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Review

The implication of hepatokines in metabolic syndrome

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ABSTRACT

Hepatokines are liver–derived proteins with equivocal roles in metabolic syndrome (MetS). These proteins have prominent role in pathogenesis of MetS component such as obesity, insulin resistance, dyslipidemia and hypertension. The identification and functional characterization of hepatokines may provide significant insights that could help in better understanding of MetS pathogenesis. Fetuin-A, Hepatocyte-derived fibrinogen-related protein 1, Fibroblast growth factor 21, Angiopoietin–related growth factor, Selenoprotein-P, Angiopoietin like proteins, Leukocyte cell-derived chemotaxin 2 are regarded as the most significant hepatokines. We describe recent data on these new hormones in progression of MetS. Understanding of the accurate role of these proteins in pathophysiology of MetS can help improving prevention and treatment of this syndrome.

1. Introduction

The liver has major function in regulation of systemic metabolism and energy hemostasis [1]. Hepatokines, liver–derived proteins, are new hormones with equivocal roles in metabolic syndrome (MetS) [1]. They may control energy hemostasis by the regulation of glucose and lipid metabolism [2]. The identification and functional characterization of hepatokines may provide significant insights that could help in better understanding of MetS pathogenesis. Hepatokines may be attractive target for the diagnosis and treatment of obesity and related disease.

Fetuin-A (AHSG), as a hepatokine, involves in insulin resistance (IR) via inhibition of insulin receptor and pro-inflammatory cytokine expression. This protein decreases adiponectin expression, a significant protein against metabolic syndrome [3], in adipocytes and monocytes [4,5]. Fetuin-A has positive association with liver fat accumulation, endothelial dysfunction, sub-clinical atherosclerosis [6–9] and negative association with insulin sensitivity [10]. The gene locus for this protein is 3q27 which is linked to diabetes and MetS [11]. Human single nucleotide polymorphisms in fetuin-A is associated with type-2 diabetes mellitus (T2DM) [12]. The plasma high levels of fetuin-A which are reported in obesity, MetS and T2DM [2], are foreseeable marker for T2DM incidence after adjusting for risk factors [12]. Caloric restriction significantly reduces plasma level of fetuin-A [13], also pioglitazone, an antidiabetic drug, decreases mRNA expression of fetuin-A in hepatic mice [14]. Exercise training has shown different effects on serum fetuin-A level: 3 months aerobic exercise training can decrease fetuin-A serum levels in T2DM regarding to decreased waist circumference (WC) and weight whereas increased adiponectin levels [15]; In obese old subject, this lowering level may refer to improvement in IR [16]. As well, increasing in fetuin-A serum levels after 6 months aerobic training plus weight loss program in healthy overweight/obese old men was observed that was referred to increase in aerobic capacity and cardio-protective features of exercise intervention [17]. This hepatokine may be an appropriate target for development of treatment strategy for T2D [2].

Hepatocyte-derived fibrinogen-related protein 1 (HFREP1, also called Fgl1 or hepassocin), a novel hepatokine, involved in development of IR via ERK1/2 dependent mechanisms [18]. This protein is expressed in adipose tissue and regulates lipid metabolism [19]. HFREP1 plasma levels have independent association with FPG, HOMA-IR, prediabetes and diabetes [18]. It is suggested that high level of HFREP1 may be a risk factor for IR and diabetes.

Fibroblast growth factor 21 (FGF-21) is considered as a strong metabolic regulator [20], a necessary hormone for adaptive starvation [21], a myokine and an adipokine [10]. FGF-21 regulates lipid and carbohydrate metabolism also affects oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction [22–25].

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FGF-21 has positive effect on weight loss and improvement in lipid profile [26]. This hepatokine up-regulates GLU-1 in human skeletal muscle. FGF-21 has positive correlation with body mass index (BMI) and fasting insulin in T2D [26]. Also, FGF-21 analog (LY2405319) significantly improved dyslipidemia in obese patients with T2DM and has favorite effect on body weight, fasting insulin and adiponectin level [27]. Some studies suggested the role of FGF-21 as a significant mediator of PPAR-γ actions [28], that is important in metabolic balance [29]. Also, FGF-21 has role in modulation of peroxisome proliferator-activated receptor gamma coactivator protein 1 alpha (PGC-1α) and induction of browning in white adipose tissue [30]. From this point, it seems that there is a crosstalk between FGF-21 and Irisin as a myokine with prominent function in metabolic disorder [31]. In MetS, patient's nutritional statues has effect on FGF-21 level [32]. However, some studies indicated that FGF-21 suppressed adiponectin and promoted leptin and IL-6 release in differentiating preadipocytes [33]. Some MetS components indicated the relevance with this hepatokine; hsCRP (best defined biomarker of inflammation) has significant association with FGF-21 in diabetic patients [34] and TNF-α (a pro inflammatory cytokine) may decrease transcription and release of FGF-21 [35,36]. Plasma levels of FGF-21 are independently associated with hypertension [37]; however, the mechanisms are not known.

