Review Article

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Role of hepatokines in non-alcoholic fatty liver disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is closely associated with metabolic diseases like type 2 diabetes and obesity. In recent decades, accumulating evidence has revealed that the hepatokines, proteins mainly secreted by the liver, play important roles in the development of NAFLD by acting directly on the lipid and glucose metabolism. As a member of organokines, the hepatokines establish the communication between the liver and the adipose, muscular tissues. In this review, we summarize the current understanding of the hepatokines and how they modulate the pathogenesis of metabolic disorders especially NAFLD.

Key words: non-alcoholic fatty liver disease, hepatokine, Fetuin A, FGF21, selenoprotein P

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, which affects approximately up to 33% adult population.[1,2] NAFLD is defined by the accumulation of lipids in the liver, in the absence of excessive alcohol consumption, viral hepatitis and other causes of hepatic steatosis, and encompasses a spectrum of conditions, including the simple hepatic steatosis, non-alcoholic steatohepatitis (NASH), hepatic fibrosis and cirrhosis.[3] Clinically, hepatic steatosis is referred to as a hepatic triglyceride content exceeding 5% of the total liver weight.[4] Although the pathogenesis of NAFLD still remained unclear, it is believed that NAFLD is a hepatic manifestation of the metabolic syndrome, and NAFLD significantly increases the risks of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), hyperuricemia and obesity.[5,6] As liver plays a central role in lipid metabolism and glycogen storage, the dysregulation of hepatic glycogen could directly lead to dysglycemia. In pathological conditions, the disturbance of lipid metabolism and defect of insulin signaling pathway gradually contribute to T2DM. In turn, glucose toxicity caused by hyperglycemia upregulates the activity of lipase and cholesteryl ester transfer protein, which further promotes lipogenesis, cholesterol transformation and ultimately, liver inflammation.[3]

In the recent decades, accumulating evidence revealed that liver may modulate the processes of NAFLD and other metabolic co-morbidities by secreting hepatokines, including fetuin-A, angiopoietin-related growth factor (AGF), fibrosis growth factor 21 (FGF 21), insulin-like growth factors (IGF), selenoprotein P (SeP), leukocyte derived chemotaxin 2 (LECT2), and so on.[7,8] Like the other members of organokines such as adipokine, myokine, hepatokine is defined as proteins or protein-like substances secreted mainly or exclusively by liver in an endocrine or paracrine way. In 2006, the Japanese scholar Hotamisligil put forward a hypothesis about metabolism and inflammation. From a genetic and evolutionary perspective, the liver, adipose and hematopoietic tissue maintain their developmental heritage and

share evolutionary underpinnings. There are overlapping pathways regulating both metabolic and immune functions through key regulatory molecules and signaling pathways like JNK, NF-kB pathways. He speculated that the immune response and metabolic regulation are highly integrated and dependent on each other. Dysfunction of central homeostatic mechanism can lead to a punch of chronic metabolic disorders, particularly NAFLD, T2DM and CVD. These diseases also trigger inflammatory responses through metabolic excess, leading to stress and inflammation.[9] In the micro-environment consisting of the secreted organokines, and cells like hepatocytes, hepatic macrophages and Kuffer cells, hepatokines play an essential role, mainly as liver-derived pro-inflammatory factors, to modulate the metabolic progress and pathological conditions of the body. In this review, we outline the recent updates on hepatokines and how they influence the pathogenesis of NAFLD.

