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.

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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

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 Ca^{2+} 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)

FGF, 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 rector-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 ob/ob 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 browning 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 inulin, 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, tubule 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, adenovirus-mediated 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* injection 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 A*kt* 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 mammalian 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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References

[1] M.M. Finucane, G.A. Stevens, M.J. Cowan, G. Danaei, J.K. Lin, C.J. Paciorek, G.M. Singh, H.R. Gutierrez, Y. Lu, A.N. Bahalim, F. Farzadfar, L.M. Riley, M. Ezzati, National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants, Lancet 377 (2011) 557–567.
[2] C.J. Stein, G.A. Colditz, The epidemic of obesity, J. Clin. Endocrinol. Metab. 89 (2004) 2522–2525.
[3] J.P. Despres, I. Lemieux, Abdominal obesity and metabolic syndrome, Nature 444 (2006) 881–887.
[4] N. Ouchi, J.L. Parker, J.J. Lugus, K. Walsh, Adipokines in inflammation and metabolic disease, Nat. Rev. Immunol. 11 (2011) 85–97.
[5] Q.M. Anstee, G. Targher, C.P. Day, Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis, Nat. Rev. Gastroenterol. Hepatol. 10 (2013) 330–344.
[6] V.G. Athyros, K. Tziomalos, N. Katsiki, M. Doumas, A. Karagiannis, D.P. Mikhailidis, Cardiovascular risk across the histological spectrum and the clinical manifestations of non-alcoholic fatty liver disease: an update, World J. Gastroenterol. 21 (2015) 6820–6834.
[7] N. Stefan, K. Kantartzis, J. Machann, F. Schick, C. Thamer, K. Rittig, B. Balletshofer, F. Machicao, A. Fritsche, H.U. Haring, Identification and characterization of metabolically benign obesity in humans, Arch. Intern. Med. 168 (2008) 1609–1616.
[8] E. Fabbrini, F. Magkos, B.S. Mohammed, T. Pietka, N.A. Abumrad, B.W. Patterson, A. Okunade, S. Klein, Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 15430–15435.
[9] A. Iroz, J.P. Couty, C. Postic, Hepatokines: unlocking the multi-organ network in metabolic diseases, Diabetologia 58 (2015) 1699–1703.
[10] G.S. Hotamisligil, Inflammation and metabolic disorders, Nature 444 (2006) 860–867.
[11] J.M. Olefsky, C.K. Glass, Macrophages, inflammation, and insulin resistance, Annu. Rev. Physiol. 72 (2010) 219–246.
[12] T. Kadowaki, T. Yamauchi, N. Kubota, K. Hara, K. Ueki, K. Tobe, Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome, J. Clin. Invest. 116 (2006) 1784–1792.
[13] N. Stefan, A.M. Hennige, H. Staiger, J. Machann, F. Schick, E. Schleicher, A. Fritsche, H.U. Haring, High circulating retinol-binding protein 4 is associated with elevated liver fat but not with total, subcutaneous, visceral, or intramyocellular fat in humans, Diabetes Care 30 (2007) 1173–1178.
[14] X. Ma, Z. Zhou, Y. Chen, Y. Wu, Y. Liu, RBP4 functions as a hepatokine in the regulation of glucose metabolism by the circadian clock in mice, Diabetologia 59 (2016) 354–362.
[15] B.K. Pedersen, M.A. Febbraio, Muscles, exercise and obesity: skeletal muscle as a secretory organ, Nat. Rev. Endocrinol. 8 (2012) 457–465.

[16] R.S. Ahima, H.K. Park, Connecting myokines and metabolism, Endocrinol. Metab. 30 (2015) 235–245.

[17] M. Catoire, S. Kersten, The search for exercise factors in humans, FASEB J. 29 (2015) 1615–1628.

[18] D. Cai, M. Yuan, D.F. Frantz, P.A. Melendez, L. Hansen, J. Lee, S.E. Shoelson, Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB, Nat. Med. 11 (2005) 183–190.

[19] K. Kantartzis, A. Peter, F. Machicao, J. Machann, S. Wagner, I. Konigsrainer, A. Konigsrainer, F. Schick, A. Fritsche, H.U. Haring, N. Stefan, Dissociation between fatty liver and insulin resistance in humans carrying a variant of the patatin-like phospholipase 3 gene, Diabetes 58 (2009) 2616–2623.

