Implication of hepatokines in metabolic disorders and cardiovascular diseases

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Abstract

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The liver is a central regulator of systemic energy homeostasis and has a pivotal role in glucose and lipid metabolism. Impaired gluconeogenesis and dyslipidemia are often observed in patients with nonalcoholic fatty liver disease (NAFLD). The liver is now recognized to be an endocrine organ that secretes hepatokines, which are proteins that regulate systemic metabolism and energy homeostasis. Hepatokines are known to contribute to the pathogenesis of metabolic syndrome, NAFLD, type 2 diabetes (T2DM), and cardiovascular diseases (CVDs). In this review, we focus on the roles of two major hepatokines, fetuin-A and fibroblast growth factor 21 (FGF21), as well as recently-redefined hepatokines, such as selenoprotein P, angiopoietin-like protein 4 (ANGPTL4), and leukocyte cell-derived chemotaxin 2 (LECT2). We also assess the biology and molecular mechanisms of hepatokines in the context of their potential as therapeutic targets for metabolic disorders and cardiovascular diseases.

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1. Introduction

The prevalence of obesity is increasing worldwide, and is a serious public health problem in many countries [1]. In particular, abdominal obesity is well known to be a critical factor in the development and progression of type 2 diabetes (T2DM), cardiovascular disease (CVD), hypertension, stroke, cancer, sleep apnea, and nonalcoholic fatty liver disease (NAFLD) [2]. Obesity-associated lipolysis induces the release of free fatty acids into the blood stream [3] and increases subclinical inflammation, thereby aggravating insulin resistance in various tissues [4]. NAFLD, which has been regarded as a hepatic manifestation of metabolic syndrome, is a spectrum of chronic liver diseases including simple steatosis, non-alcoholic steatohepatitis (NASH), and liver cirrhosis [5]. Evidences suggest that NAFLD is a risk factor for CVD independent of traditional risk factors [6–8].

Organokines are predominantly produced by and secreted from their respective tissues (e.g. adipokines from adipose tissue and...
Table 1
Implication of hepatokines in cardiometabolic disorders.

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Abbreviation
FGF21: fibroblast growth factor 21.
ANGPTL4: angiopoietin-like 4.
LECT2: leukocyte-derived chemotaxin 2.
T2DM: type 2 diabetes mellitus.
NAFLD: non-alcoholic fatty liver disease.
CVD: cardiovascular disease.
Carotid IMT: carotid intima-media thickness.

myokines from muscle) and affect metabolism through autocrine, paracrine, and endocrine activity. Recent studies have shown that the liver may control whole body energy homeostasis through the regulation of glucose and lipid metabolism by the secretion of hepatokines, which are liver-derived proteins [9]. In this review, we summarize recent findings about major hepatokines and evaluate the underlying molecular mechanisms that may contribute to understanding the pathogenesis of cardiometabolic disease as well as the development of novel treatments.

1.1. Adipose tissue and muscle as endocrine organs

Adipose tissue functions as an endocrine organ by secreting adipokines as well as storing triglycerides. In adipose tissue, increased energy storage leads to not only an accumulation of lipids but also inflammation, contributing to the infiltration and activation of immune cells [10]. This interaction between adipocytes and immune cells results in the altered secretion of adipokines, which significantly affects the metabolic state of other tissues including the liver, skeletal muscle, brain, and vascular system [4,10,11]. Adiponectin is a representative adipokine that has been shown to be a biomarker of T2DM and CVD and is also involved in the pathogenesis of these disorders [12]. Other adipokines such as leptin, resistin, adipocyte fatty acid binding protein (A-FABP), and retinol-binding protein 4 (RBP4) which is also expressed in liver [13,14], are now being actively studied as therapeutic targets for the treatment of T2DM and CVD [4].

Recently, skeletal muscle is also recognized as an endocrine organ, which was comprehensively reviewed by Pedersen and Febbraio [15]. Myokines such as irisin, interleukin-6, interleukin-15, IGF-I, brain-derived neurotrophic factor (BDNF), and follistatin-related protein 1 are involved in insulin signaling and energy metabolism [16,17]. Furthermore, myokines mediate communication between muscle and adipose tissue, the liver, the brain, and other organs [16,17].

