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Hepatokines as Biomarkers of Obesity-Associated Liver Pathophysiology: Deciphering Advances in Basic and Clinical Aspects

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Abstract

Hepatokines are specialized secretory proteins of the liver that play pivotal role in regulation of metabolic homeostasis as well as ensure crosstalk of liver to other organs. In recent years, the correlation of hepatokines and hepatic diseases has been exhibited, positively. Several stimuli, particularly hepatic steatosis provoke dysregulation in metabolic homeostasis and subsequently, pathogenesis of liver diseases that influence expression and release of hepatokines. In this review, we have interlinked the association of hepatic steatosis, a hallmark of obesity, to liver and liver-derived hepatokines. Furthermore, we summarized briefly the impact of several etiologically and epidemiologically important hepatokines, including Fetuin-A, fibroblast growth factor-21 (FGF-21), selenoprotein P, sexual hormone binding globulin (SHBG), angiopoietin like 4 (ANGPTL4) and leukocyte cell-derived chemotaxin (LECT2), in health and disease. Such hepatokines could serve as non-invasive biomarkers of early stages of liver pathogenesis and might contribute in improving patient safety profile for screening purposes and expediting drug development.

Keywords: Hepatokines; Obesity; Liver Pathophysiology; Liver Diseases; Cellular Crosstalk

Introduction

Obesity-associated physiological dysfunctions, including insulin resistance (IR) dyslipidemia, dysregulation of hepatic metabolic processes and exaggerated inflammatory events, impair integrity of liver, thus, result in liver pathophysiology [1]. Obesity provokes increased hepatic steatosis or fatty liver, leading to metabolic associated fatty liver disease (MAFLD) and/or non-alcoholic fatty liver disease (NAFLD). NAFLD-induced non-alcoholic steatohepatitis (NASH) is an active form, characterized by hepatic neuroinflammation and faster fibrosis progression that provokes hepatic pathophysiology to hepatocellular carcinoma (HCC). Therefore, obesity positively correlates with burden of liver-related morbidities and mortalities on health care system, worldwide. The incidence of NAFLD-related HCC is peaking in several Asia-Pacific regions with an increase in epidemics of obesity and diabetes (~30% of population). Similar

situation of prevailing incidence of obesity and diabetes was reported in Pakistan by Jafar and colleagues [2,3]. Thus, the increasing epidemic count of obesity and liver diseases proposes a health care concern in near future [4]. Indeed, liver histopathology and some other prognostic markers are gold standards for diagnosis of NAFLD-associated HCC [5], but estimation of disease state is still elusive.

The implications of NAFLD-induced hepatic pathophysiology have profound effects on secretions of hepatokines- proteins that are secreted from liver cells and influence metabolic processes. The hepatokines assist the communication of liver with other organs including, the brain, adipose tissues, and skeletal muscles via autocrine, paracrine and endocrine signaling, and transmit information regarding the metabolic status of the liver. Recently, several experimental and epidemiological studies have been documented the role of hepatokines in development of obesity and *vice versa*. Hepatokines are hormone-like secretory proteins are released from hepatocytes. Obesity-associated steatotic overload alters gene and protein expression in liver, thereby, exhibits clinical manifestations of liver pathophysiology in experimental models [1,6,7]. Moreover, hepatokines-related fluctuations in physiological states (fed, fasted, etc) impact on maintenance of metabolic homeostasis, thereby, altered expression levels of certain hepatokines are considered as biomarkers of metabolic dysfunction [8,9]. In this review, several emerging evidences of epidemiological and etiological studies have been considered about the role of hepatokines in regulation of Obesity-associated metabolic dysregularities in liver and *vice versa*. Currently, hepatokines have drawn attention in terms of novel targets to study the regulation of liver-derived energy homeostasis, so that fine tuning of interlinked pathways would be acclaimed for an appropriate therapeutic strategy.

Mechanistic Approaches for a Nexus among Obesity, Hepatokines and the Liver Disease

Obesity is primarily characterized by lipid overload along with chronic-low grade inflammation which ultimately contributes to various metabolic disorders, particularly MAFLD. MAFLD is an umbrella term that denotes a spectrum of liver pathophysiology ranging from metabolic steatohepatitis to MAFLD-related cirrhosis and HCC while involving altered gene and protein expressions at molecular level in the liver [10]. Accumulating evidences of omics-based techniques have been revealed that the liver encodes ~ 4000 proteins that show plausible role in homeostasis, hence, recognized as a centralized site for regulation of metabolic homeostasis of whole body [11-15]. Maintenance of homeostasis by liver is highly dependent on endocrine functions through which liver secrets several proteins, including hepatokines in systemic circulation and subsequently, enables inter-organ communication of liver [10,16]. The altered gene expression dynamically promote fluctuations in levels of hepatokines at disease states, including obesity, insulin resistance, MAFLD and NAFLD, reflecting important hepatokines-related roles in maintenance of metabolic homeostasis [8].

