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REVIEW ARTICLE

Hepatokines: unveiling the molecular and cellular mechanisms connecting hepatic tissue to insulin resistance and inflammation

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Abstract

Insulin resistance arising from Non-Alcoholic Fatty Liver Disease (NAFLD) stands as a prevalent global ailment, a manifestation within societies stemming from individuals' suboptimal dietary habits and lifestyles. This form of insulin resistance emerges as a pivotal factor in the development of type 2 diabetes mellitus (T2DM). Emerging evidence underscores the significant role of hepatokines, as hepatic-secreted hormone-like entities, in the genesis of insulin resistance and eventual onset of type 2 diabetes. Hepatokines exert influence over extrahepatic metabolism regulation. Their principal functions encompass impacting adipocytes, pancreatic cells, muscles, and the brain, thereby playing a crucial role in shaping body metabolism through signaling to target tissues. This review explores the most important hepatokines, each with distinct influences. Our review shows that Fetuin-A promotes lipid-induced insulin resistance by acting as an endogenous ligand for Toll-like receptor 4 (TLR-4). FGF21 reduces inflammation in diabetes by blocking the nuclear translocation of nuclear factor-κB (NF-κB) in adipocytes and adipose tissue, while also improving glucose metabolism. ANGPTL6 enhances AMPK and insulin signaling in muscle, and suppresses gluconeogenesis. Follistatin can influence insulin resistance and inflammation by interacting with members of the TGF-β family. Adropin show a positive correlation with phosphoenolpyruvate carboxykinase 1 (PCK1), a key regulator of gluconeogenesis. This article delves into hepatokines' impact on NAFLD, inflammation, and T2DM, with a specific focus on insulin resistance. The aim is to comprehend the influence of these recently identified hormones on disease development and their underlying physiological and pathological mechanisms.

Keywords Diabetes · Hepatokines · Inflammation · Insulin resistance · Liver · Obesity

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
T2DM	Type 2 diabetes mellitus
TLR-4	Toll-like receptor 4
FGF-21	Fibroblast growth factor 21
ANGPTLs	Angiopoietin-like proteins
GDF15	Growth/Differentiation Factor-15
AMPK	Adenosine monophosphate-activated protein kinase
GLUT4	Glucose transporter type 4
MAPKs	Mitogen-activated protein kinases
JNK	c-Jun N-terminal kinases
ERK5	Extracellular signal-regulated kinases 5
IRS1	insulin receptor substrate 1
mTOR	Mammalian target of rapamycin
Fet A	Fetuin A
NF-κB	Nuclear factor-κB
WAT	white adipose tissue
LPLs	Lipoprotein lipase gene
FAK	Focal adhesion kinase
IL-6	Interleukin 6
ICAM-1	Intercellular adhesion molecule 1
VLDLs	Very-low-density lipoproteins

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LXR	Liver X receptor
PPAR	Peroxisome proliferator-activated receptor
FFA	Free fatty acid
CVD	Cardiovascular diseases
G6P	glucose-6-phosphatase
GH	Growth hormone
HDL	High-density lipoprotein
ACC	AMPK-acetyl coenzyme A carboxylase
NASH	non-alcoholic steatohepatitis
MIC-1	Macrophage inhibitory cytokine-1
GDNF	Glial cell-derived neurotrophic factor
UPR	unfolded protein response
MCP-1	Monocyte chemoattractant protein-1
RTK	Receptor tyrosine kinase
HMGB1	High mobility group box protein 1
PAMPs	Pathogen-associated molecular patterns
TGF-β	Transforming growth factor-β
IGF-1	Insulin-like growth factor 1
FSH	Follicle-stimulating hormone
TNF-α	Tumor Necrosis Factorα
CHM2	Chondromodulin II
BMI	Body mass index
HFREP1	Hepatocyte-derived fibrinogen-related protein 1
IL	Interleukin
EC	Extracellular calcium
TY	Thyroglobulin-like
CRP	C-reactive protein
NO	Nitric oxide
GHR	GH receptor
JAK2	Janus Kinase 2
BAT	Brown Adipose Tissue
SNS	Sympathetic nervous system
HFD	High-fat diet
CPT1α	Carnitine palmitoyltransferase-1α
ChREBP	carbohydrate response element binding protein
TSK	Tsukushi
LCN-13	Lipocalin-13
HSL	Hormone-sensitive lipase
PKA	Protein Kinase A
HUVEC	Human Umbilical Vein Endothelial CellsActR: Activin A receptors, PCK1:Phosphoenolpyruvate carboxykinase 1
LBP	Lipopolysaccharide binding protein
PEPCK	Phosphoenolpyruvate carboxykinase
LPS	Lipopolysaccharide
G6PC	Glucose-6-phosphatase catalytic subunit

Introduction

The extensive impact of insulin resistance caused by non-alcoholic fatty liver disease (NAFLD) is highlighted by its global prevalence. This condition is a result of people's less-than-ideal food choices and lifestyle trends [1]. Among the many risk factors for developing type 2 diabetes mellitus (T2DM), insulin resistance due to NAFLD stands out [2]. It has been established that hepatokines are liver-secreted hormone-like substances. Despite their role in metabolism; recent findings suggest the participation of some these hepatokines, as endocrine messengers in the development of insulin resistance and ultimately, type 2 diabetes. [3]. Hepatokines constitute a category of substances released by the liver that function in the regulation of metabolism beyond hepatic tissues. Their principal roles include influencing adipocytes, pancreatic cells, muscles, and the brain, thereby exerting a substantial impact on body metabolism through signaling to target tissues [4, 5].

