased in patients with acute MI, and also that fetuin-B was regulate the migration of monocytes and macrophages, levels of vascular plaque-stabilizing factors, and increased atherosclerotic plaque rupture in mice. A subsequent study revealed that fetuin-B contributed to plaque rupture by inducing the expression of PTA1-1 and MMP-2 in VSMCs through TGF-βR/Smad signaling. Increased levels of fetuin-B also led to the inhibition of cardiac insulin-induced signaling and thus exacerbating myocardial I/R injury.

**α1-microglobulin**

α1-microglobulin is a glycoprotein synthesized and secreted mainly by the liver and serves as an indicator of renal tubular dysfunction. There is accumulating evidence linking α1-microglobulin to CVDs. In a retrospective analysis of patients with ST-elevation MI, urinary α1-microglobulin at admission was showed to be an independent predictor of inhospital mortality. In patients with acute HF, urinary α1-microglobulin concentrations at admission were associated with all-cause mortality independent of glomerular function and provided additional prognostic value. In non-diabetic patients with chronic kidney disease, urinary α1-microglobulin levels were also found to be associated with CVDs events and mortality. In addition, despite increased urinary excretion of α1-microglobulin has been reported in patients undergoing myocardial revascularization surgery with cardiopulmonary bypass, and the increases were greater with longer duration of cardiopulmonary bypass, it was shown that preoperative but not postoperative urinary α1-microglobulin levels were positively associated with acute kidney injury, progressive chronic kidney disease, and all-cause mortality after cardiac surgery. However, the role of α1-microglobulin on CVDs is still controversial. Hakuno et al. demonstrated that α1-microglobulin can promote macrophage infiltration and inflammation and impair fibrotic repair after MI in mice. Nevertheless, it was shown to suppress oxidation of LDL, hemoglobin and lipids isolated from atherosclerotic plaques, and protect the endothelial cells from oxidative damage. More studies are needed to confirm the causal relationships between α1-microglobulin and CVDs.

**MicroRNA-122**

MicroRNAs (miRNAs) are a class of endogenous small non-coding RNA molecules that are evolutionarily conserved and have a critical role in regulating gene expression at the post-transcriptional level. It was found that plasma miRNAs are not only diagnostic biomarkers but also potential therapeutic targets for CVDs. MiR-122 is predominantly generated in the liver and constantly released into the circulation and has been shown to be significantly elevated in patients with acute HF. In a cohort study of population who experienced sudden cardiac arrest due to ventricular fibrillation, miR-122 levels were found to be higher in participants who died in hospital or survived to discharge compared with those who died in the field. However, the plasma levels of miR-122-5p at admission did not correlate to shock at admission or all-cause mortality among patients admitted due to out-of-hospital cardiac arrest. By contrast, circulating miR-122 was found to predict all-cause and cardiovascular mortality in patients with chronic systolic HF, and also improve current risk stratification. However, the roles and underlying mechanisms of circulating miR-122 in these pathophysiological processes remain to be elucidated. Because a significant increase in plasma miR-122 has been observed after liver injury, it is unclear whether the elevated miR-122 in the circulation have regulatory roles in the pathogenesis of CVDs or are simply biomarkers of hepatic damages. And the findings presented by Wang et al. might shed some light on this. In addition, based on its high content in the liver, miR-122 has been used to increase the specificity of adeno-associated virus-mediated cardiac gene transfer, while minimizing liver exposure to the vectors.

**Others**

Very recently, coagulation factor XI was found to be capable of protecting against cardiac diastolic dysfunction by suppressing inflammation and fibrosis through cleaving BMP7 precursor and activating the BMP7-SMAD1/5 pathway. The effects of plasma protein factor XII (FXII) on vascular function have previously been thoroughly reviewed by Mailer and colleagues. FXII is synthesized by the liver and released as an inactivezymogen into the circulation, and plays an important role in promoting endothelial dysfunction, vascu-
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**Conclusion**

LDSFs presented here are a group of hepatic mediators that exclusively or mainly produced and released by the liver, including TMAO, EVs, proteins and miR-122, and are thought to exert their pleiotropic actions on cardiovascular system through an endocrine manner (Fig. 1). Accumulating evidence highlights the importance of these LDSFs in CVDs, such as atherosclerosis, CHD, thrombosis, MI, HF, metabolic cardiomyopathy, arterial hypertension, and pulmonary hypertension. These LDSFs primarily act on VECs, VSMCs, cardiomyocytes, fibroblasts, macrophages and platelets, and the predominant underlying mechanisms involve the regulation of eNOS/NO, endothelial function, energy metabolism, inflammation, oxidative stress, and dystrophic calcification (Fig. 2). Some LDSFs, including TMAO, EVs, fetuin-B, FXII and upd3 have been proven to be detrimental, and some, including adipon, FGF21 and factor XI, are protective. The activity of others, including selenoprotein P, fetuin-A, α1-microglobulin and miR-122, is not clear. A variety of factors may be responsible. First, the composition of the investigated populations was not the same across studies. Second, source of these LDSFs was not restricted to the liver, they can have their origins from other organs/tissues. The situation is complicated under pathophysiological conditions. Third, each LDSF may influence multiple targets within the cardiovascular system and show pleiotropic effects through different molecular mechanisms. Therefore, more studies are needed to better understand the functional roles of these LDSFs in cardiovascular diseases.
Fig. 2. Effects of liver-derived secretory factors on targeted cells and the underlying mechanisms. These factors mainly act on VECs, VSMCs, CMs, FBs, Mo/Μφ and platelets, and the effects and mechanisms presented in the studies are summarized. Parts of the figure were obtained from Servier Medical Art (https://smart.servier.com/). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License. CMs, cardiomyocytes; EVs, extracellular vesicles; FBs, fibroblasts; Mo/Μφ, monocytes/macrophages; TMAO, trimethylamine N-oxide; VECs, vascular endothelial cells; VSMCs, vascular smooth muscle cells.
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required to further identify the causal relationships between LDSFs and CVDs and elucidate the exact mechanisms, which may reveal novel molecular targets for the prevention and treatment of CVDs. Furthermore, in the case of patients with liver disease, awareness should be given to the implications of these abnormalities in the cardiovascular system. These studies also underline the importance of early recognition and intervention of liver abnormalities in the practice of cardiovascular care, and a multidisciplinary approach combining hepatologists and cardiologists would be more preferable for such patients. There are, however, some limitations of this review. First, the liver and the heart can crosstalk and affect each other to contribute to various diseases, and the underlying pathways are diverse. Here, we just addressed the unidirectional impact of liver on heart with a focus on LDSFs. Secondly, the definition of LDSFs might have been too broad, and there is a possibility that some important factors or literature may be missed. Thirdly, many of the studies included were observational, and only provided evidence of association, not cause. Further investigations are required to determine the roles and precise mechanisms of some LDSFs such as α1-microglobulin and miR-122. Finally, the functional states of the liver may determine the activities of LDSFs, but its histopathological and biochemical alterations were not clearly reported in many studies.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study conception and design (XL, JC), manuscript review and editing (XL, YS, LH, RZ), manuscript drafting (XL), manuscript revision (JC), and study supervision (JC). All authors have made a significant contribution to this study and have approved the final manuscript.

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