



Review Article

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

Xiang Liu^{1,2}, Yijia Shao³, Linjiang Han^{1,2}, Ruyue Zhang^{1,2} and Jimei Chen^{1,2*}

¹Department of Cardiac Surgery, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China; ²Guangdong Provincial Key Laboratory of South China Structural Heart Disease, Guangzhou, Guangdong, China; ³Department of Geriatrics, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Received: 22 November 2022 | Revised: 19 December 2022 | Accepted: 27 February 2023 | Published online: 12 May 2023

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.

Citation of this article: Liu X, Shao Y, Han L, Zhang R, Chen J. Emerging Evidence Linking the Liver to the Cardiovascular System: Liver-derived Secretory Factors. *J Clin Transl Hepatol* 2023;11(5):1246–1255. doi: 10.14218/JCTH.2022.00122.

Keywords: Liver; Cardiovascular system; Metabolite; Extracellular vesicle; Hepatokine.

Abbreviations: ACC, acetyl-CoA carboxylase; Akt, protein kinase B; AMI, acute myocardial infarction; AMPK, AMP-activated protein kinase; apoE^{-/-}, Apolipoprotein E knockout; ARE, antioxidant response elements; Arl-2, ADP-ribosylation factor-like 2; BAD, BCL2 associated agonist of cell death; BMP7, bone morphogenetic protein 7; BP, blood pressure; CHD, coronary artery disease; CVDs, cardiovascular diseases; DM, diabetes mellitus; eNOS, endothelial nitric oxide synthase; ERK1/2, extracellular signal-regulated kinase 1/2; EVs, extracellular vesicles; FGF21, fibroblast growth factor 21; FGFR1, fibroblast growth factor receptor 1; FXII, factor XII; upd3, unpaired 3; GPR19, G protein-coupled receptor 19; HF, heart failure; HMGB1, high mobility group box 1; ICAM-1, intercellular adhesion molecule 1; I/R, ischemia/reperfusion; ISR, in-stent restenosis; JAK2, Janus kinase 2; KLF4, KLF transcription factor 4; LAMP1, lysosomal associated membrane protein 1; LDL, low-density lipoprotein; Ldlr, low-density lipoprotein receptor; Ldlr^{-/-}, low-density lipoprotein receptor knockout; LDSFs, liver-derived secretory factors; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinases; MI, myocardial infarction; MMP-2, matrix metalloproteinase 2; NAFLD, non-alcoholic fatty liver disease; NF-κB, nuclear factor-kappaB; NLRP3, NLR family pyrin domain containing 3; Nrf2, transcription factor NF-E2-related 2; PAI-1, plasminogen activator inhibitor-1; PDK4, pyruvate dehydrogenase kinase 4; PERK, protein kinase R-like endoplasmic reticulum kinase; PI3K, phosphoinositide 3-kinase; RISK, reperfusion injury salvage kinase; PON1, paraoxonase 1; ROS, reactive oxygen species; SDHB, succinate dehydrogenase complex subunit B; SIRT1, sirtuin 1; SMAD2, SMAD family member 2; STAT3, signal transducer and activator of transcription 3; TGF-βRI, transforming growth factor-beta receptor type 1; TMAO, trimethylamine N-oxide; TNF-α, tumor necrosis factor-alpha; VECs, vascular endothelial cells; VEGFR2, vascular endothelial growth factor receptor-2; VSMCs, vascular smooth muscle cells.

*Correspondence to: Jimei Chen, Department of Cardiac Surgery, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, No. 106, Zhongshan 2nd Road, Guangzhou, Guangdong 510080, China. ORCID: <https://orcid.org/0000-0002-7866-7564>. Tel: +86-20-83827812, E-mail: jimei_1965@outlook.com

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.⁷ 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.⁸ 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 monooxygenases in the liver.^{9,10} 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).⁹⁻¹⁴ Mechanistically, TMAO was able to accelerate the progression of atherosclerosis by inducing vascular endothelial cells (VECs) pyroptosis through SDHB/ROS pathway,¹⁵ contribute to endothelial dysfunction by increasing HMGB1 expression and disrupting cell-cell junction proteins,¹⁶ promote vascular calcification by inducing osteogenic differentiation of vascular smooth muscle cells (VSMCs) via NLRP3 inflammatory and NF- κ B pathway,¹⁷ and exacerbate cardiac function and cardiac fibrosis after MI by promoting the transition of fibroblasts into myofibroblasts through TGF- β RI/Smad2 axis.¹⁸ 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- κ B signaling was necessary for TMAO-mediated tissue factor expression.¹⁹ 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.²⁰ Similarly, circulating TMAO levels were found to increase with aging, and further study demonstrated that TMAO accelerated VECs senescence and vascular aging by reducing SIRT1 expression and enhancing oxidative stress,²¹ which caused aging-associated endothelial insufficiency by impairing endothelial nitric oxide synthase (eNOS) and enhancing the production of inflammatory cytokine and superoxide.²² Increased inflammation and oxidative stress were also responsible for TMAO-induced inhibition of angiogenesis and perfusion recover after hindlimb ischemia.²³

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.²⁴ In addition, TMAO has been reported to affect the miRNA composition and function of the exosomes secreted from hepatocytes.^{25,26} 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.²⁷ 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 vasoconstrictor responses and reduction of blood pressure (BP).²⁸ 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.²⁹ Jiang and colleagues³⁰ found that EVs isolated from palmitic acid-treated hepatocytes can promote inflammation and atherogenesis by delivering miR-1 to VECs, thereby inhibiting KLF4 expression and activating NF- κ B signaling. In addition, increased arginase activity was detected in the EVs produced by hepatocytes challenged with hepatotoxicant, and was responsible for EVs-induced impairment of endothelium-dependent relaxation.³¹ Also, among patients with low-coronary flow reserve, miR-224-5p levels 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.³² Additionally, liver-secreted exosomal miR-122 was found to contribute to the development of metabolic cardiomyopathy by inhibiting *Arl-2* and affecting cardiac mitochondrial function.³³ 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.³⁴ 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.^{25,26} Not 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 protein in the liver and reduced the number and size of atherosclerotic plaques in *Ldlr*^{-/-} mice.³⁵ 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.³⁶ 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

glucose and lipid homeostasis.³⁷ 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.^{38,39} 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,⁴⁰ and even lower values were found in the endothelial dysfunction group and had a positive correlation with the flow-mediated dilatation values.^{41,42} Additionally, serum adropin was reduced in patients with coronary artery disease (CHD),⁴³ and lower levels were associated with hyperhomocysteinemia and more severe coronary disease⁴⁴ and poor coronary collateral circulation.⁴⁵ Also, in patients underwent drug-eluting stent implantation, serum adropin concentrations were significantly decreased among the in-stent restenosis (ISR) group, and its levels were inversely correlated with the neointimal volume in both groups.⁴⁶ Moreover, plasma adropin concentrations were significantly decreased in hypertensive patients compared with normotensive subjects,^{47,48} and showed a negative correlation with endothelin-1, an indicator for endothelial dysfunction.⁴⁸ However, another study reported opposite results regarding the association between adropin and hypertension.⁴⁹ And in obese children, no correlation was observed between serum adropin levels and BP variables.⁵⁰

Mechanically, adropin has been confirmed to regulate mitochondrial energy metabolism through GPR19-p44/42-PDK4 pathway,⁵¹ activate cardiac insulin signaling and improve cardiac efficiency,⁵² enhance cardiac glucose oxidation under high fat diet conditions⁵³ and improve diastolic function by alleviating myocardial fibrosis in diabetic cardiomyopathy rats.⁵⁴ Although short-term administration of adropin may fail to exert a protective effect on cardiac function in obese animals.⁵⁵ Besides, adropin could promote eNOS activation and perfusion recovery after hindlimb ischemia by upregulating VEGFR2,⁵⁶ suppress proliferation and phenotypic modulation of VSMCs induced by angiotensin II via AMPK/ACC signaling,⁴⁶ and attenuate vascular calcification by repressing VSMCs osteogenic differentiation through JAK2/STAT3 signaling,⁵⁷ 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.⁵⁸ 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.⁵⁹