Within this comprehensive review, we delve into the intriguing realm of the most important hepatokines, each wielding a distinctive influence. These remarkable substances wield their effects by modulating the quantity of liver insulin receptors, exemplified by activin E [6], orchestrating a surge in glucose overload within liver or muscle cells, as demonstrated by Fibroblast growth factor 21 (FGF21) [7]. Furthermore, hepatokines such as Angiopoietin-like proteins (ANGPTLs) [8] orchestrate a metabolic shift towards fat.

As well as, hepatokines could potentially influence the molecular mechanisms that result in inflammation within the liver, adipose tissues, or muscles, for instance like Growth/Differentiation Factor-15 (GDF15), intricately navigate inflammatory pathways. This exploration illuminates the captivating interplay of hepatokines, unraveling their multifaceted roles in pathophysiological mechanisms [9]. In this regards, this article endeavors to unravel the intricacies of hepatokines, delving into their impact on NAFLD, inflammation, and ultimately, T2DM, with a specific emphasis on the intricate dynamics of insulin resistance. Through this exploration, we aim to elucidate the influence of these recently unveiled hormones on the pathogenesis of the mentioned diseases, offering valuable insights into their physiological mechanisms.

Insulin resistance, inflammation and hepatokines

As mentioned before, new research indicates that hepatokines may play a role as endocrine messengers in the progression of insulin resistance and, ultimately, the development

of T2DM [3]. Insulin resistance denotes a diminution in the responsiveness of tissues to insulin, a hormone pivotal in facilitating glucose movement to muscles, adipose tissues, and the liver [10]. The impediment of insulin signal transduction, primarily attributed to mutations and polymorphisms in insulin receptors [11], stands as a predominant cause of insulin resistance. Another mechanism that might lead to insulin resistance is disruption of lipid storage in the skeletal muscles and liver. This insulin resistance has been linked to a number of metabolic disorders, including T2DM, atherosclerosis, and NAFLD [12].

Insulin resistance may manifest at multiple junctures along the intricate insulin signaling pathway, exerting a direct influence on the modulation of glucose levels, protein synthesis, and the onset of T2DM along with its associated complications. The intricacies of insulin resistance are elucidated through diverse molecular mechanisms [2, 13, 14].

On the other hand, hepatokines are acknowledged as a category of hormones instrumental in the physiological modulation of inflammation. The ensuing instances elucidate three scenarios wherein hepatokines influence the molecular pathways underpinning inflammation and insulin resistance. Illustratively, fetuin-A (FetA) facilitates the development of lipid-induced insulin resistance through its role as an endogenous ligand for TLR-4 [15–18]. Moreover, this protein exerts a pronounced impact on expediting the assimilation of exogenous fatty acids into cellular triglycerides [19]. Functioning as an upstream modulator, FetA plays a regulatory role in the polarization of M1 macrophages and the activation of TLR4 induced by free fatty acids in adipocytes. Consequently, FetA emerges as a potential novel therapeutic target for addressing T2DM mellitus and inflammation associated with obesity [20, 21]. Recent investigations have associated FGF21 with a spectrum of anti-inflammatory effects, contributing to the expanding body of research elucidating its advantageous implications for metabolic processes [7, 21]. Notably, FGF21 mitigates inflammation in diabetes by impeding the nuclear translocation of nuclear factor-κB (NF-κB) in adipocytes and adipose tissue under insulin-resistant conditions, concurrently augmenting glucose metabolism [7, 22].

Hepatic function and secretion: insights into essential dynamics

The energy metabolism of mammals intricately hinges upon nutrient intake, wherein the liver assumes a pivotal responsibility for assessing and orchestrating the utilization of these nutrients across various tissues. Glucose, along with other monosaccharides, stands as the predominant substrate for metabolism in living organisms. The liver, in its regulatory capacity, modulates blood glucose levels through dynamic interactions with the pancreas, which releases insulin to sustain a consistent blood glucose concentration. Furthermore, during phases of satiety, the liver actively assimilates blood glucose, converting and storing it in the form of glycogen [23].

Findings from proteomic studies involving both human subjects and rodents indicate that around 40% of the proteins originate from hepatic sources [24, 25]. With the help of hormones like hepatokines, myokines, adipokines, and neurokines, the liver is able to interact with other organs. These hormones elicit physiological effects, contributing to conditions such as atherosclerosis and insulin resistance [26]. The dynamic modulation of hepatokine levels during the evolution and manifestation of metabolic disorders significantly influences metabolic processes. Understanding the dynamic interactions between hepatokines and other organs is essential not only for unraveling their diverse physiological roles and potential implications in systemic health, but also for revealing metabolic disorders significantly influences metabolic processes [5, 27]. In this regard, the following information, summarized in Table 1, furnishes a comprehensive overview of diverse hepatokines and their influence on critical physiological aspects such as insulin resistance, liver function, lipid metabolism, metabolic conditions, and lifestyle factors.

Angiopoietin-like proteins (ANGPTL)

They derive their nomenclature from the resemblance of their protein domains to the angiopoietin family. These glycoproteins, secreted by hepatocytes, operate as vascular growth factors. Notably, a coiled-coil domain in their N-terminal facilitates subunit binding and the assembly of homo-oligomers. Furthermore, they feature a fibrinogen-like domain in their C-terminal, which binds to the Tie2 receptor, endowing them with a structural similarity to angiopoietin proteins [28, 29]. As a physiological function, these hepatokines assume a pivotal role in the modulation of white adipose tissue (WAT) function and the regulation of the lipoprotein lipase gene (LPLs) expression [30]. Located on the inner surface of capillaries, lipoprotein lipase is accountable for the hydrolysis of triglycerides into fatty acids, subsequently releasing them into the tissues that lipoproteins aim to reach [31]. The Golgi system experiences regulation by ANGPTL1-8, exerting inhibitory effects on LPLs expression at the post-translational level [30]. Within the ANGPTL protein family, ANGPTL2, 4, and 8 predominantly participate in inflammatory processes, while other members can also contribute to the overall inflammatory milieu [32].