FETUIN A

Fetuin A, also named α2-HS-glycoprotein (AHSG), is encoded by human *Ahsg* gene. Fetuin A is secreted primarily by the liver, and also by other tissues, including the placenta, adipose tissue and tongue.[10,11] Fetuin A was first discovered as an inhibitor of insulin receptor tyrosine kinase in liver and muscles; nowadays, it is thought to be an important mediator of metabolism, constituting a link between insulin resistance, obesity and NAFLD.[12] In 2002, the *Ahsg* gene defected mice was reported with improved insulin sensitivity, indicating its role in insulin regulation pathways.[13] Further, studies of genome-wide association studies (GWAS) revealed that single nucleotide polymorphisms (SNPs) of *Ahsg* gene was associated with the pathogenesis of T2DM.[14] Clinically, case control and cohort studies found that serum fetuin A level is significantly elevated in patients with T2DM, NAFLD and atherosclerosis, which makes fetuin A a potential marker of disease predicting and diagnosis.[15–18] In mice with hepatic steatosis, upregulated mRNA level of fetuin A was observed in the liver tissue. Excessive amount of free fatty acid and glucose activated NF-kB and ERK-1/ERK-2 signaling pathway respectively, causing the over-expression of fetuin A.[19] On the other hand, fetuin-A is reported with involvement in low-grade inflammation in NAFLD, acting as an endogenous ligand and scaffold protein for toll like receptor 4 (TLR4), which further promoted the lipid-induced pro-inflammatory response and insulin resistance.[20,21] Fetuin A was also found to greatly promote the secretion of pro-inflammatory cytokines in monocytes and adipose tissue and inhibit the expression of an insulin sensitizing protein, the adiponectin.[22] Moreover, lipid-induced expression of fetuin-A took a part in the induction of induce macrophage migration and polarization in adipose tissues.[10] Therefore, fetuin A participated in the pathogenesis in NAFLD by inducing insulin resistance and activating the inflammatory pathways, acting as a bridge between metabolic dysregulation and inflammatory responses.[23]

FIBROBLAST GROWTH FACTOR 21

Fibroblast growth factor 21 (FGF21) is a 209-amino acid protein mainly secreted by the liver, which can also be detected in pancreas, testis and adipose tissues.[24,25] Growing evidence suggested that FGF21 was a protective factor acting through glucose and lipid metabolism in an insulin independent manner.[26–28] According to the 'multiple strikes" theory of the pathogenesis of NAFLD, FGF21 modulates the process of oxidation stress, endoplasmic reticulum stress, mitochondria dysfunction and low-grade inflammation to ameliorate the development of NAFLD.[24,29,30]

FGF21 expression was positively induced by fasting through the activation of peroxisome proliferator-activated receptor (PPAR) alpha by non-esterified fatty acid. GWAS revealed that SNPs of *Fgf21* was associated with the pathogenesis of NFALD.[31] Further studies found that serum FGF21 was elevated in patients with NAFLD verified by MRI or ultrasonography.[26,32–34] Serum FGF21 level was positively correlated with hepatic liver fraction indicated by MRI and liver triglycerides content indicated by biopsy. The tendency of *Fgf21* mRNA in NAFLD patients was parallel with that of serum FGF21.[26,35] In the methionine-choline-deficient diet-induced mouse model of NASH, circulating FGF21 was elevated at an early phase, but decreased when severity of NASH aggravated.[36] Moreover, tumor necrosis factor alpha (TNFα) and oxidation related transcription factor NEF2 could inhibit the transcription of FGF21, leading to down-regulated expression of the protein.[37,38] Based on the evidence above, it is reasonable to believe that FGF21 is a promising biomarker in diagnosis and grading of NAFLD, and that elevated FGF21 in NAFLD patients is a protective feedback to lipotoxicity in lipid metabolism.[39] Consistent with this opinion, studies found that exogenous introduced FGF21 may help slow the progression of NAFLD. After purified FGF21 was injected, the obesity mice induced by high fat diet showed alleviated hepatic steatosis, decreased triglycerides level both in the liver and peripheral blood. The protective effect of FGF21 was partially achieved by down-regulating the expression of fatty acid synthase (FAS) and the transcription factor sterol regulatory element-binding protein 1 (SREBP-1).[40–42] In addition to modulating the lipid metabolism, FGF21 could also enhance the insulin sensitivity of NAFLD mice, decreasing the blood glucose.[43] FGF21-deficient mice showed an impaired glucose homeostasis and weight gain.[44] Moreover,