1.2. The liver and hepatokines

In conditions of overnutrition, augmented gluconeogenesis and dyslipidemia in the liver induces glucotoxicity and lipotoxicity. Hepatic lipid accumulation leads to subacute hepatic inflammation via nuclear factor κB (NFκB) activation by releasing proinflammatory cytokines such as interleukin-6 (IL-6), IL-1β, and tumor necrosis factor (TNFα) [18], although hepatic triglycerides accumulation does not induce insulin resistance and subclinical inflammation under certain conditions [19–21]. Moreover, hepatic steatosis induces endoplasmic reticulum (ER) stress, leading to the activation of c-Jun, Tumor-specific kinase (JNK), which can inhibit the phosphorylation of insulin receptor substrates-1 (IRS-1) [22]. Therefore, the liver plays a crucial role in the development of metabolic disorders. Analogous to the action of adipokines and myokines, the hepatokines produced by the liver regulate whole body energy homeostasis, and are now considered potential targets for the treatment of cardiometabolic disorders. Recently, Stefan and Häring systematically reviewed the role of hepatokines in metabolism [23].

2. Fetuin-A

Fetuin-A (also known as α2-HS-glycoprotein), a 64-kDa phosphorylated glycoprotein, is expressed predominantly in the liver [24]. Fetuin-A was identified as an endogenous inhibitor of insulin receptor tyrosine kinase in the liver and skeletal muscle of rodents [25]. Fetuin-A deficient mice showed improved insulin sensitivity, suggesting that fetuin-A has a major role in the regulation of insulin signaling [26]. Moreover, single nucleotide polymorphisms in human fetuin-A were associated with T2DM [27,28]. High levels of serum fetuin-A are predictable marker for the incidence of T2DM after adjusting for risk factors [29,30]. Stefan et al. demonstrated that serum fetuin-A concentrations are positively associated with hepatic steatosis measured using magnetic resonance spectroscopy (MRS) in humans [31]. Pioglitazone, an insulin sensitizing anti-diabetic drug of the thiazolidinedione class, significantly reduces circulating fetuin-A levels, accompanied by an improvement in visceral fat, glucose levels, blood pressure, and lipid profiles in overweight women with type 2 diabetes [33].

Fetuin-A plays an important role in palmitate-induced hepatic lipid accumulation in hepatocytes. Saturated free fatty acids, such as palmitate, contribute to the augmentation of fetuin-A expression through the activation of the NFκB-dependent pathway [34]. In addition, high glucose augments transactivation of fetuin-A expression levels by an ERK1/2-mediated pathway [35]. Fetuin-A stimulates inflammatory cytokines in monocytes and adipocytes, and suppresses adiponection, which is an adipokine with anti-inflammatory properties [36]. Our previous study showed that palmitate-induced fetuin-A expression stimulates triacylglycerol accumulation in hepatocytes and that adiponection inhibits hepatocellular expression via the adenosin monophosphate-activated protein kinase (AMPK)-NFκB pathway [37]. A recent study reported that fetuin-A serves as an adaptor protein for saturated fatty acid and consequently activates Toll-like receptor 4 (TLR4), triggering production of proinflammatory cytokines [38]. Human clinical data performed by Stefan and Häring also support this finding [39]. Therefore, fetuin-A induces an inflammatory response and insulin resistance, which may result in the development of T2DM [40].

However, the association between fetuin-A and CVD appears to be more complicated. Circulating fetuin-A levels are positively associated with markers of early atherosclerosis and components of metabolic...
syndrome in humans [41,42]. Weikert et al. demonstrated that high levels of serum fetuin-A can predict the incidence of myocardial infarction and ischemic stroke independent of other cardiovascular risk parameters [43]. In particular, a Mendelian randomization approach showed a causal relationship between serum fetuin-A levels and myocardial infarction risk suggesting that serum fetuin-A levels may be an effective predictive biomarker for CVD [44]. However, fetuin-A can bind with Ca²⁺ and inhibits ectopic calcification in the vasculature [45]. In studies of patients with chronic kidney disease (CKD), fetuin-A concentrations were inversely associated with vascular calcification, CV events, and mortality [46]. Ix et al. reported that fetuin-A levels are inversely associated with coronary artery calcification among community-living individuals without CVD [47]. Further research is needed to explore the exact influence of fetuin-A in atherosclerosis, vascular calcification, and CVD according to the diverse underlying clinical conditions.