As mentioned before, the ANGPTL protein family is involved in inflammatory processes in various bodily

Table 1 Comprehensive overview of hepatokines: effects on insulin resistance, liver function, l,ipid metabolism, metabolic conditions, and lifestyle

Hepatokines	Insulin resistance	Metabolic conditions	Adipose tissue and lipid profile	Liver tissue	Life style
Activin E	Exacerbation of insulin resistance associated with obesity.		Facilitation of thermogenesis in brown adipose tissue	The control of insulin membrane receptor density in hepatocytes	Elevated levels in mice undergoing obesity induced by a high-fat diet.
ANGPTL3	Insulin, at the mRNA expression level, inhibits ANGPTL3 production downregulation of genes associated with the gluconeogenesis reduction in the efficiency of insulin-mediated VLDL secretion	elevated serum levels in T2DM	Correlation of elevated ANGPTL3 expression with higher plasma triglyceride levels and reduced free fatty acids. the accumulation of triglycerides in white adipose tissue cells Suppression of VLDL Breakdown	Regulatory influence of LXR on ANGPTL3 concentrations	
ANGPTL4	An increase in insulin sensitivity via its glucose-lowering effect and enhanced glucose processing	Lower serum level in individual with obesity, diabetes, and atherosclerosis	As fasting-induced adipose factor, is secreted by adipose tissue. Increased serum triglyceride levels both by inhibiting lipoprotein lipases and triglyceride clearance Facilitation of lipid accumulation in adipocytes, contributing to steatosis	As Fasting-induced adipose factor, is secreted by hepatocytes Development of T2DM by enhancing lipid buildup in liver cells	the release of fatty acids in response to catechamine-induced short-term fasting and glucocorticoids-induced long-term fasting
ANGPTL6	Enhancement of AMPK and insulin signaling in muscle			Suppression of gluconeogenesis, catabolic shift in sugar metabolism induced by inhibiting the G6Pase gene	Direct correlation with fasting insulin and fasting blood sugar levels
ANGPTL8	Potential enhancement of insulin sensitivity by directly affecting Akt phosphorylation	Polymorphism in NAFLD Development	Its inhibitory effect on LPL influenced by ANGPTL3 and ANGPTL4		
Adropin	Therapeutic potential to increase glucose tolerance and insulin sensitivity	Lower serum levels in Obesity and T2DM		Lower levels in response to more liver availability of lipid Impact of hepatic steatosis on ENHO gene expression encoding adropin A positive correlation between adropin and PCK1 in hepatic steatosis	Upregulation in hepatic steatosis induced by lipid-rich diet
Selenoprotein P	SELENOP synthesis triggered by AMPK activation, achievable through the use of anti-inflammatory or insulin-sensitizing medications. Dysregulation of Glucose Metabolism	Positive correlation with NAFL Elevation of its mRNA level in T2DM			

Table 1 (continued)

Hepatokines	Insulin resistance	Metabolic conditions	Adipose tissue and lipid profile	Liver tissue	Life style
Fibroblast growth factor 21	As an insulin-dependent hormone in humans Improved insulin and leptin sensitivity Enhanced glucose uptake and utilization Glucose Homeostasis and β-Cell Protection	Protective effects against T2DM, hyperglycemia, dyslipidemia, Non-Alcoholic Steatohepatitis, NAFLD	Stimulating adipose tissue lipolysis Independent glucose uptake in adipocytes and systemic insulin resistance reduction	Decreased hepatic steatosis Direct promotion of liver fatty acid oxidation Improving Hepatic Insulin Sensitivity	Fasting-induced metabolic changes regulated by FGF21 in liver
Growth differentiation factor 15	Preventive effect against obesity and insulin resistance	Efficacy of GDF15 in ameliorating NAFLD and mitigating obesity	Metabolic shift from glucose to fat generation in response to stress p53-mediated expression of GDF15 in adipose tissue for influencing lipid catabolism, heat generation, and oxidative metabolism		Central appetite-suppressing effects in response to stress conditions, Severe Ailments and GDF15-Induced Anorexia-Cachexia Syndrome
Fetuin-A	Positive Correlation with Insulin Resistance Antagonistic effect on insulin-stimulated insulin receptor tyrosine kinase	Positive Correlation with T2DM and NAFLD Dualistic Inflammatory Properties Protective role against HMGB1 release in severe systemic inflammation	Modulation of adiponectin levels via Wnt-PPARγ pathway in lipid-induced inflamed adipocytes		
Follistatin	Association between FST, insulin resistance, glucose intolerance and mild inflammation	Moderate increase in plasma FST levels in individuals with T2DM	An increase in white adipose tissue fat breakdown and the blood levels of glycerol and non-esterified fatty acids		
Leukocyte cell-derived chemotaxin-2	Insulin sensitivity enhancement in Lect2–/– mice A causative factor in skeletal muscle insulin resistance Contribution of hepatic LECT2 to JNK phosphorylation and insulin resistance	Obesity-related insulin resistance		liver regeneration A direct correlation between hepatic LECT2 mRNA levels and obesity	
Hepassocin	The lower hepatic hepassocin level, the more insulin sensitivity Insulin resistance in skeletal muscle mediated by hepassocin	Association with obesity Key role in NAFLD development Insulin resistance and diabetes may increase with high hepassocin levels.		Mitogenic effects on liver cells Hepatic lipid accumulation via a ERK1/2-dependent mechanism	
Secreted modular calcium-binding protein 1	Insulin sensitivity enhancement	Lower circulating levels in obesity Potential therapeutic for glycemic control and insulin sensitivity in T2DM		Downregulation of gluconeogenic gene expression Suppression of hepatic glucose production	

Table 1 (continued)