[20] N. Stefan, H.U. Haring, The metabolically benign and malignant fatty liver, Diabetes 60 (2011) 2011–2017.

[21] N. Stefan, M. Ramsauer, P. Jordan, B. Nowotny, K. Kantartzis, J. Machann, J.H. Hwang, P. Nowotny, S. Kahl, J. Harreiter, S. Hornemann, A.J. Sanyal, P.M. Stewart, A.F. Pfeiffer, A. Kautzky-Willer, M. Roden, H.U. Haring, S. Furst-Recktenwald, Inhibition of 11beta-HSD1 with RO5093151 for non-alcoholic fatty liver disease: a multicentre, randomised, double-blind, placebo-controlled trial, Lancet Diab. Endocrinol. 2 (2014) 406–416.

[22] M.J. Czaja, JNK regulation of hepatic manifestations of the metabolic syndrome, Trends Endocrinol. Metab. 21 (2010) 707–713.

[23] N. Stefan, H.U. Haring, The role of hepatokines in metabolism, Nat. Rev. Endocrinol. 9 (2013) 144–152.

[24] J.F. Trepanowski, J. Mey, K.A. Varady, Fetuin-A: a novel link between obesity and related complications, Int. J. Obes. 39 (2015) 734–741.

[25] S.T. Mathews, N. Chellam, P.R. Srinivas, V.J. Cintron, M.A. Leon, A.S. Goustin, G. Grunberger, Alpha2-HSG, a specific inhibitor of insulin receptor autophosphorylation, interacts with the insulin receptor, Mol. Cell. Endocrinol. 164 (2000) 87–98.

[26] S.T. Mathews, G.P. Singh, M. Ranalletta, V.J. Cintron, X. Qiang, A.S. Goustin, K.L. Jen, M.J. Charron, W. Jahnen-Dechent, G. Grunberger, Improved insulin sensitivity and resistance to weight gain in mice null for the Ahsg gene, Diabetes 51 (2002) 2450–2458.

[27] G. Andersen, K.S. Burgdorf, T. Sparso, K. Borch-Johnsen, T. Jorgensen, T. Hansen, O. Pedersen, AHSG tag single nucleotide polymorphisms associate with type 2 diabetes and dyslipidemia: studies of metabolic traits in 7,683 white Danish subjects, Diabetes 57 (2008) 1427–1432.

[28] A. Siddiq, F. Lepretre, S. Hercberg, P. Froguel, F. Gibson, A synonymous coding polymorphism in the alpha2-Heremans-schmid glycoprotein gene is associated with type 2 diabetes in French Caucasians, Diabetes 54 (2005) 2477–2481.

[29] J.H. Ix, C.L. Wassel, A.M. Kanaya, E. Vittinghoff, K.C. Johnson, A. Koster, J.A. Cauley, T.B. Harris, S.R. Cummings, M.G. Shlipak, Fetuin-A and incident diabetes mellitus in older persons, JAMA 300 (2008) 182–188.

[30] N. Stefan, A. Fritsche, C. Weikert, H. Boeing, H.G. Joost, H.U. Haring, M.B. Schulze, Plasma fetuin-A levels and the risk of type 2 diabetes, Diabetes 57 (2008) 2762–2767.

[31] N. Stefan, A.M. Hennige, H. Staiger, J. Machann, F. Schick, S.M. Krober, F. Machicao, A. Fritsche, H.U. Haring, Alpha2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans, Diabetes Care 29 (2006) 853–857.

[32] A. Ochi, K. Mori, M. Emoto, S. Nakatani, T. Morioka, K. Motoyama, S. Fukumoto, Y. Imanishi, H. Koyama, E. Ishimura, M. Inaba, Direct inhibitory effects of pioglitazone on hepatic fetuin-A expression, PLoS One 9 (2014) e88704.

[33] K.M. Choi, K.A. Han, H.J. Ahn, S.Y. Lee, S.Y. Hwang, B.H. Kim, H.C. Hong, H.Y. Choi, S.J. Yang, H.J. Yoo, S.H. Baik, D.S. Choi, K.W. Min, The effects of caloric restriction on fetuin-A and cardiovascular risk factors in rats and humans: a randomized controlled trial, Clin. Endocrinol. 79 (2013) 356–363.