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.⁶⁰ And among patients with HF, circulating adropin levels were significantly increased with the progressive deterioration in cardiac function,⁶¹ which could be effectively decreased by HF treatment.⁶²

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, de-

pending upon which organ is implicated.⁶³ 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.⁶⁴ 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 FGFR1/ β -Klotho-PI3K-Akt1-BAD signaling.⁶⁵ Also, Pan *et al.*⁶⁶ 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.⁶⁷ 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.⁶⁸ FGF21 has also been reported to protect against diabetic cardiomyopathy in part through the activation of the AMPK-PON1 signaling⁶⁹ and cardiac hypertrophy and fibrosis during hypertension,⁷⁰ as well as suppress lipid- or diabetes-stimulated cardiac apoptosis via ERK1/2-p38 MAPK-AMPK pathway.⁷¹ Additionally, FGF21 could alleviate doxorubicin-induced cardiac insults by inhibiting oxidative stress, inflammation, and apoptosis via SIRT1/LKB1/AMPK pathway.⁷² However, it should be noted 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.⁷³ 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.⁷⁴ 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.⁷⁵ The population with lowest plasma concentrations of selenoprotein P have a higher risk of cardiovascular morbidity and mortality,⁷⁶ and among patients with CVDs, circulating selenoprotein P levels were significantly lower in individuals with metabolic syndrome.⁷⁷ And another study has suggested that plasma selenoprotein P can bind to proteoglycans on the vascular endothelium and form a protective layer against oxidants.⁷⁸ Further, selenoprotein P was showed to protect low density lipids (LDLs) from oxidation⁷⁹ 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.⁸⁰ In addition, selenoprotein P was reported to exert a protective effect in cardiac fibrosis.⁸¹ However, the influence of selenoprotein P on the cardiovascular system reminds 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.⁸² And inhibition of selenoprotein P protected the heart from I/R injury by activating RISK pathway.⁸³ 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.⁸⁴ 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.⁸⁵ 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 disease⁸⁶ and valvular calcification in patients with end-stage renal disease.⁸⁷ In patients on dialysis, low serum fetuin-A was reported to increase the risk of all-cause and cardiovascular mortality.⁸⁸ Data from patients with type 2 DM and without renal dysfunction further suggested that fetuin-A may suppress the calcification of atherosclerotic plaques independently of the dialysis conditions.⁸⁹ Moreover, fetuin-A-deficient mice spontaneously developed significant myocardial calcification, characterized by myocardial stiffness, cardiac remodeling and fibrosis, and diastolic dysfunction.⁹⁰ 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.⁹¹ Fetuin-A also influenced the expression of proinflammatory and angiogenic proteins associated with atherosclerosis.⁹² 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,⁹³ and urinary fetuin-B levels were higher in individuals with cardiovascular risk factors than healthy subjects.⁹⁴ A recent study showed that plasma fetuin-B levels were significantly elevated in patients with ISR compared with non-ISR patients and healthy controls.⁹⁵ 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.⁹⁶ A subsequent study revealed that fetuin-B contributed to plaque rupture by inducing the expression of PAI-1 and MMP-2 in VSMCs through TGF- β R/Smad signaling.⁹⁷ Increased levels of fetuin-B also led to the inhibition of cardiac insulin-induced signaling and thus exacerbating myocardial I/R injury.⁹⁸

α 1-microglobulin

α 1-microglobulin is a glycoprotein synthesized and secreted mainly by the liver and serves as an indicator of renal tubular dysfunction.⁹⁹ There is accumulating evidence linking α 1-microglobulin to CVDs. In a retrospective analysis of patients with ST-elevation MI, urinary α 1-microglobulin at admission was showed to be an independent predictor of in-hospital mortality.¹⁰⁰ In patients with acute HF, urinary α 1-microglobulin concentrations at admission were associated

with all-cause mortality independent of glomerular function and provided additional prognostic value.¹⁰¹ In non-diabetic patients with chronic kidney disease, urinary α 1-microglobulin levels were also found to be associated with CVDs events and mortality.¹⁰² In addition, despite increased urinary excretion of α 1-microglobulin has been reported in patients undergoing myocardial revascularization surgery with cardiopulmonary bypass,¹⁰³ and the increases were greater with longer duration of cardiopulmonary bypass,¹⁰⁴ it was shown that preoperative but not postoperative urinary α 1-microglobulin levels were positively associated with acute kidney injury, progressive chronic kidney disease, and all-cause mortality after cardiac surgery.¹⁰⁵ However, the role of α 1-microglobulin on CVDs is still controversial. Hakuno *et al.*¹⁰⁶ demonstrated that α 1-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.^{107,108} More studies are needed to confirm the causal relationships between α 1-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.¹⁰⁹ It was found that plasma miRNAs are not only diagnostic biomarkers but also potential therapeutic targets for CVDs.¹¹⁰ MiR-122 is predominantly generated in the liver and constantly released into the circulation¹¹¹ and has been shown to be significantly elevated in patients with acute HF.¹¹² 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.¹¹³ 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.¹¹⁴ 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.¹¹⁵ 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,¹¹⁶ 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.³³ 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.¹¹⁷

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.¹¹⁸ The effects of plasma protein factor XII (FXII) on vascular function have previously been thoroughly reviewed by Mailer and colleagues.¹¹⁹ FXII is synthesized by the liver and released as an inactive zymogen into the circulation, and plays an important role in promoting endothelial dysfunction, vascu-