knockout of FGF-21 in murine models by adenovirus infection resulted in hepatic steatosis, hyperlipidemia and impairment of signaling pathways of lipid metabolism.[39,45] FGF21 is believed to be a metabolic hormone with diverse beneficial effects on energy balance as well as glucose and lipid metabolism, offering a promising strategy to treat NAFLD/NASH. Pre-clinical studies observed that a short-term FGF21 analogues (LY2405319) could effectively improve the insulin sensitivity and lower the serum lipidemia in ob/ob mice.[46,47] Patients with T2DM and obesity received the treatment of LY2405319 reached a similar conclusion. LY2405319 could significantly alleviate insulin resistance, overweight and obesity, and reduce adiponectin level in patients.[47] However, the efficacy of FGF21 in treating metabolic disorders needed to be verified by large-scale and multi-centered trials in the future.

SELENOPROTEIN P

Selenoprotein P (SeP), weighted 42KD, is also a glycoprotein mainly produced and secreted by liver and adipose tissue. Human SeP was encoded by gene *Sepp1*, located on chromosome 5q31.[48] SeP is a member of the selenoproteins, which plays an important role in the transport of selenium, carrying the selenium from liver to other organs like brain and testis.[49,50] It is notable that the N-terminal of the SeP protein has a thioredoxin domain with more than one selenocysteine residuals, which makes SeP an potential enzyme in redox reactions.[49] The earliest study found that sepp1 KO mice showed higher risk of neuropathies and infertility.[51] Misu and his colleagues first identified SeP as a hepatokine, which is associated with insulin resistance in humans by using serial analysis of gene expression and DNA chip methods.[52] They further found that both liver specific sepp1 KO mice and sepp1 siRNA treated hepatocytes showed alleviated insulin resistance. On the other hand, purified SeP protein was adopted to treat the mice model and cultured hepatocytes. The *in vivo* and *in vitro* studies collectively revealed that SeP might promote the muscular insulin resistance through the muscle adenosine monophosphate-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC).[52] In the recent decades, more focus was paid to the working mechanisms of SeP in metabolic disorders. The serum level of SeP was significantly higher in patients with T2DM, positively correlated with fast plasma glucose (FPG) and glycosylated hemoglobin A1c. Also, the *Sepp1* mRNA in the liver was positively correlated with the metabolic clearance rate, glucose infusion rate and FPG.[52] Similarly, in another study about the CVD patients, SeP was found to be positively correlated with the risk factors of CVD, including waist circumference, triglyceride level and thickness of carotid internal media,[53] but negatively correlated with the serum adiponectin level.[53] A Korean study reported that serum SeP was significantly higher in patients with NAFLD and that it was positively correlated with liver attenuation index under CT, HOMA-IR and visceral fat area. SeP showed a consistence variation tendency in the components of the metabolism disorders, which make it a potential biomarker in predicting NAFLD. Misu *et al.* further investigated the redox function of SeP, and found that SeP may induce excise resistance via its muscular receptor, low-density lipoprotein receptor-related protein 1 (LRP1). The SeP deficient mice showed longer "excise endurance" than the wildtype in the excise test. Meanwhile, the muscular reactive oxygen species (ROS), phosphorylation of AMPK and expression of peroxisome proliferative activated receptor γ coactivator-1α (PGC1-α) was observed to show distinct patterns between the two groups. However, in the treatment of the antioxidant acetylcysteine, the SeP deficient mice exhibited a low level of muscular ROS and shorter excise endurance. In vitro, the purified SeP protein was found to reduce the AMPK phosphorylation and PCG1-α expression through LRP1 receptor in the myocytes.[54] As a member of hepatokine, SeP establishes the crosstalk between the liver, the muscle and the adipose tissue. The existence of SeP-LRP1 axis offers a potential therapeutic target for excise sensitizing drugs, improve the efficacy of excise.