Latest research designs have been investigating the role of several old and/or newly identified hepatokines and related implications in regulation of liver health as well as hepatokines-organokines-axis [17,18]. The first indication (as per our knowledge) based on an experimental study reported that endoplasmic reticulum-associated protein synthesis deprived in obese translatome. Furthermore, polysome and related transcriptional profiling analyses also revealed about the down regulation of protein synthesis machinery, mitochondrial components and bile acid metabolism in liver of obese mouse [19]. In this context, another epidemiological study reported the decreased levels of selenoprotein P1 (SEPP1), a hepatokine, in patients of hepatitis C virus (HCV). However, SEPP1 levels were restored in patients after treatment, thus, proposing SEPP1 as a biomarker for diagnosis of HCV-induced HCC [20]. Hence, several hepatokines, including Fetuin-A, fibroblast growth factor-21 (FGF-21), selenoprotein P, sexual hormone binding globulin (SHBG), angiopoietin like 4 (ANGPTL4) and leukocyte cell-derived chemotaxin (LECT2) have been focused as well as studied to date. Nonetheless, comprehensive experimental and clinical research studies have investigated association of hepatokines levels in liver disease and related other comorbidities (Table 1).

Hepatokines	Model/clinical study	Expression	Outcome(s)	Reference
Fetuin-A and fetuin-B	Clinical study design (patients having donated liver tissue)	Upregulated	Altered glucose homeostasis and insulin signaling	[21]
Ectodysplasin A (EDA)	C57BL/6 mice and HepG2 cells to study NAFLD	Upregulated	EDA promoted lipogenesis in NAFLD	[22]
Fibroblast growth factor 21 (FGF-21) and fetuin-A	Double-blind randomized clinical trial of NAFLD patients	Upregulated	NAFLD induced expression of several genes, including FGF-21 and fetuin-A	[23]

LECT-2, FGF-21, ANGPTL4	Hepatocyte-specific PTEN (Phosphatase and tensin homolog) knockout mice	Upregulated	PTEN deficiency and steatosis altered the expression/secretion of hepatokines regulating insulin sensitivity in muscles and the lipid metabolism in adipose tissue	[24]
Growth differentiation factor 15 (GDF15)	Gdf15−/−, Nrf2−/− and wild-type C57BL/6J mice	Downregulated	Inflammatory signalling in myeloid cells was inhibited in a GDF15-dependent manner, by positive regulation of SHP-1 (PTPN6) phosphatase.	[25]
Epidermal growth factor receptor (EGFR)	Type 2 diabetic Japanese patient	Upregulated	Insuline resistance-induced aberrant levels of circulating soluble EGFR in plasma and upregulated gene expression of EGFR	[26]
selenoprotein P (SeP), SHBG, FGF21	A case control study of NAFLD in patients with polycystic ovary syndrome (PCOS)	Downregulation of SeP, SHBG and upregulation of FGF21	Altered levels of SeP, SHBG and FGF21	[27]
Tsukushi (TSK), a novel hepatokine	Clinical study design of NAFLD patients with and without diabetes	Upregulated	Altered levels of TSK in patients with and without diabetes and caused severity of liver fibrotic conditions	[28]

Table 1: Aspects of hepatokines as diagnostic biomarkers in liver disease and associated comorbidities.

Conclusion

Hepatic steatosis is a key player in provoking metabolic dysregulation and, ultimately ends up the severity of hepatic pathegenesis, ranging from NAFLD to HCC. Screening of hepatic manifestations at early stage disease still challenges health care system for diagnostic purposes, thereby, exhibiting negative correlation to selection of an effective therapeutic strategy. Whereas, liver biopsy is still benchmark as a gold diagnostic standard for staging of NAFLD that increases health risks, high cost and sometime, variations in samples. In past decade, a significant boon in clinical and applied research arena based on omics techniques highlighted the endocrine status of the liver in health and disease. Hepatokines play crucial and pivotal role in modulation of multiple pathways of energy homeostasis, however, altered levels of such hepatokines are confined to indication of specific disease. Indeed, hepatokines can serve as an early non-invasive biomarkers in comparison to traditional diagnostic techniques for screening of NAFLD and NAFLD-induced hepatic pathogenesis while enabling personalized medicine, improving patient safety and expediting drug development.

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