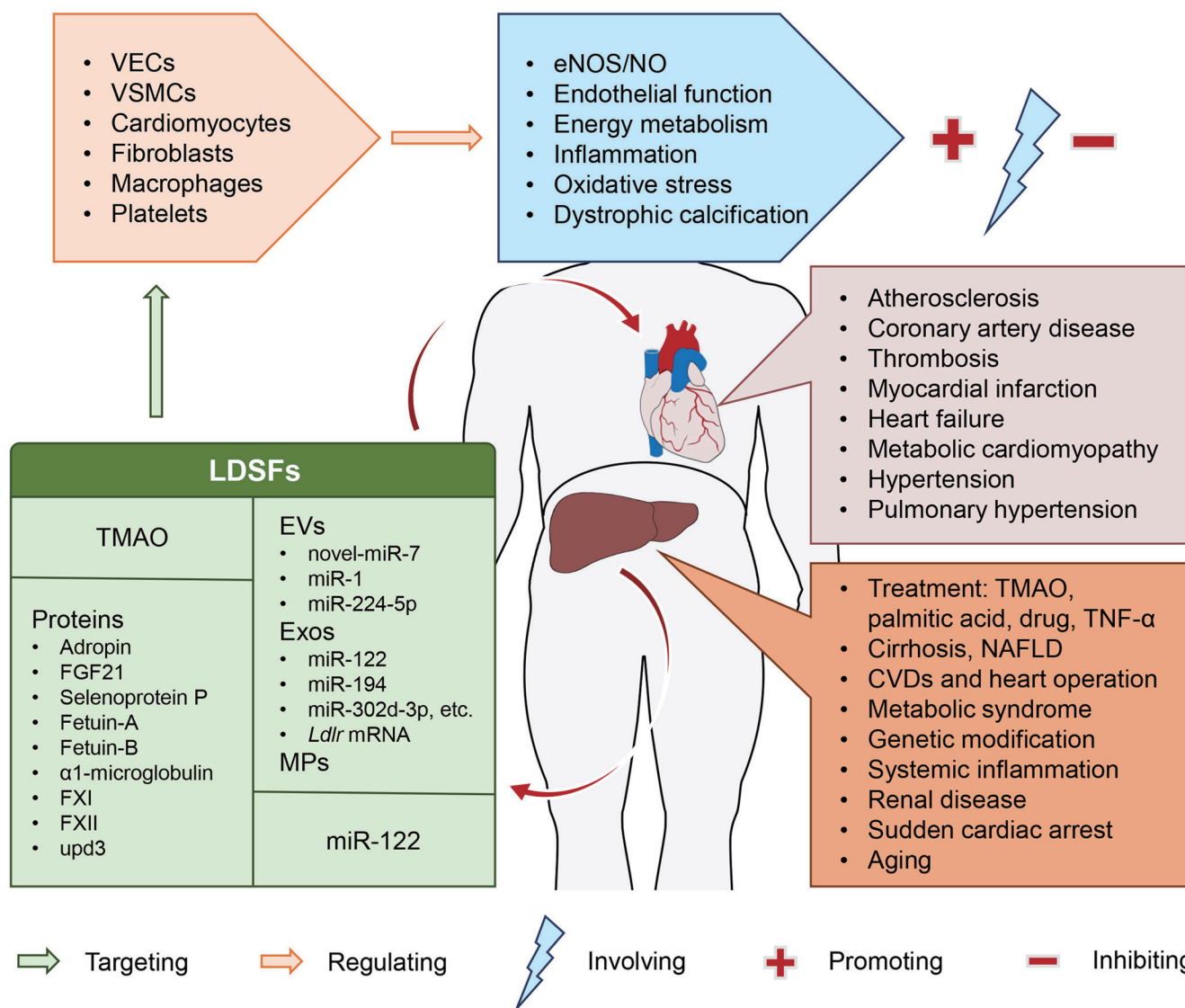


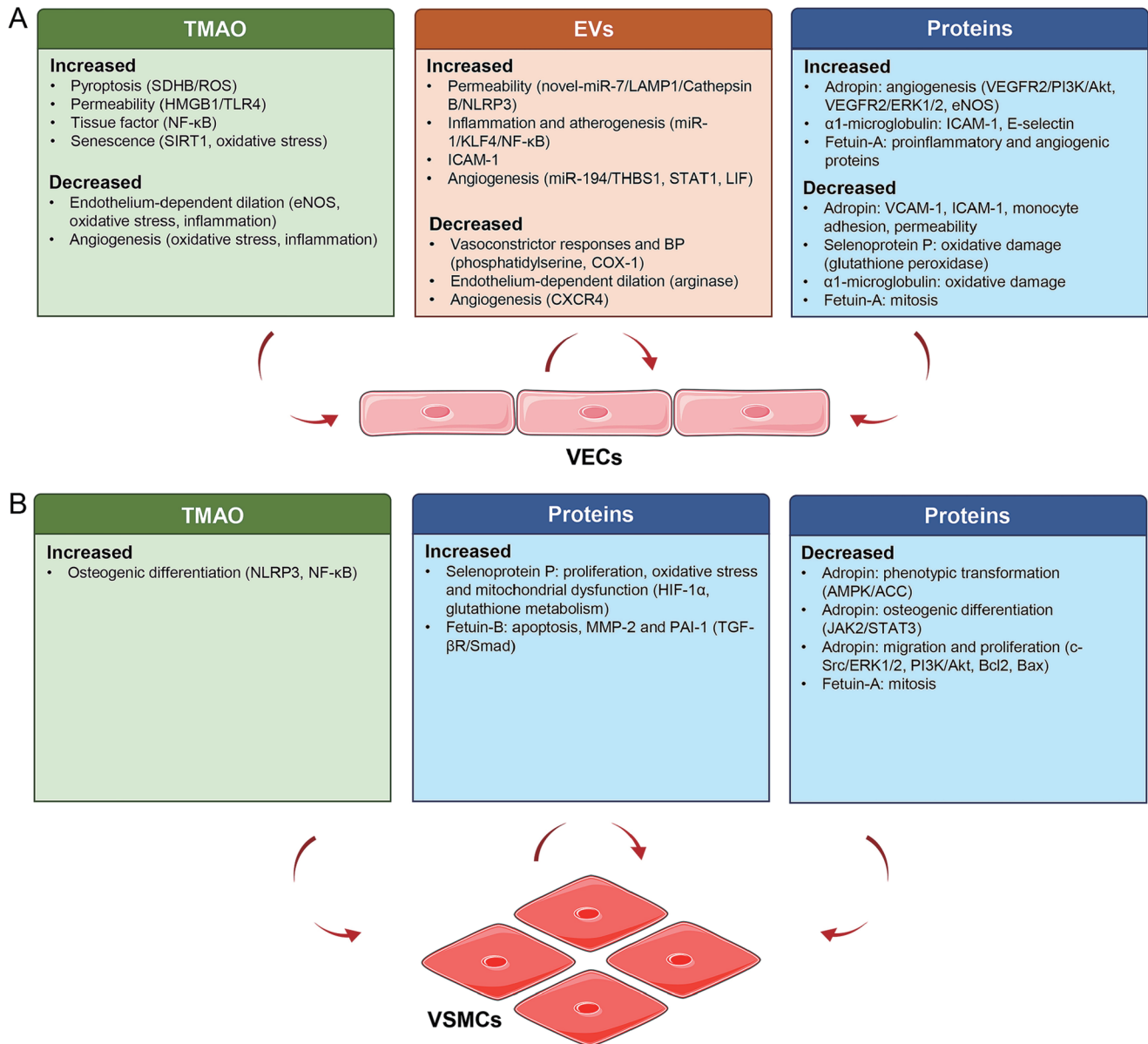
Fig. 1. Representative scheme of the release of liver-derived secretory factors in different physiological and pathophysiological states and their roles in cardiovascular disease. Parts of the figure were obtained from Servier Medical Art (<https://smart.servier.com/>). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License. CVDs, cardiovascular diseases; EVs, extracellular vesicles; Exos, exosomes; MPs, microparticles; NAFLD, non-alcoholic fatty liver disease; TMAO, trimethylamine N-oxide; VECs, vascular endothelial cells; VSMCs, vascular smooth muscle cells.

lar inflammation, and atherosclerosis. By using *Drosophila* oenocytes as a hepatocyte model, Huang *et al.* found that peroxisomal import was impaired in aged oenocytes, thus promoting the release of upd3, an IL-6-like proinflammatory cytokine, from oenocytes and inducing cardiac arrhythmia.¹²⁰

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 adropin, 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



(continued)

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/Mφ 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/Mφ, monocytes/macrophages; TMAO, trimethylamine N-oxide; VECs, vascular endothelial cells; VSMCs, vascular smooth muscle cells.