SEX HORMONE-BINDING GLOBULIN

Sex hormone-binding globulin (SHBG) is mainly expressed in the liver. The human SHBG locus is located on chromosome 17 p12-p13.[55,56] SHBG binds to the sex hormones and basically functions as a transporter for androgens and estrogens in the blood. However, the level of circulating SHBG has also been shown to be associated with glucose metabolism, quantity of the adipose tissue and metabolism disorders.[57,58] The SHBG level in the liver and peripheral was significantly lower in patients with hepatic steatosis, where serum SHBG was found to be negatively associated with insulin resistance and hyperinsulinemia.[59,60] SHBG level was also shown to be significantly lower in menopausal women patients with NAFLD verified by liver biopsy. After the normalization of age, waistline and BMI, SHBG was an independent risk factor for NAFLD.[61] Similar results were obtained in T2DM patients that they had lower serum SHBG than healthy controls.[62] Serum SHBG levels have been shown to be negatively correlated with the lipid content in the liver. Alleviation of fatty liver through lifestyle interventions resulted in the elevated serum levels of SHBG.[63] The correlation between fatty liver and SHBG has been later supported in subsequent studies.[58,64] A study suggested that adiponectin may decrease SHBG expression by activating AMPK signaling.[65] However, another study claimed that the association of SHBG and insulin resistance is

independent of adiponectin.[57] Moreover, the induction of TNFα in response to the activation of JNK and NF-kB signaling further suppressed the SHBG production in HepG2 cells, indicating that the lower expression of SHBG in NAFLD may be secondary to inflammation.[66] Recent studies showed that the overexpression of SHBG downregulated the lipogenesis by reducing key lipogenic enzymes and reduced the hepatic steatosis, indicating its protective role in NAFLD.[67,68] Therefore, further study is needed to elucidate the role of SHBG in insulin resistance and lipid metabolism.

ANGIOPOIETIN-RELATED GROWTH FACTOR

Angiopoietin-related growth factor (AGF) also named angiopoietin-related protein 6 (ANGPTL6), is encoded by the *Angptl6* gene. It is synthesized in the liver and secreted into the peripheral system.[69] In 2013, Oike *et al.* found a role of AGF in metabolic diseases. AGF KO mice showed obesity, insulin resistance and deposition of fat in the liver and muscle tissues. Overexpression of *Angptl6* in the liver by adenovirus infection resulted in increased blood AGF levels. In human studies, researchers have found that patients with T2DM had increased serum AGF levels.[70,71] In addition, AGF level has been shown to be positively correlated with serum biomarkers for insulin resistance, and negatively correlated with HDL. Moreover, it was found that AGF was elevated in the serum of patients with metabolic disorders, and that AGF may serve as an independent risk factor.[72]. Combining animal study and clinical case-control studies, Namkung *et al.* argued that the discrepancy between human phenotype and animal model may be attributed to AGF resistance.[72] A later study conducted by Kitazawa *et al.* found the inhibition of glycol-synthesis by AGF in hepatocytes was dose dependent. AGF may hinder the expression of glucose-6-phosphatase at the transcription and translation level. This regulatory process may involve the phosphatidylinositol and protein kinase B dependent nuclear export of FOXO1.[73] The role of AGF in the development of NAFLD is unclear, however, existing data suggest that AGF may act as a protective factor for the development of NAFLD.

CONCLUSION

NAFLD is becoming the most common liver disease worldwide, and the prevalence is predicted to skyrocket during the next decades.[74] NAFLD and its metabolic co-morbidities tremendously increase the economic cost of public health and welfare.[75] The hepatic steatosis on one hand aggravates the dysregulation of glucose and lipid metabolism, but also make the liver a hotbed for systemic inflammation. During the past two decades, massive studies have revealed that the hepatokine could engage into a network of organokines and modulate metabolisms and pathogenesis of metabolic disorders both in the liver and in distant tissues. Further studies are needed to elucidate the crosstalk between hepatokines and other organokines. The discovery of new hepatokines and further understanding of the working mechanisms of these proteins provide novel strategies to prediction and treatment of the metabolic diseases.

Conflict of Interest

None declared.

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