3. Fibroblast growth factor 21 (FGF21)

FGF21, a 181-amino acid peptide hormone, acts as a potent metabolic regulator that is primarily secreted by the liver and to a lesser extent from adipose tissue and skeletal muscle [48,49]. The expression of FGF21 is induced in response to various kinds of stress, such as starvation, cold exposure, excess of nutrient, mitochondrial stress, and autophagy deficiency [49]. FGF21 is regulated by several transcription factors including peroxisome proliferator-activated receptor α (PPARα), PPARγ, retinoic acid receptor β (RAR)β, and carbohydrate responsive element-binding protein (ChREBP) [50,51]. FGF21 activity depends on cofactor β-Klotho, which enhances the ability of FGF receptors (FGFRs) to bind FGF21 [52]. β-Klotho is predominantly expressed in the liver, white adipose tissue, pancreas, and kidney [51,52]. FGF21 is a metabolic hormone with diverse beneficial effects on energy balance as well as glucose and lipid metabolism. FGF21-deficient mice show an impairment of glucose homeostasis and weight gain [53]. Moreover, FGF21-knockout (KO) mice fed a ketogenic diet demonstrate marked impairment in ketogenesis and develop hepatic steatosis [53]. Conversely, the administration of FGF21 decreases plasma glucose and triglyceride levels in both db/db and db/db mice without hypoglycemia or weight gain [54]. FGF21 also improves insulin sensitivity and ameliorates hepatic steatosis in diet-induced obesity (DIO) mice [55]. The overexpression of FGF21 suppresses hepatic lipogenesis through the inhibition of sterol regulatory element-binding protein 1c (SREBP1c) and fatty acid synthase (FAS) levels in HepG2 cells [56]. FGF21 increases the hepatic expression of peroxisome proliferator-activated receptor gamma coactivator protein 1α (PGC1α) during the adaptive starvation response [57]. Moreover, FGF21 modulates PGC1α and induces burning in white adipose tissue as a defense mechanism against hypothermia [58]. On the other hand, FGF21 improves the function and survival of β-cells through activation of the ERK1/2 and Akt pathways, which may contribute to the favorable effects of FGF21 on glucose homeostasis in diabetic animals [59]. FGF21 acts as a key mediator of the physiologic and pharmacologic effects of the PPARγ agonist rosiglitazone [60]. Therefore, FGF21 has the potential to be a promising target for T2DM because of its effect of reducing blood glucose independently of insulin [61]. However, paradoxical increases of FGF21 levels are observed in obesity [62], insulin resistance [63], T2DM [64], and NAFLD [65], despite the beneficial effects of FGF21 on glucose and lipid metabolism. Furthermore, in human differentiating preadipocytes, FGF21 has adiponectin-suppressive and leptin and interleukin-6 release-promoting effects [66]. Although the exact mechanism is not clear, “FGF21 resistance” may be provoked by obesity and insulin resistance in rodents and humans [67]. Fisher et al. reported that DIO mice respond poorly to exogenous FGF21 and that obesity is an FGF21-resistant state [68]. In a recent randomized clinical trial, treatment with LY2405319, an analog of FGF21, resulted in significant improvements in the dyslipidemia of obese human subjects with T2DM [69].