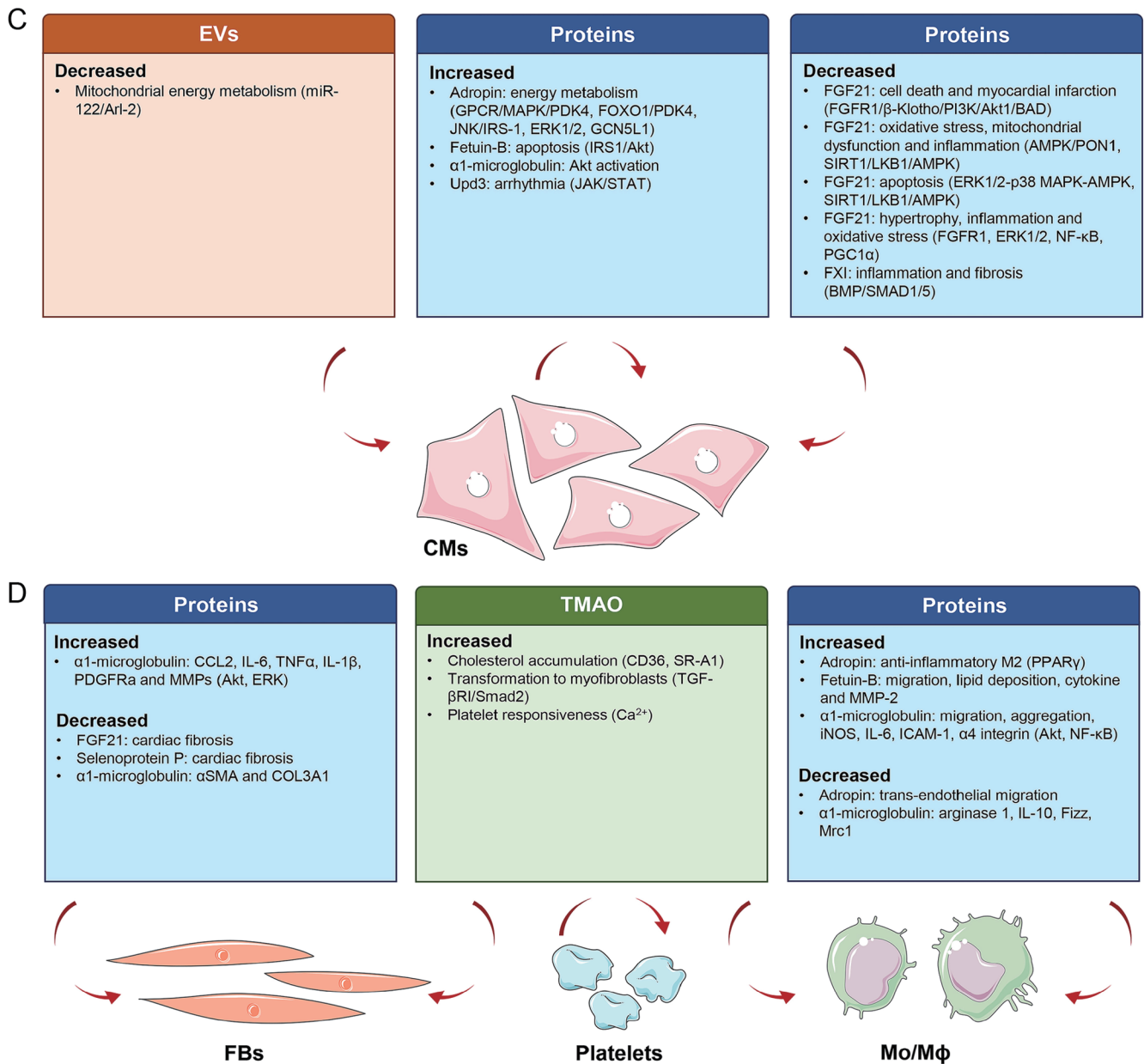


Fig. 2. (continued)

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 α 1-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.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82200435).

Conflict of interest

The authors have no conflict of interests 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.

References

[1] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, *et al*. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020;76(25):2982-3021. doi:10.1016/j.jacc.2020.11.010, PMID:33309175.

[2] Lee JS, Ward WO, Knapp G, Ren H, Vallanat B, Abbott B, *et al*. Transcriptional ontogeny of the developing liver. *BMC Genomics* 2012;13:33. doi:10.1186/1471-2164-13-33, PMID:22260730.

[3] de Haan W, Dheedene W, Apelt K, Décombas-Deschamps S, Vincier S, Verhulst S, *et al*. Endothelial Zeb2 preserves the hepatic angioarchitecture and protects against liver fibrosis. *Cardiovasc Res* 2022;118(5):1262-1275. doi:10.1093/cvr/cvab148, PMID:33909875.

[4] Ji Y, Yin Y, Sun L, Zhang W. The Molecular and Mechanistic Insights Based on Gut-Liver Axis: Nutritional Target for Non-Alcoholic Fatty Liver Disease (NAFLD) Improvement. *Int J Mol Sci* 2020;21(9):3066. doi:10.3390/ijms21093066, PMID:32357561.

[5] Seo JA, Kang MC, Yang WM, Hwang WM, Kim SS, Hong SH, *et al*. Apolipoprotein J is a hepatokine regulating muscle glucose metabolism and insulin sensitivity. *Nat Commun* 2020;11(1):2024. doi:10.1038/s41467-020-15963-w, PMID:32332780.

[6] Møller S, Bernardi M. Interactions of the heart and the liver. *Eur Heart J* 2013;34(36):2804-2811. doi:10.1093/eurheartj/ehz246, PMID:23853073.

[7] Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. *Gut* 2020;69(9):1691-1705. doi:10.1136/gutjnl-2020-320622, PMID:32321858.

[8] Brown JM, Hazen SL. Microbial modulation of cardiovascular disease. *Nat Rev Microbiol* 2018;16(3):171-181. doi:10.1038/nrmicro.2017.149, PMID:29307889.

[9] Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, *et al*. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 2011;472(7341):57-63. doi:10.1038/nature09922, PMID:21475195.

[10] Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, *et al*. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med* 2013;19(5):576-585. doi:10.1038/nm.3145, PMID:23563705.

[11] Zhu W, Gregory JC, Org E, Buffa JA, Gupta N, Wang Z, *et al*. Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk. *Cell* 2016;165(1):111-124. doi:10.1016/j.cell.2016.02.011, PMID:26972052.

[12] Li XS, Obeid S, Klिंगenberg R, Gencer B, Mach F, Räber L, *et al*. Gut microbiota-dependent trimethylamine N-oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors. *Eur Heart J* 2017;38(11):814-824. doi:10.1093/eurheartj/ehw582, PMID:28077467.

[13] Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, *et al*. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med* 2013;368(17):1575-1584. doi:10.1056/NEJMoa1109400, PMID:23614584.

[14] Tang WH, Wang Z, Fan Y, Levison B, Hazen JE, Donahue LM, *et al*. Prognostic value of elevated levels of intestinal microbe-generated metabolite trimethylamine-N-oxide in patients with heart failure: refining the gut hypothesis. *J Am Coll Cardiol* 2014;64(18):1908-1914. doi:10.1016/j.jacc.2014.02.617, PMID:25444145.

[15] Wu P, Chen J, Chen J, Tao J, Wu S, Xu G, *et al*. Trimethylamine N-oxide promotes apoE(-/-) mice atherosclerosis by inducing vascular endothelial cell pyroptosis via the SDHB/ROS pathway. *J Cell Physiol* 2020;235(10):6582-6591. doi:10.1002/jcp.29518, PMID:32012263.

[16] Singh GB, Zhang Y, Boini KM, Koka S. High Mobility Group Box 1 Mediates TMAO-Induced Endothelial Dysfunction. *Int J Mol Sci* 2019;20(14):3570. doi:10.3390/ijms20143570, PMID:31336567.

[17] Zhang X, Li Y, Yang P, Liu X, Lu L, Chen Y, *et al*. Trimethylamine-N-Oxide Promotes Vascular Calcification Through Activation of NLRP3 (Nucleotide-Binding Domain, Leucine-Rich-Containing Family, Pyrin Domain-Containing-3) Inflammasome and NF-κB (Nuclear Factor κB) Signals. *Arterioscler Thromb Vasc Biol* 2020;40(3):751-765. doi:10.1161/ATVBAHA.119.313414, PMID:31941382.

[18] Wang W, Zhang S, Zhu J, Jiang H, Jia D, Ou T, *et al*. Gut microbe-derived metabolite trimethylamine N-oxide accelerates fibroblast-myofibroblast differentiation and induces cardiac fibrosis. *J Mol Cell Cardiol* 2019;134:119-130. doi:10.1016/j.yjmcc.2019.07.004, PMID:31299216.

[19] Cheng X, Qiu X, Liu Y, Yuan C, Yang X. Trimethylamine N-oxide promotes

tissue factor expression and activity in vascular endothelial cells: A new link between trimethylamine N-oxide and atherosclerotic thrombosis. *Thromb Res* 2019;177:110-116. doi:10.1016/j.thromres.2019.02.028, PMID:30875490.

[20] Brunt VE, Gioscia-Ryan RA, Casso AG, VanDongen NS, Ziemba BP, Sapsinsley ZJ, *et al*. Trimethylamine-N-Oxide Promotes Age-Related Vascular Oxidative Stress and Endothelial Dysfunction in Mice and Healthy Humans. *Hypertension* 2020;76(1):101-112. doi:10.1161/HYPERTENSIONAHA.120.14759, PMID:32520619.

[21] Ke Y, Li D, Zhao M, Liu C, Liu J, Zeng A, *et al*. Gut flora-dependent metabolite Trimethylamine-N-oxide accelerates endothelial cell senescence and vascular aging through oxidative stress. *Free Radic Biol Med* 2018;116:88-100. doi:10.1016/j.freeradbiomed.2018.01.007, PMID:29325896.

[22] Li T, Chen Y, Gua C, Li X. Elevated Circulating Trimethylamine N-Oxide Levels Contribute to Endothelial Dysfunction in Aged Rats through Vascular Inflammation and Oxidative Stress. *Front Physiol* 2017;8:350. doi:10.3389/fphys.2017.00350, PMID:28611682.