Angiopoietin–related growth factor (AGF) is another hepatokine which may have significant role in lipid and carbohydrate metabolism [38]. Animal studies demonstrated that AGF deficiency associated with obesity, IR and lipid accumulation in liver and skeletal muscle [22]. In vitro analysis denoted that AGF decreased hepatic gluconeogenesis [39]. On the other hand, human studies indicated that serum level of this hepatokine increased in diabetic [40,41] and MetS patients [42]. Also AGF has positive correlation with IR marker and negative correlation with HDLc plasma level [40].

The other hepatokine is Selenoprotein-P [43]. Diabetic, Non-alcoholic Fatty Liver Disease and visceral obesity patients had high level of SeP [10]. The high levels of SeP are significantly associated with IR, WC, hsCRP, triglyceride level and carotid intima thickness [44]. However the other studies reported that SeP plasma level were reduced in MetS patients with cardiovascular disease [45]. Also high levels of SeP have independent association with decreased risk of MetS in children [46]. Recently, it is showed that adiponectin and salsalate have anti-diabetic effect in hepatocytes by inhibition of SeP via AMPK–Forkhead box protein O1α (FOXO1 α) pathway [47]. The serum level of SeP showed negative association with adiponectin serum level in T2DM patients [48]. The studies suggested that SeP may be suitable purpose for management of IR-associated disease [38].

The Angiopoietin like proteins (ANGPTL 1–8), as a group of secreted glycoprotein, have emerged as important regulators of plasma lipid metabolism [49]. Angiopoietin-like protein 4 (ANGPTL4) is mainly expressed in the liver, adipose tissue and muscle [12]. Animal researches indicated that ANGPTL4 plays prominent function in lipid metabolism via lipid storage and mobilization [50]. Fasting, nutritional state and exercise have effects on ANGPTL4 expression and plasma level [51]. Also fatty acids and fatty acid activated PPARs controls transcription of ANGPTL4 [52]. ANGPTL4 provokes intercellular lipolysis induced by fasting via cAMP signaling regulation in adipocytes. This hepatokine may be associated with IR as an abnormal lipolysis disorder [53]. In vivo studies suggested that overexpression of ANGPTL4 involved in maintenance of glucose tolerance, but this caused hyperlipidemia and hepatic steatosis [54]. The serum level of ANGPTL4 decreased in T2DM patients so it is possible that low level of this protein may be a causative factor for T2DM [54]. AGPTL4 has role in regulation of oxidative stress and inflammatory response [55].

ANGPTL8 (Also named as betatrophin, lipasin, RIFL and TD26) is a novel hepatokine which plays role in regulating lipid metabolism [56]. Some studies revealed negative association between ANGPTL8 and HDL-cholesterol [57,58] and positive association with triglyceride level [59,60]. It is indicated that these effects are mediated via inhibition of LPL (in collaboration with ANGPTL3) and increase in VLDL secretion in liver [61]. This hepatokine is positively correlated with hsCRP and is associated with increased incidence of MetS [62]. ANGPTL8 plasma level increased in T2D and pre-diabetic patients [56], however some studies indicated inconsistent results [63–65]. Some of discrepancies are resulted from ELISA kits [61]. In MetS [62] and dyslipidemia patients [66], ANGPTL8 levels were associated with biomarkers of renal function and hsCRP. The studies identified that ANGPTL8 involved in IR [67]. The high level of ANGPTL8 and ANGPTL4 are seen in hypertension patients [68]. ANGPTLs are regarded as potential therapeutic target in dyslipidemia.

Leukocyte cell-derived chemotaxin 2 (LECT2) as an energy-sensing protein [69], is associated with hepatic inflammatory signaling and natural killer T cells homeostasis [70,71]. This hepatokine may associate with obesity and IR in skeletal muscle [10,69]. The studies reported that a positive association between plasma LECT2 levels, BMI and IR, HbA1C [69], obesity and fatty liver [72]. High fat diet and exercise have opposite effects on serum and hepatic level of LECT2 (increase and decrease, respectively) via AMPK pathway (blocking and activation, respectively) [69]. In vitro studies showed that LECT2 treatment enhanced pro-inflammatory cytokines and adhesion molecules expression [73]. Also this protein increased mammalian target of rapamycine (mTOR) phosphorylation, lipid accumulation and IR in HepG2 cells [74].

2. Concluding remarks

Hepatokines, secretory proteins produced in the liver, have significant association with MetS component such as obesity, IR, dyslipidemia and hypertension. Most hepatokines are novel proteins and several questions must be answered. Some hepatokines have cross-talk with other organokines such as adipokines or myokines. Further studies are required to clarify exact role of these proteins in MetS and diabetes. Better understanding of the accurate role of these proteins in pathophysiology of MetS development will lead to improved prevention or even treatment of this syndrome.

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