[34] S. Dasgupta, S. Bhattacharya, A. Biswas, S. Majumdar, S. Mukhopadhyay, S. Ray, NF-kappaB mediates lipid-induced fetuin-A expression in hepatocytes that impairs adipocyte function effecting insulin resistance, Biochem. J. 429 (2010) 451–462.

[35] H. Takata, Y. Ikeda, T. Suehiro, A. Ishibashi, M. Inoue, Y. Kumon, Y. Terada, High glucose induces transactivation of the alpha2-HS glycoprotein gene through the ERK1/2 signaling pathway, J. Atheroscler. Thromb. 16 (2009) 448–456.

[36] A.M. Hennige, H. Staiger, C. Wicke, F. Machicao, A. Fritsche, H.U. Haring, N. Stefan, Fetuin-A induces cytokine expression and suppresses adiponectin production, PLoS One 3 (2008), e1765.

[37] T.W. Jung, B.S. Youn, H.Y. Choi, S.Y. Lee, H.C. Hong, S.J. Yang, H.J. Yoo, B.H. Kim, S.H. Baik, K.M. Choi, Salsalate and adiponectin ameliorate hepatic steatosis by inhibition of the hepatokine fetuin-A, Biochem. Pharmacol. 86 (2013) 960–969.

[38] D. Pal, S. Dasgupta, R. Kundu, S. Maitra, G. Das, S. Mukhopadhyay, S. Ray, S.S. Majumdar, S. Bhattacharya, Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance, Nat. Med. 18 (2012) 1279–1285.

[39] N. Stefan, H.U. Haring, Circulating fetuin-A and free fatty acids interact to predict insulin resistance in humans, Nat. Med. 19 (2013) 394–395.

[40] J. Heinrichsdorff, J.M. Olefsky, Fetuin-A: the missing link in lipid-induced inflammation, Nat. Med. 18 (2012) 1182–1183.

[41] T. Dogru, H. Genc, S. Tapan, F. Aslan, C.N. Ercin, F. Ors, M. Kara, E. Sertoglu, Y. Karslioglu, S. Bagci, I. Kurt, A. Sonmez, Plasma fetuin-A is associated with endothelial dysfunction and subclinical atherosclerosis in subjects with nonalcoholic fatty liver disease, Clin. Endocrinol. 78 (2013) 712–717.

[42] J.H. Ix, M.G. Shlipak, V.M. Brandenburg, S. Ali, M. Ketteler, M.A. Whooley, Association between human fetuin-A and the metabolic syndrome: data from the heart and soul study, Circulation 113 (2006) 1760–1767.

[43] C. Weikert, N. Stefan, M.B. Schulze, T. Pischon, K. Berger, H.G. Joost, H.U. Haring, H. Boeing, A. Fritsche, Plasma fetuin-a levels and the risk of myocardial infarction and ischemic stroke, Circulation 118 (2008) 2555–2562.

[44] E. Fisher, N. Stefan, K. Saar, D. Drogan, M.B. Schulze, A. Fritsche, H.G. Joost, H.U. Haring, N. Hubner, H. Boeing, C. Weikert, Association of AHSG gene polymorphisms with fetuin-A plasma levels and cardiovascular diseases in the EPIC-Potsdam study, Circ. Cardiovasc. Genet. 2 (2009) 607–613.

[45] K. Mori, M. Emoto, M. Inaba, Fetuin-A and the cardiovascular system, Adv. Clin. Chem. 56 (2012) 175–195.

[46] R. Mehrotra, Emerging role for fetuin-A as contributor to morbidity and mortality in chronic kidney disease, Kidney Int. 72 (2007) 137–140.

[47] J.H. Ix, R. Katz, I.H. de Boer, B.R. Kestenbaum, C.A. Peralta, N.S. Jenny, M. Budoff, M.A. Allison, M.H. Criqui, D. Siscovick, M.G. Shlipak, Fetuin-A is inversely associated with coronary artery calcification in community-living persons: the multi-ethnic study of atherosclerosis, Clin. Chem. 58 (2012) 887–895.

[48] J. Dushay, P.C. Chui, G.S. Gopalakrishnan, M. Varela-Rey, M. Crawley, F.M. Fisher, M.K. Badman, M.L. Martinez-Chantar, E. Maratos-Flier, Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease, Gastroenterology 139 (2010) 456–463.