[23] Chen L, Jin Y, Wang N, Yuan M, Lin T, Lu W, *et al*. Trimethylamine N-oxide impairs perfusion recovery after hindlimb ischemia. *Biochem Biophys Res Commun* 2020;530(1):95-99. doi:10.1016/j.bbrc.2020.06.093, PMID:32828321.

[24] Chen S, Henderson A, Petriello MC, Romano KA, Gearing M, Miao J, *et al*. Trimethylamine N-Oxide Binds and Activates PERK to Promote Metabolic Dysfunction. *Cell Metab* 2019;30(6):1141-1151.e5. doi:10.1016/j.cmet.2019.08.021, PMID:31543404.

[25] Liu X, Shao Y, Tu J, Sun J, Dong B, Wang Z, *et al*. TMAO-Activated Hepatocyte-Derived Exosomes Impair Angiogenesis via Repressing CXCR4. *Front Cell Dev Biol* 2021;9:804049. doi:10.3389/fcell.2021.804049, PMID:35174166.

[26] Liu X, Shao Y, Tu J, Sun J, Li L, Tao J, *et al*. Trimethylamine-N-oxide-stimulated hepatocyte-derived exosomes promote inflammation and endothelial dysfunction through nuclear factor-kappa B signaling. *Ann Transl Med* 2021;9(22):1670. doi:10.21037/atm-21-5043, PMID:34988179.

[27] Pitt JM, Kroemer G, Zitvogel L. Extracellular vesicles: masters of intercellular communication and potential clinical interventions. *J Clin Invest* 2016;126(4):1139-1143. doi:10.1172/JCI87316, PMID:27035805.

[28] Rautou PE, Bresson J, Sainte-Marie Y, Vion AC, Paradis V, Renard JM, *et al*. Abnormal plasma microparticles impair vasoconstrictor responses in patients with cirrhosis. *Gastroenterology* 2012;143(1):166-76.e6. doi:10.1053/j.gastro.2012.03.040, PMID:22465620.

[29] Zuo R, Ye LF, Huang Y, Song ZQ, Wang L, Zhi H, *et al*. Hepatic small extracellular vesicles promote microvascular endothelial hyperpermeability during NAFLD via novel-miRNA-7. *J Nanobiotechnology* 2021;19(1):396. doi:10.1186/s12951-021-01137-3, PMID:34838052.

[30] Jiang F, Chen Q, Wang W, Ling Y, Yan Y, Xia P. Hepatocyte-derived extracellular vesicles promote endothelial inflammation and atherogenesis via microRNA-1. *J Hepatol* 2020;72(1):156-166. doi:10.1016/j.jhep.2019.09.014, PMID:31568800.

[31] Royo F, Moreno L, Mleczko J, Palomo L, Gonzalez E, Cabrera D, *et al*. Hepatocyte-secreted extracellular vesicles modify blood metabolome and endothelial function by an arginase-dependent mechanism. *Sci Rep* 2017;7:42798. doi:10.1038/srep42798, PMID:28211494.

[32] James K, Bryl-Gorecka P, Olde B, Gidlof O, Tornegren K, Erlinge D. Increased expression of miR-224-5p in circulating extracellular vesicles of patients with reduced coronary flow reserve. *BMC Cardiovasc Disord* 2022;22(1):321. doi:10.1186/s12872-022-02756-w, PMID:35850658.

[33] Wang Y, Jin P, Liu J, Xie X. Exosomal microRNA-122 mediates obesity-related cardiomyopathy through suppressing mitochondrial ADP-ribosylation factor-like 2. *Clin Sci (Lond)* 2019;133(17):1871-1881. doi:10.1042/CS20190558, PMID:31434696.

[34] Chen L, Han Y, Li Y, Chen B, Bai X, Belguise K, *et al*. Hepatocyte-derived exosomal MIR-194 activates PMVECs and promotes angiogenesis in hepatopulmonary syndrome. *Cell Death Dis* 2019;10(11):853. doi:10.1038/s41419-019-2087-y, PMID:31700002.

[35] Li Z, Zhao P, Zhang Y, Wang J, Wang C, Liu Y, *et al*. Exosome-based Ldlr gene therapy for familial hypercholesterolemia in a mouse model. *Theranostics* 2021;11(6):2953-2965. doi:10.7150/tno.49874, PMID:33456582.

[36] Meex RCR, Watt MJ. Hepatokines: linking nonalcoholic fatty liver disease and insulin resistance. *Nat Rev Endocrinol* 2017;13(9):509-520. doi:10.1038/nrendo.2017.56, PMID:28621339.

[37] Kumar KG, Trevaskis JL, Lam DD, Sutton GM, Koza RA, Chouljenko VN, *et al*. Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. *Cell Metab* 2008;8(6):468-481. doi:10.1016/j.cmet.2008.10.011, PMID:19041763.

[38] Zhang H, Jiang L, Yang YJ, Ge RK, Zhou M, Hu H, *et al*. Aerobic exercise improves endothelial function and serum adropin levels in obese adolescents independent of body weight loss. *Sci Rep* 2017;7(1):17717. doi:10.1038/s41598-017-18086-3, PMID:29255252.

[39] Fujie S, Hasegawa N, Kurihara T, Sanada K, Hamaoka T, Iemitsu M. Association between aerobic exercise training effects of serum adropin level, arterial stiffness, and adiposity in obese elderly adults. *Appl Physiol Nutr Metab* 2017;42(1):8-14. doi:10.1139/apnm-2016-0310, PMID:27897440.

[40] Wu L, Fang J, Chen L, Zhao Z, Luo Y, Lin C, *et al*. Low serum adropin is associated with coronary atherosclerosis in type 2 diabetic and non-diabetic patients. *Clin Chem Lab Med* 2014;52(5):751-758. doi:10.1515/cclm-2013-0844, PMID:24323892.

[41] Oruc CU, Akpinar YE, Dervisoglu E, Amikishiyev S, Salmaslioglu A, Gurdol F, *et al*. Low concentrations of adropin are associated with endothelial dysfunction as assessed by flow-mediated dilatation in patients with metabolic syndrome. *Clin Chem Lab Med* 2017;55(1):139-144. doi:10.1515/cclm-2016-0329, PMID:27474839.

