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Implication of hepatokines in metabolic disorders and cardiovascular diseases

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ABSTRACT

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.

Contents

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

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Table 1
Implication of hepatokines in cardiometabolic disorders.

Hepatokine	Experimental study	Reference	Clinical study	Reference
Fetuin-A	Insulin resistance	[25,26]		
	T2DM	[35]	T2DM	[27–30]
	NAFLD	[34,37]	NAFLD	[31]
	Inflammation	[36,38,40]	Atherosclerosis	[41,42]
			Myocardial infarction	[43,44]
FGF21	Glucose homeostasis	[53]	T2DM	[61,64]
	NAFLD	[53,55,56]	Dyslipidemia	[69]
	Insulin resistance	[55]	Carotid IMT	[73]
	β-cell survival	[59]	Arterial stiffness	[74]
	Cardiac hypertrophy	[70]	Obesity	[62]
			Insulin resistance	[63]
			NAFLD	[65]
Selenoprotein P	Insulin resistance	[77,78,83]	Insulin resistance	[77,79]
	Angiogenesis	[82]	T2DM	[77,80]
			NAFLD	[81]
ANGPTL4	Lipid storage	[88]	T2DM	[91]
	Lipid mobilization	[88]	Carotid artery sclerosis	[96]
	Lipolysis	[89,90]		
	Insulin resistance	[90]		
	NAFLD	[91]		
	Glucose tolerance	[91]		
	Hyperlipidemia	[91]		
	Atherosclerosis	[92,93,96]		
	Inflammation	[94]		
	Myocardial infarct	[95]		
LECT2	Inflammation	[100,106]	Tumorigenesis	[102]
	Hepatitis	[101]	Insulin resistance	[103]
	Tumorigenesis	[102]	NAFLD	[104]
	Insulin resistance	[103,105]		
	NAFLD	[105]		

Abbreviation
FGF21; fibroblast growth factor 21.
ANGPTL4; angiopoietin-like 4.
LECT2; leukocyte cell-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, including 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 factorα (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. N-terminal 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 systemically 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 hepatic fetuin-A mRNA expression in mice [32]. We previously reported that 12 weeks of caloric restriction significantly decreases 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 adiponectin, 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 adiponectin inhibits hepatic fetuin-A 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