[49] K.H. Kim, M.S. Lee, FGF21 as a stress hormone: the roles of FGF21 in stress adaptation and the treatment of metabolic diseases, Diab. Metab. J. 38 (2014) 245–251.

[50] K. Iizuka, J. Takeda, Y. Horikawa, Glucose induces FGF21 mRNA expression through ChREBP activation in rat hepatocytes, FEBS Lett. 583 (2009) 2882–2886.

[51] Y.C. Woo, A. Xu, Y. Wang, K.S. Lam, Fibroblast growth factor 21 as an emerging metabolic regulator: clinical perspectives, Clin. Endocrinol. 78 (2013) 489–496.

[52] G. Musso, M. Cassader, S. Cohney, S. Pinach, F. Saba, R. Gambino, Emerging liver-kidney interactions in nonalcoholic fatty liver disease, Trends Mol. Med. 21 (2015) 645–662.

[53] M.K. Badman, A. Koester, J.S. Flier, A. Kharitonenkov, E. Maratos-Flier, Fibroblast growth factor 21-deficient mice demonstrate impaired adaptation to ketosis, Endocrinology 150 (2009) 4931–4940.

[54] A. Kharitonenkov, T.L. Shiyanova, A. Koester, A.M. Ford, R. Micanovic, E.J. Galbreath, G.E. Sandusky, L.J. Hammond, J.S. Moyers, R.A. Owens, J. Gromada, J.T. Brozinick, E.D. Hawkins, V.J. Wroblewski, D.S. Li, F. Mehrbod, S.R. Jaskunas, A.B. Shanafelt, FGF-21 as a novel metabolic regulator, J. Clin. Invest. 115 (2005) 1627–1635.

[55] J. Xu, D.J. Lloyd, C. Hale, S. Stanislaus, M. Chen, G. Sivits, S. Vonderfecht, R. Hecht, Y.S. Li, R.A. Lindberg, J.L. Chen, D.Y. Jung, Z. Zhang, H.J. Ko, J.K. Kim, M.M. Veniant, Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice, Diabetes 58 (2009) 250–259.

[56] Y. Zhang, T. Lei, J.F. Huang, S.B. Wang, L.L. Zhou, Z.Q. Yang, X.D. Chen, The link between fibroblast growth factor 21 and sterol regulatory element binding protein 1c during lipogenesis in hepatocytes, Mol. Cell. Endocrinol. 342 (2011) 41–47.

[57] M.J. Potthoff, T. Inagaki, S. Satapati, X. Ding, T. He, R. Goetz, M. Mohammadi, B.N. Finck, D.J. Mangelsdorf, S.A. Kliewer, S.C. Burgess, FGF21 induces PGC-1alpha and regulates carbohydrate and fatty acid metabolism during the adaptive starvation response, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 10853–10858.

[58] F.M. Fisher, S. Kleiner, N. Douris, E.C. Fox, R.J. Mepani, F. Verdeguer, J. Wu, A. Kharitonenkov, J.S. Flier, E. Maratos-Flier, B.M. Spiegelman, FGF21 regulates PGC-1alpha and browning of white adipose tissues in adaptive thermogenesis, Genes Dev. 26 (2012) 271–281.

[59] W. Wente, A.M. Efanov, M. Brenner, A. Kharitonenkov, A. Koster, G.E. Sandusky, S. Sewing, I. Treinies, H. Zitzer, J. Gromada, Fibroblast growth factor-21 improves pancreatic beta-cell function and survival by activation of extracellular signal-regulated kinase 1/2 and Akt signaling pathways, Diabetes 55 (2006) 2470–2478.

[60] P.A. Dutchak, T. Katafuchi, A.L. Bookout, J.H. Choi, R.T. Yu, D.J. Mangelsdorf, S.A. Kliewer, Fibroblast growth factor-21 regulates PPARgamma activity and the antidiabetic actions of thiazolidinediones, Cell 148 (2012) 556–567.

[61] A. Kharitonenkov, A.C. Adams, Inventing new medicines: the FGF21 story, Mol. Metab. 3 (2014) 221–229.

[62] X. Zhang, D.C. Yeung, M. Karpisek, D. Stejskal, Z.G. Zhou, F. Liu, R.L. Wong, W.S. Chow, A.W. Tso, K.S. Lam, A. Xu, Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans, Diabetes 57 (2008) 1246–1253.