[42] Topuz M, Celik A, Aslantas T, Demir AK, Aydin S, Aydin S. Plasma adro-

- pin levels predict endothelial dysfunction like flow-mediated dilatation in patients with type 2 diabetes mellitus. *J Investig Med* 2013;61(8):1161-1164. doi:10.2310/JIM.0000000000000003, PMID:24113736.
- [43] Zhao LP, Xu WT, Wang L, You T, Chan SP, Zhao X, *et al*. Serum adropin level in patients with stable coronary artery disease. *Heart Lung Circ* 2015;24(10):975-979. doi:10.1016/j.hlc.2015.03.008, PMID:25912996.
- [44] Zhao LP, You T, Chan SP, Chen JC, Xu WT. Adropin is associated with hyperhomocysteine and coronary atherosclerosis. *Exp Ther Med* 2016;11(3):1065-1070. doi:10.3892/etm.2015.2954, PMID:26998038.
- [45] Akkaya H, Güntürk EE, Akkaya F, Karabiyik U, Güntürk İ, Yılmaz S. Assessment of the Relationship Between the Adropin Levels and the Coronary Collateral Circulation in Patients with Chronic Coronary Syndrome. *Arq Bras Cardiol* 2022;119(3):402-410. doi:10.36660/abc.20210573, PMID:35766616.
- [46] Wang L, Zhao LP, Chen YQ, Chang XS, Xiong H, Zhang DM, *et al*. Adropin inhibits the phenotypic modulation and proliferation of vascular smooth muscle cells during neointimal hyperplasia by activating the AMPK/ACC signaling pathway. *Exp Ther Med* 2021;21(6):560. doi:10.3892/etm.2021.9992, PMID:33850532.
- [47] Gulen B, Eken C, Kucukdagli OT, Serinken M, Kocycigit A, Kilic E, *et al*. Adropin levels and target organ damage secondary to high blood pressure in the ED. *Am J Emerg Med* 2016;34(11):2061-2064. doi:10.1016/j.ajem.2016.04.014, PMID:27592461.
- [48] Gu X, Li H, Zhu X, Gu H, Chen J, Wang L, *et al*. Inverse Correlation Between Plasma Adropin and ET-1 Levels in Essential Hypertension: A Cross-Sectional Study. *Medicine (Baltimore)* 2015;94(40):e1712. doi:10.1097/MD.0000000000001712, PMID:26448026.
- [49] Çelik HT, Akkaya N, Erdamar H, Gök S, Kazanci F, Demircelik B, *et al*. The Effects of Valsartan and Amlodipine on the Levels of Irisin, Adropin, and Perilipin. *Clin Lab* 2015;61(12):1889-1895. doi:10.7754/clin.lab.2015.150420, PMID:26882812.
- [50] Altincik A, Sayin O. Evaluation of the relationship between serum adropin levels and blood pressure in obese children. *J Pediatr Endocrinol Metab* 2015;28(9-10):1095-1100. doi:10.1515/jpem-2015-0051, PMID:26030787.
- [51] Thapa D, Stoner MW, Zhang M, Xie B, Manning JR, Guimaraes D, *et al*. Adropin regulates pyruvate dehydrogenase in cardiac cells via a novel GPCR-MAPK-PDK4 signaling pathway. *Redox Biol* 2018;18:25-32. doi:10.1016/j.redox.2018.06.003, PMID:29909017.
- [52] Altamimi TR, Gao S, Karwi QG, Fukushima A, Rawat S, Wagg CS, *et al*. Adropin regulates cardiac energy metabolism and improves cardiac function and efficiency. *Metabolism* 2019;98:37-48. doi:10.1016/j.metabol.2019.06.005, PMID:31202835.
- [53] Thapa D, Xie B, Zhang M, Stoner MW, Manning JR, Huckestein BR, *et al*. Adropin treatment restores cardiac glucose oxidation in pre-diabetic obese mice. *J Mol Cell Cardiol* 2019;129:174-178. doi:10.1016/j.yjmc.2019.02.012, PMID:30822408.
- [54] Liu M, Ai J, Shuai Z, Tang K, Li Z, Huang Y. Adropin Alleviates Myocardial Fibrosis in Diabetic Cardiomyopathy Rats: A Preliminary Study. *Front Cardiovasc Med* 2021;8:688586. doi:10.3389/fcvm.2021.688586, PMID:34322528.
- [55] Thapa D, Xie B, Mushala BAS, Zhang M, Manning JR, Bugga P, *et al*. Diet-induced obese mice are resistant to improvements in cardiac function resulting from short-term adropin treatment. *Curr Res Physiol* 2022;5:55-62. doi:10.1016/j.crphys.2022.01.005, PMID:35128468.
- [56] Lovren F, Pan Y, Quan A, Singh KK, Shukla PC, Gupta M, *et al*. Adropin is a novel regulator of endothelial function. *Circulation* 2010;122(11 Suppl):S185-S192. doi:10.1161/CIRCULATIONAHA.109.931782, PMID:20837912.
- [57] Wang L, Jin F, Wang P, Hou S, Jin T, Chang X, *et al*. Adropin Inhibits Vascular Smooth Muscle Cell Osteogenic Differentiation to Alleviate Vascular Calcification via the JAK2/STAT3 Signaling Pathway. *Biomed Res Int* 2022;2022:9122264. doi:10.1155/2022/9122264, PMID:35937397.
- [58] Sato K, Yamashita T, Shirai R, Shibata K, Okano T, Yamaguchi M, *et al*. Adropin Contributes to Anti-Atherosclerosis by Suppressing Monocyte-Endothelial Cell Adhesion and Smooth Muscle Cell Proliferation. *Int J Mol Sci* 2018;19(5):1293. doi:10.3390/ijms19051293, PMID:29701665.
- [59] Dodd WS, Patel D, Lucke-Wold B, Hosaka K, Chalouhi N, Hoh BL. Adropin decreases endothelial monolayer permeability after cell-free hemoglobin exposure and reduces MCP-1-induced macrophage transmigration. *Biochem Biophys Res Commun* 2021;582:105-110. doi:10.1016/j.bbrc.2021.10.032, PMID:34710824.
- [60] Yang M, Pei Q, Zhang J, Weng H, Jing F, Yi Q. Association between adropin and coronary artery lesions in children with Kawasaki disease. *Eur J Pediatr* 2021;180(7):2253-2259. doi:10.1007/s00431-021-03977-5, PMID:33712900.
- [61] Lian W, Gu X, Qin Y, Zheng X. Elevated plasma levels of adropin in heart failure patients. *Intern Med* 2011;50(15):1523-1527. doi:10.2169/intermalmedicine.50.5163, PMID:21804276.
- [62] Xu W, Qian L, Yuan X, Lu Y. Combined effects of hydralazine and nitrate on serum biochemistry and left ventricular remodeling in chronic heart failure patients. *Pak J Pharm Sci* 2021;34(1 Special):381-386. doi:10.36721/pjps.2021.34.1.Sp.381-386.1, PMID:34275783.
- [63] Fisher FM, Maratos-Flier E. Understanding the Physiology of FGF21. *Annu Rev Physiol* 2016;78:223-241. doi:10.1146/annurev-physiol-021115-105339, PMID:26654352.
- [64] Huen SC, Wang A, Feola K, Desrouleaux R, Luan HH, Hogg R, *et al*. Hepatic FGF21 preserves thermoregulation and cardiovascular function during bacterial inflammation. *J Exp Med* 2021;218(10):e20202151. doi:10.1084/jem.20202151, PMID:34406362.
- [65] Liu SQ, Roberts D, Kharitonov A, Zhang B, Hanson SM, Li YC, *et al*. Endocrine protection of ischemic myocardium by FGF21 from the liver and adipose tissue. *Sci Rep* 2013;3:2767. doi:10.1038/srep02767, PMID:24067542.