Hepatokines	Insulin resistance	Metabolic conditions	Adipose tissue and lipid profile	Liver tissue	Life style
Insulin-like growth factor 1	Structurally similar to insulin The more IGF1, the better insulin sensitivity in both individuals with and without T2DM Overexpression of IGFBP1 mitigates hypoglycemic impact, but induces insulin resistance in skeletal muscle	Reduced plasma IGF1 levels as a prognostic indicator for T2DM onset Association of lower IGF Levels with NAFLD and Obesity	Role of IGF1 in energy homeostasis regulation in brown adipose tissue through sympathetic nervous system activity		Modulates glucose metabolism in mice subjected to regular or high-fat diets The regulation of appetite
Lipocalin-13		An inverse correlation with obesity Therapeutic candidate for T2DM and NAFLD	Enhancement of adipocytes' insulin sensitivity facilitating glucose absorption in both insulin-independent and insulin-dependent manners	Inhibition of hepatic gluconeogenesis Prevention of obesity-related hepatic steatosis by enhancing fatty acid β-oxidation and reducing lipogenesis Insulin-independent regulation of glucose metabolism in liver regulation of lipid metabolism via CPT1α	A reduction in circulating LCN13 levels after a high-fat diet
Tsukushi		Induction by obesity and cold exposure Interplay between TSK and inflammation Prolonged TSK elevation in obesity, Atherosclerosis, and NAFLD	Deletion of TSK induces thermogenesis in brown adipose tissue	Liver Steatosis Liver regulation of TSK expression by inflammation and ER stress Hepatocytes respond to proinflammatory cytokines by promoting the transcription of TSK Protective role of initial TSK surge in stressed liver cells	Deletion of TSK provides protection against diet-induced obesity
Hepcidin	Affect iron metabolism in adipose tissue, liver ferroptosis and development of diabetes and insulin resistance	Dysregulation of hepcidin leads to various metabolic diseases such as obesity, type 2 diabetes, and insulin resistance		Dysregulation of hepcidin leads to liver ferroptosis inactivation of the hepcidin-coding gene in liver cells results in the activation of Akt and glycogen synthase kinase-3β (GSK3β)	
Lipopolysaccharide binding protein	By changing the lipid metabolism can affect insulin sensitivity		Participating in the metabolism of triglycerides and high-density lipoprotein (HDL) cholesterol		The serum level of LPS increases with a high-fat diet

conditions. Although the first member of this family, ANGPTL1, has an unclear role in inflammation, it does interfere with inflammatory pathways in cancer. ANGPTL1 inhibits the integrin a1ß1/focal adhesion kinase (FAK)-Src/JAK/STAT3 signaling pathway by binding to integrin a1ß1 in liver cancer cells, thus suppressing metastasis and angiogenesis. Furthermore, ANGPTL1's binding to integrin a1ß1 inhibits the expression of zinc finger protein SLUG, which has an inhibitory effect on lung cancer [33–36].

Moreover, ANGPTL2 plays a role in inflammatory responses and various metabolic disorders. This hepatokine, which is also released from adipose tissue, exerts a favorable impact on inflammation, obesity, and systemic insulin resistance in both humans and mice. Figure 2 shows, in a research study, recombinant ANGPTL2 was utilized to treat human umbilical vein endothelial cells, leading to the activation of Rac1 and NF-κB via integrin α5ß1, thereby enhancing the inflammatory pathway [33, 37]. Additionally, this treatment was applied to endothelial cells in atherosclerosis, where the interaction of this hepatokine with integrin α5ß1 resulted in increased degradation of IκBα and elevated secretion of pro-inflammatory cytokines and