[63] P. Domingo, J.M. Gallego-Escuredo, J.C. Domingo, M. Gutierrez Mdel, M.G. Mateo, I. Fernandez, F. Vidal, M. Giralt, F. Villarroya, Serum FGF21 levels are elevated in association with lipodystrophy, insulin resistance and biomarkers of liver injury in HIV-1-infected patients, AIDS 24 (2010) 2629–2637.

[64] A.O. Chavez, M. Molina-Carrion, M.A. Abdul-Ghani, F. Folli, R.A. Defronzo, D. Tripathy, Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance, Diabetes Care 32 (2009) 1542–1546.

[65] Y. Yilmaz, F. Eren, O. Yonal, R. Kurt, B. Aktas, C.A. Celikel, O. Ozdogan, N. Imeryuz, C. Kalayci, E. Avsar, Increased serum FGF21 levels in patients with nonalcoholic fatty liver disease, Eur. J. Clin. Investig. 40 (2010) 887–892.

[66] L. Berti, M. Irmler, M. Zdichavsky, T. Meile, A. Bohm, N. Stefan, A. Fritsche, J. Beckers, A. Konigsrainer, H.U. Haring, M.H. de Angelis, H. Staiger, Fibroblast growth factor 21 is elevated in metabolically unhealthy obesity and affects lipid deposition, adipogenesis, and adipokine secretion of human abdominal subcutaneous adipocytes, Mol. Metab. 4 (2015) 519–527.

[67] M.J. Potthoff, S.A. Kliewer, D.J. Mangelsdorf, Endocrine fibroblast growth factors 15/19 and 21: from feast to famine, Genes Dev. 26 (2012) 312–324.

[68] F.M. Fisher, P.C. Chui, P.J. Antonellis, H.A. Bina, A. Kharitonenkov, J.S. Flier, E. Maratos-Flier, Obesity is a fibroblast growth factor 21 (FGF21)-resistant state, Diabetes 59 (2010) 2781–2789.

[69] G. Gaich, J.Y. Chien, H. Fu, L.C. Glass, M.A. Deeg, W.L. Holland, A. Kharitonenkov, T. Bumol, H.K. Schilske, D.E. Moller, The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes, Cell Metab. 18 (2013) 333–340.

[70] A. Planavila, I. Redondo, E. Hondares, M. Vinciguerra, C. Munts, R. Iglesias, L.A. Gabrielli, M. Sitges, M. Giralt, M. van Bilsen, F. Villarroya, Fibroblast growth factor 21 protects against cardiac hypertrophy in mice, Nat. Commun. 4 (2013) 2019.

[71] X. Wu, Y.F. Qi, J.R. Chang, W.W. Lu, J.S. Zhang, S.P. Wang, S.J. Cheng, M. Zhang, Q. Fan, Y. Lv, H. Zhu, M.K. Xin, Y. Lv, J.H. Liu, Possible role of fibroblast growth factor 21 on atherosclerosis via amelioration of endoplasmic reticulum stress-mediated apoptosis in apoE(−/−) mice, Heart Vessel. 30 (2015) 657–668.

[72] W. Shang, X. Yu, H. Wang, T. Chen, Y. Fang, X. Yang, P. Zhou, F. Nie, Q. Zhou, J. Zhou, Fibroblast growth factor 21 enhances cholesterol efflux in THP-1 macrophage-derived foam cells, Mol. Med. Rep. 11 (2015) 503–508.

[73] W.S. Chow, A. Xu, Y.C. Woo, A.W. Tso, S.C. Cheung, C.H. Fong, H.F. Tse, M.T. Chau, B.M. Cheung, K.S. Lam, Serum fibroblast growth factor-21 levels are associated with carotid atherosclerosis independent of established cardiovascular risk factors, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 2454–2459.

[74] S.J. Yang, H.C. Hong, H.Y. Choi, H.J. Yoo, G.J. Cho, T.G. Hwang, S.H. Baik, D.S. Choi, S.M. Kim, K.M. Choi, Effects of a three-month combined exercise programme on fibroblast growth factor 21 and fetuin-A levels and arterial stiffness in obese women, Clin. Endocrinol. 75 (2011) 464–469.