- [66] Pan X, Shao Y, Wu F, Wang Y, Xiong R, Zheng J, *et al*. FGF21 Prevents Angiotensin II-Induced Hypertension and Vascular Dysfunction by Activation of ACE2/Angiotensin-(1-7) Axis in Mice. *Cell Metab* 2018;27(6):1323-1337. e5. doi:10.1016/j.cmet.2018.04.002, PMID:29706566.
- [67] Lin Z, Pan X, Wu F, Ye D, Zhang Y, Wang Y, *et al*. Fibroblast growth factor 21 prevents atherosclerosis by suppression of hepatic sterol regulatory element-binding protein-2 and induction of adiponectin in mice. *Circulation* 2015;131(21):1861-1871. doi:10.1161/CIRCULATIONAHA.115.015308, PMID:25794851.
- [68] Jia H, Cheng J, Zhou Q, Peng J, Pan Y, Han H. Fibroblast growth factor 21 attenuates inflammation and oxidative stress in atherosclerotic rat via enhancing the Nrf1-ARE signaling pathway. *Int J Clin Exp Pathol* 2018;11(3):1308-1317. PMID:31938226.
- [69] Wu F, Wang B, Zhang S, Shi L, Wang Y, Xiong R, *et al*. FGF21 ameliorates diabetic cardiomyopathy by activating the AMPK-paraoxonase 1 signaling axis in mice. *Clin Sci (Lond)* 2017;131(15):1877-1893. doi:10.1042/CS20170271, PMID:28559425.
- [70] Ferrer-Curiu G, Redondo-Angulo I, Guitart-Mampel M, Ruperez C, Mas-Stachurska A, Sitges M, *et al*. Fibroblast growth factor-21 protects against fibrosis in hypertensive heart disease. *J Pathol* 2019;248(1):30-40. doi:10.1002/path.5226, PMID:30582148.
- [71] Zhang C, Huang Z, Gu J, Yan X, Lu X, Zhou S, *et al*. Fibroblast growth factor 21 protects the heart from apoptosis in a diabetic mouse model via extracellular signal-regulated kinase 1/2-dependent signalling pathway. *Diabetologia* 2015;58(8):1937-1948. doi:10.1007/s00125-015-3630-8, PMID:26040473.
- [72] Wang S, Wang Y, Zhang Z, Liu Q, Gu J. Cardioprotective effects of fibroblast growth factor 21 against doxorubicin-induced toxicity via the SIRT1/LKB1/AMPK pathway. *Cell Death Dis* 2017;8(8):e3018. doi:10.1038/cddis.2017.410, PMID:28837153.
- [73] Planavila A, Redondo I, Hondares E, Vinciguerra M, Munts C, Iglesias R, *et al*. Fibroblast growth factor 21 protects against cardiac hypertrophy in mice. *Nat Commun* 2013;4:2019. doi:10.1038/ncomms3019, PMID:23771152.
- [74] Planavila A, Redondo-Angulo I, Villarroya F. FGF21 and Cardiac Physiopathology. *Front Endocrinol (Lausanne)* 2015;6:133. doi:10.3389/fendo.2015.00133, PMID:26379627.
- [75] Burk RF, Hill KE. Regulation of Selenium Metabolism and Transport. *Annu Rev Nutr* 2015;35:109-134. doi:10.1146/annurev-nutr-071714-034250, PMID:25974694.
- [76] Schomburg L, Orho-Melander M, Struck J, Bergmann A, Melander O. Selenoprotein-P Deficiency Predicts Cardiovascular Disease and Death. *Nutrients* 2019;11(8):1852. doi:10.3390/nu11081852, PMID:31404994.
- [77] Gharipour M, Sadeghi M, Salehi M, Behmanesh M, Khosravi E, Dianatkah M, *et al*. Association of expression of selenoprotein P in mRNA and protein levels with metabolic syndrome in subjects with cardiovascular disease: Results of the Selenogene study. *J Gene Med* 2017;19(3):e2945. doi:10.1002/jgm.2945, PMID:28190280.
- [78] Arteel GE, Franken S, Kappler J, Sies H. Binding of selenoprotein P to heparin: characterization with surface plasmon resonance. *Biol Chem* 2000;381(3):265-268. doi:10.1515/BC.2000.034, PMID:10782998.
- [79] Traulsen L, Steinbrenner H, Buchczyk DP, Klotz LO, Sies H. Selenoprotein P protects low-density lipoprotein against oxidation. *Free Radic Res* 2004;38(2):123-128. doi:10.1080/10715760320001634852, PMID:15104205.
- [80] Steinbrenner H, Bilgic E, Alili L, Sies H, Brenneisen P. Selenoprotein P protects endothelial cells from oxidative damage by stimulation of glutathione peroxidase expression and activity. *Free Radic Res* 2006;40(9):936-943. doi:10.1080/10715760600806248, PMID:17015273.
- [81] Schimmel K, Jung M, Foinquinos A, José GS, Beaumont J, Bock K, *et al*. Natural Compound Library Screening Identifies New Molecules for the Treatment of Cardiac Fibrosis and Diastolic Dysfunction. *Circulation* 2020;141(9):751-767. doi:10.1161/CIRCULATIONAHA.119.042559, PMID:31948273.
- [82] Takeishi R, Misaka T, Ichijo Y, Ishibashi S, Matsuda M, Yamadera Y, *et al*. Increases in Hepatokine Selenoprotein P Levels Are Associated With Hepatic Hypoperfusion and Predict Adverse Prognosis in Patients With Heart Failure. *J Am Heart Assoc* 2022;11(11):e024901. doi:10.1161/JAHA.121.024901, PMID:35621211.
- [83] Chadani H, Usui S, Inoue O, Kusayama T, Takashima SI, Kato T, *et al*. Endogenous Selenoprotein P, a Liver-Derived Secretory Protein, Mediates Myocardial Ischemia/Reperfusion Injury in Mice. *Int J Mol Sci* 2018;19(3):878. doi:10.3390/ijms19030878, PMID:29547524.
- [84] Kikuchi N, Satoh K, Satoh T, Yaoita N, Siddique MAH, Omura J, *et al*. Diagnostic and Prognostic Significance of Serum Levels of SeP (Selenoprotein P) in Patients With Pulmonary Hypertension. *Arterioscler Thromb Vasc Biol* 2019;39(12):2553-2562. doi:10.1161/ATVBAHA.119.313267, PMID:31665907.
- [85] Kikuchi N, Satoh K, Kurosawa R, Yaoita N, Elias-Al-Mamun M, Siddique MAH, *et al*. Selenoprotein P Promotes the Development of Pulmonary Arterial Hypertension: Possible Novel Therapeutic Target. *Circulation* 2018;138(6):600-623. doi:10.1161/CIRCULATIONAHA.117.033113, PMID:29636330.
- [86] Ix JH, Chertow GM, Shlipak MG, Brandenburger VM, Ketteler M, Whoolley MA. Association of fetuin-A with mitral annular calcification and aortic stenosis among persons with coronary heart disease: data from the Heart and Soul Study. *Circulation* 2007;115(19):2533-2539. doi:10.1161/CIRCULATIONAHA.106.682450, PMID:17485576.
- [87] Wang AY, Woo J, Lam CW, Wang M, Chan IH, Gao P, *et al*. Associations of serum fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. *Nephrol Dial Transplant* 2005;20(8):1676-1685. doi:10.1093/ndt/gfh891, PMID:15899935.
- [88] Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnen AH, Böhm