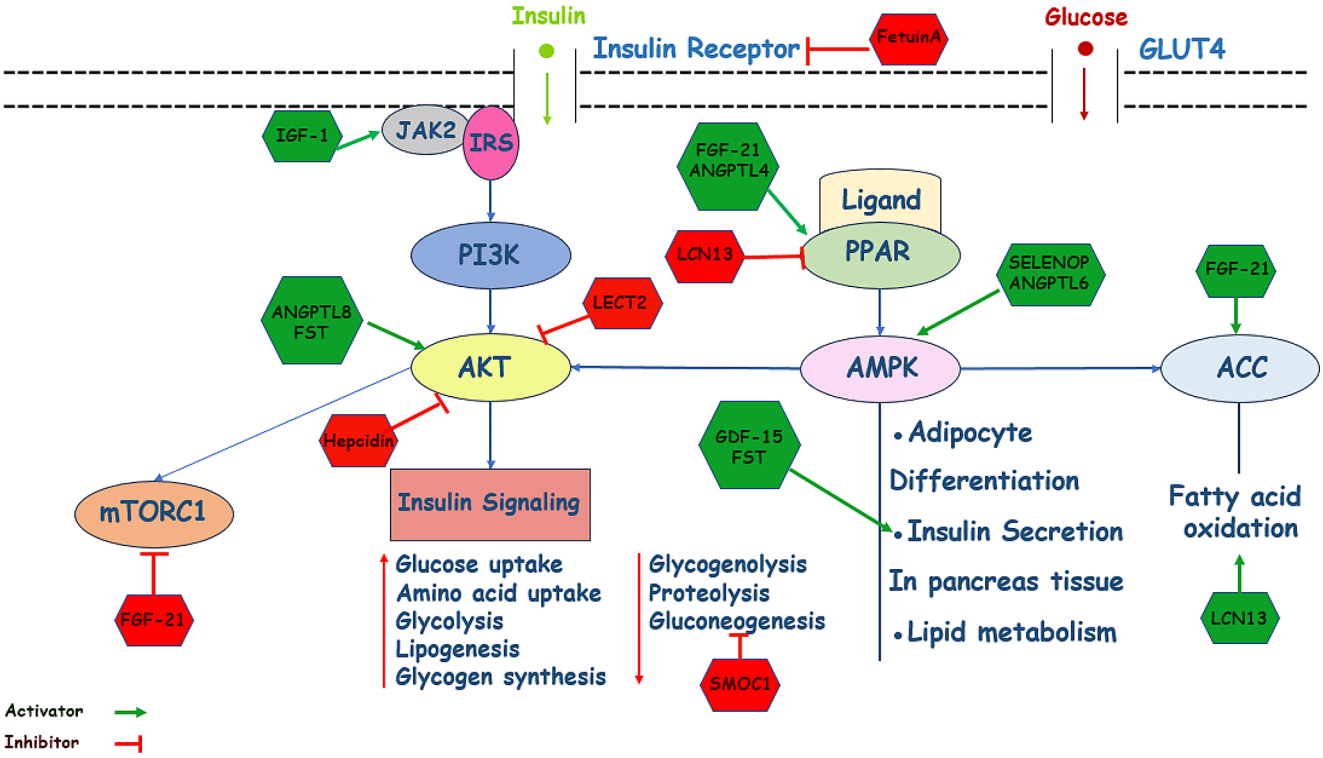

Fig. 1 The impact of hepatokines on insulin signaling pathways. GLUT4: Glucose transporter type 4, IRS: insulin receptor substrate, JAK2: Janus Kinase 2, IGF-1: Insulin-like Growth Factor 1, FGF-21: fibroblast growth factor 21, ANGPTL: Angiopoietin-like protein, SELENOP: Selenoprotein P, PPARs: Peroxisome proliferator-activated receptors, LCN13: Lipocalin 13, PI3K: Phosphoinositide 3-kinases, LECT2: Leukocyte cell-derived chemotaxin-2, FST: Follistatin, FSTL1: Follistatin-like protein 1, ACC: Acetyl-coA carboxylase, AMPK: Adenosine monophosphate-activated protein kinase, GDF-15: Growth differentiation factor 15, SMOC1: Secreted modular calcium-binding protein 1, mTORC1: Mammalian target of rapamycin complex 1

adhesive molecules such as TNF-α, interleukin 6 (IL-6), and intercellular adhesion molecule 1 (ICAM-1), as presented [33, 38, 39].

Within its structural framework, ANGPTL3 incorporates a distinctive epitope associated with lipoprotein lipase, thereby influencing the activity of lipoprotein lipase and modulating plasma triglyceride levels. The influence of ANGPTL3 on obesity, insulin resistance, and hyperlipidemia has been substantiated through rodent studies [40]. Subsequent investigations involving rodents elucidated that elevated ANGPTL3 expression correlates with increased plasma triglyceride levels and decreased levels of free fatty acids [41]. The ANGPTL3 protein was identified as a suppressor of LPLs in an in-vitro setting, resulting in consequential alterations to free fatty acid and triglyceride levels in the bloodstream [42]. Human studies have revealed that the inhibition of ANGPTL3 leads to a reduction in triglyceride levels [43]. Moreover, diabetic patients exhibit elevated serum levels of ANGPTL3 compared to non-diabetic individuals [8]. Investigations on mice have demonstrated the involvement of ANGPTL3 in the accumulation of triglycerides in white adipose tissue cells. By supplying glucose to accumulated adipocytes, ANGPTL3 KO mice have compensated for their tissue mass weight, which stayed similar to control mice [44]. Evidence suggests that the coiled-coil region of ANGPTL3 plays a pivotal role in suppressing the breakdown of very-low-density lipoproteins (VLDLs) [45]. The regulatory influence of liver X receptor (LXR) activity on ANGPLT3 concentrations has been documented as well [46]. Leptin and insulin, at the mRNA expression level, inhibit the production of ANGPTL3. Hormones like these cause hyperlipidemias and hyperfattyacidemia in those who are overweight, diabetic, or insulin-resistant [47]. Inhibiting ANGPTL3 leads to a downregulation of genes associated with the gluconeogenesis pathway and a reduction in the efficiency of insulin-mediated VLDL secretion [48]. Apart from the aforementioned functions, when ANGPTL3 binds to αVß3 integrin, it enhances the movement and attachment of endothelial cells, promoting angiogenesis and indicating the potential pro-inflammatory role of ANGPTL3. Additionally, a separate animal study demonstrated that upregulation of ANGPTL3 in mice with diabetic retinopathy led to increased levels of Bax, p53, VEGF, and inflammatory cytokines (IL-6 and IL-1B) [33, 49].

Regarding ANGPTL4, this protein displays a reduced molecular size in comparison to ANGPTL3, while yet