[75] Y. Shen, X. Ma, J. Zhou, X. Pan, Y. Hao, M. Zhou, Z. Lu, M. Gao, Y. Bao, W. Jia, Additive relationship between serum fibroblast growth factor 21 level and coronary artery disease, Cardiovasc. Diabetol. 12 (2013) 124.

[76] R.F. Burk, K.E. Hill, Selenoprotein P-expression, functions, and roles in mammals, Biochim. Biophys. Acta 1790 (2009) 1441–1447.

[77] H. Misu, T. Takamura, H. Takayama, H. Hayashi, N. Matsuzawa-Nagata, S. Kurita, K. Ishikura, H. Ando, Y. Takeshita, T. Ota, M. Sakurai, T. Yamashita, E. Mizukoshi, M. Honda, K. Miyamoto, T. Kubota, N. Kubota, T. Kadowaki, H.J. Kim, I.K. Lee, Y. Minokoshi, Y. Saito, K. Takahashi, Y. Yamada, N. Takakura, S. Kaneko, A liver-derived secretory protein, selenoprotein P, causes insulin resistance, Cell Metab. 12 (2010) 483–495.

[78] T.W. Jung, S.Y. Lee, H.C. Hong, H.Y. Choi, H.J. Yoo, S.H. Baik, K.M. Choi, AMPK activator-mediated inhibition of endoplasmic reticulum stress ameliorates carrageenan-induced insulin resistance through the suppression of selenoprotein P in HepG2 hepatocytes, Mol. Cell. Endocrinol. 382 (2014) 66–73.

[79] J.N. Hellwege, N.D. Palmer, J.T. Ziegler, C.D. Langefeld, C. Lorenzo, J.M. Norris, T. Takamura, D.W. Bowden, Genetic variants in selenoprotein P plasma 1 gene (SEPP1) are associated with fasting insulin and first phase insulin response in Hispanics, Gene 534 (2014) 33–39.

[80] S.J. Yang, S.Y. Hwang, H.Y. Choi, H.J. Yoo, J.A. Seo, S.G. Kim, N.H. Kim, S.H. Baik, D.S. Choi, K.M. Choi, Serum selenoprotein P levels in patients with type 2 diabetes and prediabetes: implications for insulin resistance, inflammation, and atherosclerosis, J. Clin. Endocrinol. Metab. 96 (2011) E1325–E1329.

[81] H.Y. Choi, S.Y. Hwang, C.H. Lee, H.C. Hong, S.J. Yang, H.J. Yoo, J.A. Seo, S.G. Kim, N.H. Kim, S.H. Baik, D.S. Choi, K.M. Choi, Increased selenoprotein p levels in subjects with visceral obesity and nonalcoholic fatty liver disease, Diab. Metab. J. 37 (2013) 63–71.

[82] K. Ishikura, H. Misu, M. Kumazaki, H. Takayama, N. Matsuzawa-Nagata, N. Tajima, K. Chikamoto, F. Lan, H. Ando, T. Ota, M. Sakurai, Y. Takeshita, K. Kato, A. Fujimura, K. Miyamoto, S. Kameo, Y. Okamoto, T. Takuwa, K. Takahashi, H. Kidoya, N. Takakura, S. Kaneko, T. Takamura, Selenoprotein P as a diabetes-associated hepatokine that impairs angiogenesis by inducing VEGF resistance in vascular endothelial cells, Diabetologia 57 (2014) 1968–1976.

[83] T.W. Jung, H.Y. Choi, S.Y. Lee, H.C. Hong, S.J. Yang, H.J. Yoo, B.S. Youn, S.H. Baik, K.M. Choi, Salsalate and adiponectin improve palmitate-induced insulin resistance via inhibition of selenoprotein P through the AMPK-FOXO1alpha pathway, PLoS One 8 (2013), e66529.

[84] H. Misu, K. Ishikura, S. Kurita, Y. Takeshita, T. Ota, Y. Saito, K. Takahashi, S. Kaneko, T. Takamura, Inverse correlation between serum levels of selenoprotein P and adiponectin in patients with type 2 diabetes, PLoS One 7 (2012), e34952.