- R, *et al*. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. *Lancet* 2003;361(9360):827–833. doi:10.1016/S0140-6736(03)12710-9, PMID:12642050.
- [89] Emoto M, Mori K, Lee E, Kawano N, Yamazaki Y, Tsuchikura S, *et al*. Fetuin-A and atherosclerotic calcified plaque in patients with type 2 diabetes mellitus. *Metabolism* 2010;59(6):873–878. doi:10.1016/j.metabol.2009.10.005, PMID:20015522.
- [90] Merx MW, Schäfer C, Westenfeld R, Brandenburg V, Hidajat S, Weber C, *et al*. Myocardial stiffness, cardiac remodeling, and diastolic dysfunction in calcification-prone fetuin-A-deficient mice. *J Am Soc Nephrol* 2005;16(11):3357–3364. doi:10.1681/ASN.2005040365, PMID:16177000.
- [91] Weikert C, Stefan N, Schulze MB, Pischon T, Berger K, Joost HG, *et al*. Plasma fetuin-a levels and the risk of myocardial infarction and ischemic stroke. *Circulation* 2008;118(24):2555–2562. doi:10.1161/CIRCULATIONAHA.108.814418, PMID:19029462.
- [92] Siegel-Axel DI, Ullrich S, Stefan N, Rittig K, Gerst F, Klingler C, *et al*. Fetuin-A influences vascular cell growth and production of proinflammatory and angiogenic proteins by human perivascular fat cells. *Atherosclerosis* 2014;57(5):1057–1066. doi:10.1007/s00125-014-3177-0, PMID:24493202.
- [93] Zhu K, Wang Y, Shu P, Zhou Q, Zhu J, Zhou W, *et al*. Increased serum levels of fetuin B in patients with coronary artery disease. *Endocrine* 2017;58(1):97–105. doi:10.1007/s12020-017-1387-1, PMID:28822077.
- [94] Martínez PJ, Baldán-Martín M, López JA, Martín-Lorenzo M, Santiago-Hernández A, Agudiez M, *et al*. Identification of six cardiovascular risk biomarkers in the young population: A promising tool for early prevention. *Atherosclerosis* 2019;282:67–74. doi:10.1016/j.atherosclerosis.2019.01.003, PMID:30690299.
- [95] Hou J, Deng Q, Liu S, Qiu X, Deng X, Zhong W, *et al*. Plasma Proteome Profiling of Patients With In-stent Restenosis by Tandem Mass Tag-Based Quantitative Proteomics Approach. *Front Cardiovasc Med* 2022;9:793405. doi:10.3389/fcvm.2022.793405, PMID:35256578.
- [96] Jung SH, Won KJ, Lee KP, Kim HJ, Seo EH, Lee HM, *et al*. The serum protein fetuin-B is involved in the development of acute myocardial infarction. *Clin Sci (Lond)* 2015;129(1):27–38. doi:10.1042/CS20140462, PMID:25671698.
- [97] Jung SH, Lee D, Jin H, Lee HM, Ko HM, Lee KJ, *et al*. Fetuin-B regulates vascular plaque rupture via TGF- β receptor-mediated Smad pathway in vascular smooth muscle cells. *Pflugers Arch* 2020;472(5):571–581. doi:10.1007/s00424-020-02385-2, PMID:32382986.
- [98] Xing W, Tan Y, Li K, Tian P, Tian F, Zhang H. Upregulated hepatokine fetuin B aggravates myocardial ischemia/reperfusion injury through inhibiting insulin signaling in diabetic mice. *J Mol Cell Cardiol* 2021;151:163–172. doi:10.1016/j.yjmcc.2020.03.002, PMID:32147518.
- [99] Yu H, Yanagisawa Y, Forbes MA, Cooper EH, Crockson RA, MacLennan IC. Alpha-1-microglobulin: an indicator protein for renal tubular function. *J Clin Pathol* 1983;36(3):253–259. doi:10.1136/jcp.36.3.253, PMID:6186698.
- [100] Cui H, Zhang X, Ding X, Zhou L, Liang S, Qiu H, *et al*. Urinary Alpha-1-Microglobulin: A New Predictor for In-Hospital Mortality in Patients with ST-Segment Elevation Myocardial Infarction. *Med Sci Monit* 2021;27:e927958. doi:10.12659/MSM.927958, PMID:33460425.
- [101] Ishiwata S, Matsue Y, Nakamura Y, Dotare T, Sunayama T, Suda S, *et al*. Clinical and prognostic values of urinary alpha1-microglobulin as a tubular marker in acute heart failure. *Int J Cardiol* 2021;338:115–120. doi:10.1016/j.ijcard.2021.06.041, PMID:34181994.
- [102] Garimella PS, Lee AK, Ambrosius WT, Bhatt U, Cheung AK, Chonchol M, *et al*. Markers of kidney tubule function and risk of cardiovascular disease events and mortality in the SPRINT trial. *Eur Heart J* 2019;40(42):3486–3493. doi:10.1093/eurheartj/ehz392, PMID:31257404.
- [103] Faulí A, Gomar C, Campistol JM, Alvarez L, Manig AM, Matute P. Pattern of renal dysfunction associated with myocardial revascularization surgery and cardiopulmonary bypass. *Eur J Anaesthesiol* 2003;20(6):443–450. doi:10.1017/s0265021503000693, PMID:12803260.
- [104] Boldt J, Brenner T, Lehmann A, Suttner SW, Kumle B, Isgro F. Is kidney function altered by the duration of cardiopulmonary bypass? *Ann Thorac Surg* 2003;75(3):906–912. doi:10.1016/s0003-4975(02)04559-9, PMID:12645715.
- [105] Amatruda JG, Estrella MM, Garg AX, Thiessen-Philbrook H, McArthur E, Coca SG, *et al*. Urine Alpha-1-Microglobulin Levels and Acute Kidney Injury, Mortality, and Cardiovascular Events following Cardiac Surgery. *Am J Nephrol* 2021;52(8):673–683. doi:10.1159/000518240, PMID:34515046.
- [106] Hakuno D, Kimura M, Ito S, Satoh J, Nakashima Y, Horie T, *et al*. Hepatokine α 1-Microglobulin Signaling Exacerbates Inflammation and Disturbs Fibrotic Repair in Mouse Myocardial Infarction. *Sci Rep* 2018;8(1):16749. doi:10.1038/s41598-018-35194-w, PMID:30425314.
- [107] Cederlund M, Dericic A, Pallon J, Sørensen OE, Åkerström B. A1M/ α 1-microglobulin is proteolytically activated by myeloperoxidase, binds its heme group and inhibits low density lipoprotein oxidation. *Front Physiol* 2015;6:11. doi:10.3389/fphys.2015.00011, PMID:25698971.
- [108] Pethő D, Gáll T, Hendrik Z, Nagy A, Beke L, Gergely AP, *et al*. Ferryl Hemoglobin and Heme Induce A(1)-Microglobulin in Hemorrhaged Atherosclerotic Lesions with Inhibitory Function against Hemoglobin and Lipid Oxidation. *Int J Mol Sci* 2021;22(13):6668. doi:10.3390/ijms22136668, PMID:34206377.
- [109] Maegdefessel L. The emerging role of microRNAs in cardiovascular disease. *J Intern Med* 2014;276(6):633–644. doi:10.1111/joim.12298, PMID:25160930.
- [110] Zhou SS, Jin JP, Wang JQ, Zhang ZG, Freedman JH, Zheng Y, *et al*. miRNAs in cardiovascular diseases: potential biomarkers, therapeutic targets and challenges. *Acta Pharmacol Sin* 2018;39(7):1073–1084. doi:10.1038/aps.2018.30, PMID:29877320.
- [111] Willeit P, Skrobilin P, Kiechl S, Fernández-Hernando C, Mayr M. Liver microRNAs: potential mediators and biomarkers for metabolic and cardiovascular disease? *Eur Heart J* 2016;37(43):3260–3266. doi:10.1093/eurheartj/ehw146, PMID:27099265.
- [112] Carsten MF, Dennert R, Jochems S, Kuznetsova T, Devaux Y, Hofstra L, *et al*. Circulating MicroRNA-208b and MicroRNA-499 reflect myocardial damage in cardiovascular disease. *Circ Cardiovasc Genet* 2010;3(6):499–506. doi:10.1161/CIRCGENETICS.110.957415, PMID:20921333.
- [113] Wander PL, Enquobahrie DA, Pritchard CC, McKnight B, Rice K, Christiansen M, *et al*. Circulating microRNAs and sudden cardiac arrest outcomes. *Resuscitation* 2016;106:96–101. doi:10.1016/j.resuscitation.2016.06.038, PMID:27423422.
- [114] Gilje P, Frydland M, Bro-Jeppesen J, Dankiewicz J, Friberg H, Rundgren M, *et al*. The association between plasma miR-122-5p release pattern at admission and all-cause mortality or shock after out-of-hospital cardiac arrest. *Biomarkers* 2019;24(1):29–35. doi:10.1080/1354750X.2018.1499804, PMID:30015516.
- [115] Stojkovic S, Koller L, Sulzgruber P, Hülsmann M, Huber K, Mayr M, *et al*. Liver-specific microRNA-122 as prognostic biomarker in patients with chronic systolic heart failure. *Int J Cardiol* 2020;303:80–85. doi:10.1016/j.ijcard.2019.11.090, PMID:31757654.
- [116] Vliegenterhart AD, Shaffer JM, Clarke JJ, Peeters LE, Caporali A, Bateman DN, *et al*. Comprehensive microRNA profiling in acetaminophen toxicity identifies novel circulating biomarkers for human liver and kidney injury. *Sci Rep* 2015;5:15501. doi:10.1038/srep15501, PMID:26489516.
- [117] Geisler A, Jungmann A, Kurreck J, Poller W, Katus HA, Vetter R, *et al*. microRNA122-regulated transgene expression increases specificity of cardiac gene transfer upon intravenous delivery of AAV9 vectors. *Gene Ther* 2011;18(2):199–209. doi:10.1038/gt.2010.141, PMID:21048795.
- [118] Cao Y, Wang Y, Zhou Z, Pan C, Jiang L, Zhou Z, *et al*. Liver-heart cross-talk mediated by coagulation factor XI protects against heart failure. *Science* 2022;377(6613):1399–1406. doi:10.1126/science.abn0910, PMID:36137043.
- [119] Mailer RK, Rangaswamy C, Konrath S, Emsley J, Renné T. An update on factor XII-driven vascular inflammation. *Biochim Biophys Acta Mol Cell Res* 2022;1869(1):119166. doi:10.1016/j.bbamcr.2021.119166, PMID:34699874.
- [120] Huang K, Miao T, Chang K, Kim J, Kang P, Jiang Q, *et al*. Impaired peroxisomal import in *Drosophila* oenocytes causes cardiac dysfunction by inducing upd3 as a peroxikine. *Nat Commun* 2020;11(1):2943. doi:10.1038/s41467-020-16781-w, PMID:32523050.