Recent studies have suggested a possible role of FGF21 in atherosclerosis and CVD. FGF21-deficient mice exhibited impaired cardiac function and cardiac hypertrophy, which was ameliorated by treatment with FGF21 [70]. Wu et al. reported that FGF21 ameliorated aortic plaques and prevented apoptosis in apoe (−/−) mice through attenuation of ER stress and improvement of dyslipidemia [71]. Furthermore, FGF21 has a protective effect on atherosclerosis through enhancement of cholesterol efflux via the induction of liver X receptor (LXR)α-mediated ATP binding cassette (ABC) A1 and G1 expression in THP-1 macrophage-derived foam cells [72]. Elevated FGF21 concentrations were associated with carotid intima-media thickness (IMT) in humans, independent of CVD risk factors [73]. We previously reported that FGF21 levels are significantly associated with brachial-ankle pulse wave velocity (baPWV) reflecting arterial stiffness [74]. Furthermore, Shen et al. recognized serum FGF21 level as an independent risk factor of coronary artery disease in multiple logistic regression analysis (OR = 2.98; 95% CI = 1.01–8.79; P = 0.05) [75].

4. Selenoprotein P

Selenoprotein P, a 42-kDa glycoprotein, is produced in the liver and plays an important role in the transport of selenium [76]. Misu et al. first identified selenoprotein P as a hepatokine associated with insulin resistance in humans using serial analysis of gene expression (SAGE) and DNA chip methods [77]. The administration of selenoprotein P impairs insulin signaling and glucose metabolism in both liver and skeletal muscle, whereas selenoprotein P-deficient mice demonstrate improved insulin resistance and glucose tolerance [77]. ER stress induced by carrageenan increases levels of selenoprotein P mRNA expression and insulin resistance, whereas AMPK activators ameliorates these changes in HepG2 cells [78]. Hellwege et al. reported that genetic variants in selenoprotein P gene were associated with the first phase insulin response and fasting insulin, supporting a role of selenoprotein P in insulin resistance [79]. We observed that circulating selenoprotein P concentrations are elevated in patients with T2DM and prediabetes [80]. Moreover, patients with NAFLD as well as those with visceral obesity exhibited increased selenoprotein P levels, suggesting that selenoprotein P is a novel biomarker for NAFLD [81]. On the other hand, we found that selenoprotein P exhibits an independent association with carotid IMT and high-sensitivity C-reactive protein (hsCRP), an indicator of systemic subclinical inflammation, even after adjusting for other confounding factors [80]. Ishikura et al. showed that selenoprotein P inhibits vascular endothelial growth factor (VEGF)-stimulated cell proliferation, tube formation, and migration in human umbilical vein endothelial cells (HUVECs) and that wound closure is impaired in mice overexpressing selenoprotein P [82]. Therefore, the authors suggested that selenoprotein P is a diabetes-associated hepatokine that impairs angiogenesis [82]. In our previous study, adiponectin ameliorated palmitate-induced insulin resistance by the inhibition of selenoprotein P in hepatocytes [83]. Moreover, Misu et al. demonstrated that circulating selenoprotein P levels are negatively associated with adiponectin in patients with T2DM [84], suggesting communication between adiponectin and selenoprotein P.

5. Angiopoietin-like protein 4 (ANGPTL4)

ANGPTL4, which is also classified as an adipokine and a myokine, is predominantly expressed in the liver, adipose tissue, and muscle [85–87]. ANGPTL4, which plays an important role in lipid storage and mobilization, is a powerful regulator of lipid metabolism [88]. The expression of ANGPTL4 can be changed by the nutritional state of human patients and animal models. ANGPTL4 is under transcriptional control by fatty acids (FA) and FA-activated PPARs [89]. ANGPTL4 suppresses lipoprotein lipase (LPL) activity and leads to lipolysis in adipose tissue [89]. Gray et al. reported that ANGPTL4 stimulates fasting-induced intracellular lipolysis by regulation of cAMP signaling in
adipocytes, suggesting that this protein may associate with diseases of abnormal lipolysis such as in insulin resistance [90]. In experimental in vivo tests, adenosinergic-modulated overexpression of ANGPTL4 decreased blood glucose levels and attenuated glucose tolerance to maintain glucose homeostasis. However, this also led to undesirable hyperlipidemia and hepatic steatosis in mice [91]. Serum ANGPTL4 concentrations were lower in patients with T2DM than in healthy controls, supporting the hypothesis that decreased ANGPTL4 might be a causative factor for T2DM [91].