[85] S. Kersten, S. Mandard, N.S. Tan, P. Escher, D. Metzger, P. Chambon, F.J. Gonzalez, B. Desvergne, W. Wahli, Characterization of the fasting-induced adipose factor FIAF, a novel peroxisome proliferator-activated receptor target gene, J. Biol. Chem. 275 (2000) 28488–28493.

[86] P. Zhu, Y.Y. Goh, H.F. Chin, S. Kersten, N.S. Tan, Angiopoietin-like 4: a decade of research, Biosci. Rep. 32 (2012) 211–219.

[87] H. Staiger, C. Haas, J. Machann, R. Werner, M. Weisser, F. Schick, F. Machicao, N. Stefan, A. Fritsche, H.U. Haring, Muscle-derived angiopoietin-like protein 4 is induced by fatty acids via peroxisome proliferator-activated receptor (PPAR)-delta and is of metabolic relevance in humans, Diabetes 58 (2009) 579–589.

[88] S. Mandard, F. Zandbergen, E. van Straten, W. Wahli, F. Kuipers, M. Muller, S. Kersten, The fasting-induced adipose factor/angiopoietin-like protein 4 is physically associated with lipoproteins and governs plasma lipid levels and adiposity, J. Biol. Chem. 281 (2006) 934–944.

[89] W. Dijk, S. Kersten, Regulation of lipoprotein lipase by Angptl4, Trends Endocrinol. Metab. 25 (2014) 146–155.

[90] N.E. Gray, L.N. Lam, K. Yang, A.Y. Zhou, S. Koliwad, J.C. Wang, Angiopoietin-like 4 (Angptl4) protein is a physiological mediator of intracellular lipolysis in murine adipocytes, J. Biol. Chem. 287 (2012) 8444–8456.

[91] A. Xu, M.C. Lam, K.W. Chan, Y. Wang, J. Zhang, R.L. Hoo, J.Y. Xu, B. Chen, W.S. Chow, A.W. Tso, K.S. Lam, Angiopoietin-like protein 4 decreases blood glucose and improves glucose tolerance but induces hyperlipidemia and hepatic steatosis in mice, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 6086–6091.

[92] L. Xu, Z.N. Guo, Y. Yang, J. Xu, S.R. Burchell, J. Tang, J. Zhang, J. Xu, J.H. Zhang, Angiopoietin-like 4: a double-edged sword in atherosclerosis and ischemic stroke? Exp. Neurol. 272 (2015) 61–66.

[93] H. Adachi, Y. Fujiwara, T. Kondo, T. Nishikawa, R. Ogawa, T. Matsumura, N. Ishii, R. Nagai, K. Miyata, M. Tabata, H. Motoshima, N. Furukawa, K. Tsuruzoe, J. Kawashima, M. Takeya, S. Yamashita, G.Y. Koh, A. Nagy, T. Suda, Y. Oike, E. Araki, Angptl 4 deficiency improves lipid metabolism, suppresses foam cell formation and protects against atherosclerosis, Biochem. Biophys. Res. Commun. 379 (2009) 806–811.

[94] L. Lichtenstein, F. Mattijssen, N.J. de Wit, A. Georgiadi, G.J. Hooiveld, R. van der Meer, Y. He, L. Qi, A. Koster, J.T. Tamsma, N.S. Tan, M. Muller, S. Kersten, Angptl4 protects against severe proinflammatory effects of saturated fat by inhibiting fatty acid uptake into mesenteric lymph node macrophages, Cell Metab. 12 (2010) 580–592.

[95] A. Galaup, E. Gomez, R. Souktani, M. Durand, A. Cazes, C. Monnot, J. Teillon, S. Le Jan, C. Bouleti, G. Briois, J. Philippe, S. Pons, V. Martin, R. Assaly, P. Bonnin, P. Ratajczak, A. Janin, G. Thurston, D.M. Valenzuela, A.J. Murphy, G.D. Yancopoulos, R. Tissier, A. Berdeaux, B. Ghaleh, S. Germain, Protection against myocardial infarction and no-reflow through preservation of vascular integrity by angiopoietin-like 4, Circulation 125 (2012) 140–149.

[96] A. Georgiadi, Y. Wang, R. Stienstra, N. Tjeerdema, A. Janssen, A. Stalenhoef, J.A. van der Vliet, A. de Roos, J.T. Tamsma, J.W. Smit, N.S. Tan, M. Muller, P.C. Rensen, S. Kersten, Overexpression of angiopoietin-like protein 4 protects against atherosclerosis development, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 1529–1537.