maintaining its structural arrangement for LPL binding [50]. Its ability to increase liver cell lipid buildup contributes to T2DM [5]. This particular protein is alternatively recognized as Fasting-induced adipose factor (Fiaf) [4]. Predominantly secreted by adipose tissue and hepatocytes, ANGPTL4 levels exhibit an increase during periods of fasting. Catechamine-induced short-term fasting appears to trigger a signaling cascade that releases fatty acids and shifts metabolism toward fat use. In response to glucocorticoids, ANGPTL4 expression is stimulated during extended fasting, leading to fatty acid release. Consequently, the impact of this protein is more pronounced during extended fasting durations [51]. As depicted in Fig. 1, augmenting ANGPTL4 expression triggers the activation of the peroxisome proliferator-activated receptor (PPAR) signaling pathway, subsequently suppressed upon refeeding [52]. When studying mice with obesity, diabetes, and atherosclerosis, researchers found that their ANGPTL4 expression was much lower. [53]. Increased serum triglyceride levels are caused by the N-terminal of ANGPTL4, which inhibits LPLs. At the same time, this protein hinders triglyceride clearance, further increasing blood lipid levels. In contrast to its effects on adipocytes, an augmentation in free fatty acid (FFA) concentration in the blood is observed, emanating from ectopic sources such as the liver or muscle cells [5, 54]. ANGPTL4 exhibits a glucose-lowering effect and enhances glucose processing capabilities, as evidenced by numerous studies. It may be possible to increase insulin sensitivity using this [4, 27, 55]. Human studies involving individuals with T2DM have reported a decrease in the serum concentration of ANGPTL4 [56]. Additionally, ANGPTL4 facilitates lipid accumulation in adipocytes, contributing to steatosis [57]. Conversely, the genetic inactivation of ANGPTL4 has shown promise in substantially reducing the risk of developing coronary artery disease and diabetes [58]. Is there a correlation between insulin resistance and serum concentrations of ANGPTL4 or not? The contradictory results of the research on this protein make it impossible to draw any firm conclusions. It seems that it has a dual role even in inflammation [58]. Stem cells have a wide range of applications in treating cardiovascular diseases (CVD). One example is the use of ANGPTL4 derived from mesenchymal stem cells, which have been found to suppress β1/αVβ3 integrin signaling by inhibiting NF-κB (Fig. 2). This contributes to the polarization of inflammatory macrophages as an anti-inflammatory molecule [33, 59]. Moreover, in other study involving mice, it was observed that ANGPTL4 levels increased in cases of acute lung injury. Furthermore, the reduction of this

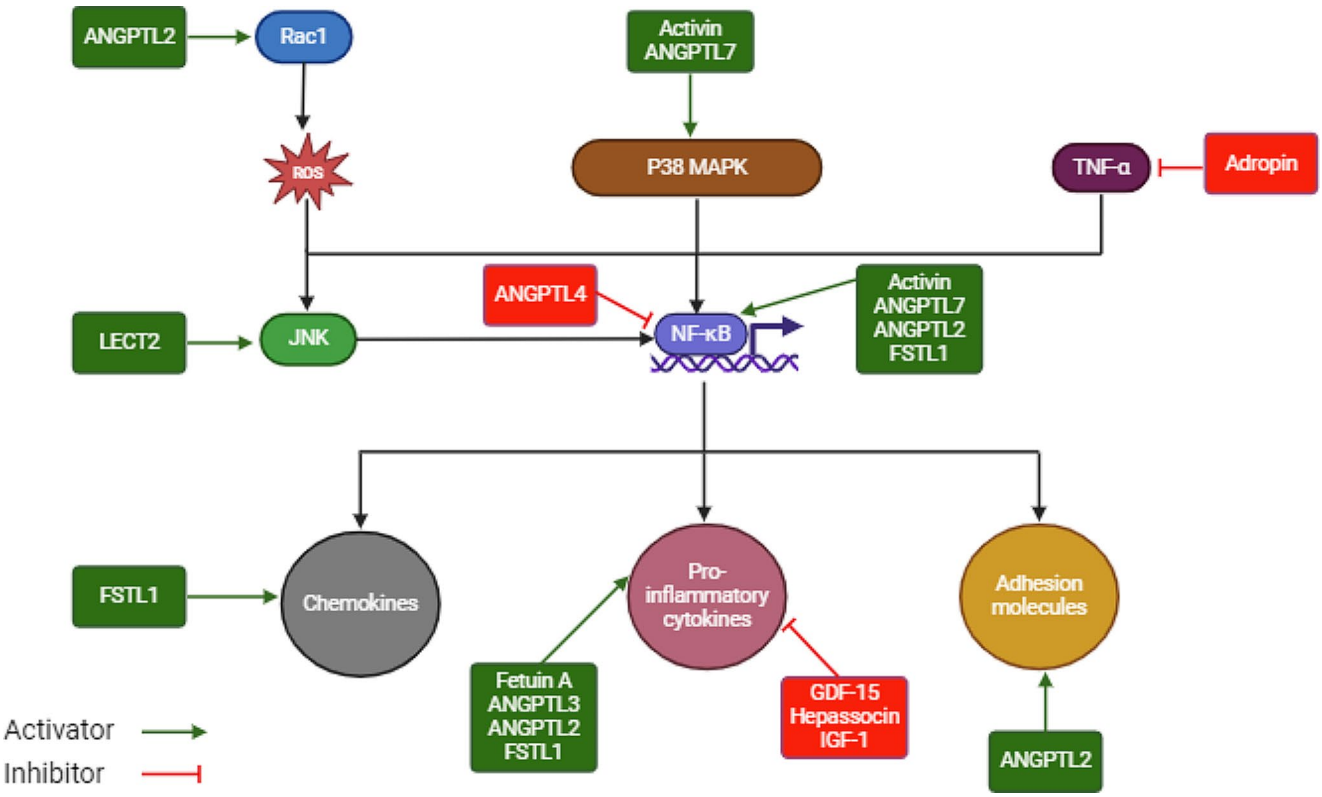

Fig. 2 The impact of hepatokines on inflammation pathways. ANGPTL: Angiopoietin-like protein, TNF-α: Tumor necrosis factor α, FSTL1: Follistatin-like protein 1, P38 MAPK: P38 mitogen-activated protein kinase, ROS: Reactive oxygen species, LECT2: Leukocyte cell-derived chemotaxin-2, NF-κB: Nuclear factor-κB, JNK: Jun N-terminal kinase, GDF-15: Growth differentiation factor 15, IGF-1: Insulin-like Growth Factor 1

hepatokine led to an increase in sirtuin1 (SIRT1), which has anti-inflammatory and antioxidant properties [33].

Previous research findings suggest that the levels of ANGPTL5 may be linked to inflammation in both obese individuals and those with type 2 diabetes. In addition, the rise in this hepatokine is correlated with level of hs-CRP [33, 60].