ANGPTL4 is also expressed in vascular endothelial cells and may play an important role in the pathophysiology of atherosclerosis [92]. ANGPTL4 is involved in the regulation of angiogenesis, vascular permeability, oxidative stress, and the inflammatory response [92]. Adachi et al. reported that ANGPTL4 deficiency suppresses foam cell formation and protects against the development and progression of atherosclerosis [93]. However, Lichtenstein et al. showed that ANGPTL4 reduces macrophage activation and foam cell formation, and protects against saturated fat-induced inflammation [94]. In vivo injection of recombinant human ANGPTL4 reduced myocardial infarct size and the extent of non-reflow through the preservation of vascular integrity in mice and rabbits [95]. Furthermore, transgenic over-expression of ANGPTL4 prevented the development of atherosclerosis via the suppression of foam cell formation [96]. Plasma ANGPTL4 levels were negatively associated with carotid artery sclerosis measured using magnetic resonance imaging (MRI) [96]. Muendlein et al. reported that plasma ANGPTL4 concentrations as well as ANGPTL4 variants can predict future cardiovascular events during a mean follow-up period of 3.5 years [97]. However, Smart-Halajko et al. did not find any relationship between plasma ANGPTL4 levels and coronary heart disease risk in the Northwick Park Heart Study II [98]. Further research is needed to assess the potential of ANGPTL4 as a therapeutic target for atherosclerosis and CVD.

6. Leukocyte cell-derived chemotaxin 2 (LECT2)

LECT2 is a 16 kDa secretory protein that acts as an energy-sensing hepatokine. It was identified as a novel neutrophil chemotactic protein predominantly expressed in the adult and fetal liver [99]. Lu et al. reported that the infiltration of polymorphonuclear neutrophils and macrophages into the peritoneum after *E. coli* infection is significantly augmented in LECT2-treated mice [100]. LECT2, which regulates the homeostasis of natural killer T (NKT) cells, might be involved in the pathogenesis of hepatitis [101]. Okabe et al. suggested that serum LECT2 may be a potential biomarker for hepatocellular carcinoma [102]. LECT2 may be a link between obesity and insulin resistance in skeletal muscle. Lan et al. reported that the administration of recombinant LECT2 impairs insulin signaling through the JNK pathway in myocytes and that LECT2 deficiency in mice improves insulin sensitivity in skeletal muscle by activation of Akt phosphorylation [103]. The authors also showed a positive relationship between circulating LECT2 levels, body mass index (BMI), and insulin resistance in humans [103]. Okumura et al. showed that circulating LECT2 concentrations are significantly increased in patients with obesity and fatty liver [104]. Recently, we reported that LECT2 treatment significantly increases mamalian target of rapamycin (mTOR) phosphorylation, SREBP-1 cleavage, lipid accumulation, and insulin resistance in the HepG2 cells, which are all attenuated by treatment with JNK inhibitor [105]. Furthermore, we showed that LECT2 treatment induces proinflammatory cytokines and adhesion molecules through CD209-mediated JNK phosphorylation in HUVECs [106]. These results suggest that LECT2 may directly mediate the progression of hepatic steatosis and atherosclerosis.

7. Conclusion

Previous studies have shown that lipid accumulation in the liver is closely associated with visceral obesity, T2DM, and CVD, conditions with altered secretory patterns of hepatokines (See Table 1). Therefore, hepatokines have been suggested to be predictive biomarkers of NAFLD, T2DM, and CVD. Moreover, preclinical studies have shown that hepatokines have robust effect on hyperglycemia, dyslipidemia, and body weight in diverse animal models. These findings have motivated continuing efforts to investigate the potential of hepatokines as therapeutic targets for cardiometabolic diseases. For example, repressing the expression of hepatic fetuin-A, selenoprotein P, and LECT2 or stimulating the expression of FGF21 may contribute to the treatment of metabolic disorders. Furthermore, the discovery of novel hepatokines may provide important insights into cardiometabolic diseases such as T2DM and CVD, leading the way toward promising therapeutics.

**Author contributions**

Tae Woo Jung, Hye Jin Yoo, and Kyung Mook Choi drafted and finalized the manuscript.

**Conflicts of interest**

The authors declare they have no conflicts of interest.

**Transparency document**

The Transparency document associated with this article can be found, in online version.

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