[97] A. Muendlein, C.H. Saely, A. Leiherer, P. Fraunberger, E. Kinz, P. Rein, A. Vonbank, D. Zanolin, C. Malin, H. Drexel, Angiopoietin-like protein 4 significantly predicts future cardiovascular events in coronary patients, Atherosclerosis 237 (2014) 632–638.

[98] M.C. Smart-Halajko, M.R. Robciuc, J.A. Cooper, M. Jauhiainen, M. Kumari, M. Kivimaki, K.T. Khaw, S.M. Boekholdt, N.J. Wareham, T.R. Gaunt, I.N. Day, P.S. Braund, C.P. Nelson, A.S. Hall, N.J. Samani, S.E. Humphries, C. Ehnholm, P.J. Talmud, The relationship between plasma angiopoietin-like protein 4 levels, angiopoietin-like protein 4 genotype, and coronary heart disease risk, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 2277–2282.

[99] S. Yamagoe, S. Mizuno, K. Suzuki, Molecular cloning of human and bovine LECT2 having a neutrophil chemotactic activity and its specific expression in the liver, Biochim. Biophys. Acta 1396 (1998) 105–113.

[100] X.J. Lu, J. Chen, C.H. Yu, Y.H. Shi, Y.Q. He, R.C. Zhang, Z.A. Huang, J.N. Lv, S. Zhang, L. Xu, LECT2 protects mice against bacterial sepsis by activating macrophages via the CD209a receptor, J. Exp. Med. 210 (2013) 5–13.

[101] T. Saito, A. Okumura, H. Watanabe, M. Asano, A. Ishida-Okawara, J. Sakagami, K. Sudo, Y. Hatano-Yokoe, J.S. Bezbradica, S. Joyce, T. Abo, Y. Iwakura, K. Suzuki, S. Yamagoe, Increase in hepatic NKT cells in leukocyte cell-derived chemotaxin 2-deficient mice contributes to severe concanavalin A-induced hepatitis, J. Immunol. 173 (2004) 579–585.

[102] H. Okabe, E. Delgado, J.M. Lee, J. Yang, H. Kinoshita, H. Hayashi, A. Tsung, J. Behari, T. Beppu, H. Baba, S.P. Monga, Role of leukocyte cell-derived chemotaxin 2 as a biomarker in hepatocellular carcinoma, PLoS One 9 (2014), e98817.

[103] F. Lan, H. Misu, K. Chikamoto, H. Takayama, A. Kikuchi, K. Mohri, N. Takata, H. Hayashi, N. Matsuzawa-Nagata, Y. Takeshita, H. Noda, Y. Matsumoto, T. Ota, T. Nagano, M. Nakagen, K. Miyamoto, K. Takatsuki, T. Seo, K. Iwayama, K. Tokuyama, S. Matsugo, H. Tang, Y. Saito, S. Yamagoe, S. Kaneko, T. Takamura, LECT2 functions as a hepatokine that links obesity to skeletal muscle insulin resistance, Diabetes 63 (2014) 1649–1664.

[104] A. Okumura, H. Unoki-Kubota, Y. Matsushita, T. Shiga, Y. Moriyoshi, S. Yamagoe, Y. Kaburagi, Increased serum leukocyte cell-derived chemotaxin 2 (LECT2) levels in obesity and fatty liver, Biosci. Trends 7 (2013) 276–283.

[105] H.J. Hwang, T.W. Jung, B.H. Kim, H.C. Hong, J.A. Seo, S.G. Kim, N.H. Kim, K.M. Choi, D.S. Choi, S.H. Baik, H.J. Yoo, A dipeptidyl peptidase-IV inhibitor improves hepatic steatosis and insulin resistance by AMPK-dependent and JNK-dependent inhibition of LECT2 expression, Biochem. Pharmacol. 98 (2015) 157–166.

[106] H.J. Hwang, T.W. Jung, H.C. Hong, J.A. Seo, S.G. Kim, N.H. Kim, K.M. Choi, D.S. Choi, S.H. Baik, H.J. Yoo, LECT2 induces atherosclerotic inflammatory reaction via CD209 receptor-mediated JNK phosphorylation in human endothelial cells, Metabolism 64 (2015) 1175–1182.