ANGPTL6, on the other hand, lacks a binding domain for LPLs, distinguishing it from the preceding two variants of ANGPTL [28]. Its liver expression is predominate, with little in other tissues [61]. This protein enhances AMPK and boosts insulin signaling in muscle (Fig. 1). Additionally, it suppresses gluconeogenesis by inhibiting the expression of the glucose-6-phosphatase (G6P) gene, leading to a catabolic shift in sugar metabolism [29, 62]. Fasting insulin and blood sugar levels are two indicators that are directly correlated with ANGPTL6 [63]. As well as, this hepatokine is involved in the inflammatory processes associated with metabolic syndromes. For instance, mice that were induced with psoriasis displayed elevated levels of epidermal ANGPTL6, resulting in more intense skin inflammation [33, 64].

Regarding ANGPTL8, this protein possesses an LPL binding domain, albeit lacking a coiled-coil or fibrinogen C-terminal [28]. The ANGPTL8 protein is primarily secreted by adipose tissue and liver cells [65]. The inhibitory effect of this protein on LPL is greatly influenced by the concentration of ANPGTL3 and 4. It emerges as a potential biomarker for the identification and treatment of metabolic irregularities on a broad scale [4]. The impact of ANGPTL8 on both NAFLD and insulin resistance remains a subject of discourse. Arguments posit that ANGPTL8 may enhance insulin sensitivity by directly affecting Akt phosphorylation [66]. Decreasing ANGPTL8 levels is associated with a reduction in insulin resistance [67]. However, polymorphism of this protein is implicated in the development of NAFLD [68]. It has been reported that overexpression of ANGPTL8 improved insulin sensitivity and glucose tolerance and decreased fasting blood glucose levels in high-fat diet/streptozotocin-induced diabetic and db/db mice. In fact, ANGPTL8 promoted glucose metabolism via the inhibition of expression of gluconeogenesis-related genes [phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase catalytic subunit (G6PC)] by activating the AKT signaling pathway [69].

It is important to note that the final member of this family also plays a role in acute inflammatory conditions by acting as an anti-inflammatory agent. For instance, in individuals with acute infections or in laboratory mice with stimulated hepatocytes, ANGPTL8 controls the NF-κB signaling pathway by promoting the targeted autophagic breakdown of IKKγ [33, 70]. Zhang et al. [71] 's study expanded on the function of selective autophagy in fine-tuned inflammatory responses and proposed the ANGPTL8/p62-IKKγ axis as a negative feedback loop that controlled NF-κB activation.

Despite various potential explanations and connections between the members of this family and inflammatory pathways, the involvement of the ANGPTL family in inflammation remains uncertain and requires additional research.

Fibroblast growth factor 21 (FGF21)

Various tissues, such as the liver (hepatocytes), adipose tissue, pancreas, heart, and brain, release this protein [7, 72]. Fasting-induced metabolic changes in the liver, such as resistance to growth hormone (GH), fatty acid oxidation, ketogenesis, and gluconeogenesis, are tightly regulated by FGF21, as a physiological function [73]. Mice treated with FGF21 have improved insulin and leptin sensitivity, decreased hepatic steatosis, increased energy expenditure, and decreased sugar and alcohol consumption [4, 74, 75].

FGF21 primarily promotes liver fatty acid oxidation while blocking lipogenesis and gluconeogenesis [76]. Second, by reducing the severity of hyperlipidemia and hyperglycemia, FGF21 indirectly affects the liver. To do this, the following mechanisms are activated: mitochondrial activity is enhanced, fatty acid oxidation is facilitated, adipose tissue lipolysis is stimulated, energy is dissipated as heat, and glucose uptake and utilization are improved. Additionally, it influences several areas of the hypothalamus and hindbrain to encourage thermogenesis and energy expenditure as well as an aversion to sweets and alcohol intake [76]. Furthermore, there is a conjecture that FGF21 resistance in both rats and humans is attributed to obesity and insulin resistance [18]. Clinical trials involving FGF21 analogues indicate an elevation in high density cholesterol (HDL) and a reduction in plasma triglyceride concentrations, although they do not exert any discernible impact on insulin sensitivity or glucose levels [77].

The metabolic impacts attributed to FGF21 are acknowledged to arise from its interactions with various tissues [78]. FGF21 directly communicates with adipose tissue, enhancing insulin sensitivity [4]. Simultaneously, it stimulates the central nervous system to elevate calorie expenditure and facilitate weight loss [79, 80].

FGF21, recognized as an insulin-dependent hormone in humans [72], also plays a pivotal role in enhancing glucose balance by safeguarding β cells. FGF21 is believed to prevent β-cell dysfunction and cell death in vivo and in vitro through its inhibition of lipid accumulation in islet cells. As illustrated in Fig. 1, this likely occurs through the activation of the PPARδ/γ and AMPK-acetyl coenzyme A carboxylase (ACC) signaling pathways [81]. Beyond its reliance on insulin-dependent mechanisms for improving glucose homeostasis, FGF21 independently facilitates glucose uptake in

adipocytes [72]. In addressing systemic insulin resistance, FGF21 demonstrates the capacity to reduce serum insulin levels and enhance insulin sensitivity [72]. In-depth investigations into the precise mechanisms underlying FGF21's enhancement of hepatic insulin sensitivity involved administering FGF21 to mice. They discovered that FGF21 can enhance insulin sensitivity via blocking liver mTORC1 (Fig. 1). FGF21-deficient mice consistently exhibit heightened hepatic insulin resistance and activation of mTORC1 [82]. Furthermore, FGF21 targets subcutaneous fat tissue as a crucial component to control systemic insulin sensitivity. To prevent systemic insulin resistance in vivo, FGF21 can encourage the growth of subcutaneous fat and raise adiponectin levels in subcutaneous fat [72].

In summary, FGF21 provides protection against T2DM by improving glucose regulation [83]. Noteworthy is its demonstrated anti-inflammatory prowess [22]. Elevated FGF21 in insulin-sensitive obese individuals worsens the polarization of M2 macrophages and controls adiponectin levels in subcutaneous adipose tissue. As well as, elevating the concentration of this growth factor impacts the transforming growth factor-β (TGF-β) signaling pathway and inhibits adipogenesis by influencing the Smad3 pathway [84, 85]. As a result, because of its effects on hepatocytes, the brain-liver axis, and adiponectin synthesis in adipose tissue, FGF21 protects against hyperglycemia, dyslipidemia, non-alcoholic steatohepatitis (NASH), and other comorbidities [86]. FGF21 emerges as a promising therapeutic avenue for the management of T2DM and NAFLD [87].

Fetuin-A

Classified as α2-Heremans-Schmid-glycoprotein, Fetuin-A is a complex glycoprotein belonging to the cystatin protease inhibitor superfamily. Predominantly synthesized by hepatocytes and adipose tissue, this protein establishes a novel nexus linking obesity, inflammation, and insulin resistance [88, 89]. Fetuin-A, a plasma protein, regulates multiple physiological processes, including cellular protein metabolism, acute inflammatory responses, neutrophil and platelet release, lymphocyte activation, and binding to fatty acids, thyroid hormones, and calcium ions [89]. It serves as a natural antagonist to the insulin-stimulated insulin receptor tyrosine kinase, impeding the autophosphorylation of the insulin receptor and subsequent downstream signaling, as evidenced in laboratory investigations [90, 91]. Notably, as showed in Fig. 1, this hepatokine has been observed to bind to the receptor tyrosine kinase (RTK) at a distinct site from the insulin binding region; however, the precise domain of fetuin-A implicated in this interaction remains unclear [92]. Numerous investigations suggest a positive correlation between heightened levels of circulating fetuin-A and insulin resistance in human subjects [93]. Consequently, this protein emerges as a prospective independent risk factor in the predisposition to T2DM [94–96]. Through its modulation of adiponectin levels in lipid-induced inflamed adipocytes via the Wingless-related integration site (Wnt)-PPARγ pathway, Fetuin-A potentially instigates insulin resistance [88, 97]. This cascade of events underscores the plausible role of Fetuin-A in the pathogenesis of type 2 diabetes. Notably, there exists a consensus within the scientific community that NAFLD can be a precursor to insulin resistance and the subsequent onset of T2DM [18, 98]. Regardless of adiposity, Fetuin-A is elevated in NAFLD, suggesting a link between fatty liver and insulin resistance. [93, 99]. The pro-inflammatory or anti-inflammatory effects of this hepatokine are dependent on the particular clinical setting in which it is activated, thereby displaying dualistic inflammatory properties [89, 92, 100]. This molecule, renowned for its proinflammatory attributes, assumes a role in the development of insulin resistance. Additionally, Fetuin-A demonstrates neuroprotective properties and plays a significant part in mitigating inflammation in conditions such as sepsis and autoimmune diseases [100]. In instances of severe systemic inflammation, the protective role of Fetuin-A is ascribed to its capacity to impede the release of high mobility group box protein 1 (HMGB1), induced by pathogen-associated molecular patterns (PAMPs) [89]. As well as, Fig. 2 displays this hepatokine enhances the polarization of M1 macrophages and boosts the release of pro-inflammatory cytokines like interleukin-1β, Tumor Necrosis Factor α (TNF- α), and IL-6 [101].

Follistatin (FST)

This glucosylated plasma protein can bind and neutralize TGF-β family members [102]. Nowadays, 5 types of this family are identified [103]. The gene responsible for its expression is discernible in diverse tissues, including the pituitary gland, placenta, ovary, testis, brain, and skeletal muscle [104, 105]. In the human system, the predominant source of circulating FST is the hepatocytes, with its production and release being augmented in response to an elevated ratio of glucagon to insulin [106]. FST primarily operates through autocrine and paracrine signaling pathways [107, 108]. The manifold physiological roles ascribed to FST encompass the regulation of follicle-stimulating hormone (FSH) production in the pituitary, facilitation of ovarian follicle maturation, control of spermatogenesis, maintenance of liver homeostasis, facilitation of wound repair, and responsiveness to inflammatory stimuli [107]. Emergent evidence suggests a potential involvement of this hepatokine in insulin resistance and mild inflammation. However, it appears that plasma FST levels exhibit a closer

association with metabolic disruptions than with low-grade inflammation [104].

Individuals with T2DM show a moderate increase in plasma FST levels, yet further investigations are imperative to elucidate whether the elevated plasma levels constitutes a causative factor or a consequence of metabolic irregularities in T2DM [104, 109]. A recent study has presented findings indicating that heightened circulating FST levels are linked to an increased susceptibility to developing type 2 diabetes, owing to their contribution to insulin resistance in adipose tissue [105]. Here, FST secretion by the liver causes insulin resistance and white adipose tissue fat breakdown. Increased levels of glycerol and non-esterified fatty acids in the bloodstream cause the liver to produce glucose uncontrollably, which ultimately results in glucose intolerance [105, 110]. Follistatin possesses the potential to influence insulin resistance and inflammation by virtue of its interaction with members of the TGF-β family. Thus, Fig. 2 presents the expression of FSTL1 is related to the activity of the NF-κB signaling pathway. Also, FSTL1 leads to the expression of various chemokines and inflammatory cytokines that are related to the NF-kB signaling pathway. Among them, CCL-2/MCP-1, TNF-α, CXCL8/IL-8, IL-1β and IL-6 can be mentioned [103]. Moreover, FSTL is attributed to its recognized capability to bind and counteract both myostatin and activin A within the circulatory system [111]. Notably, activin A, emanating from epicardial adipose tissue (in addition to liver) in individuals with T2DM, impedes insulin function by instigating the production of miR-143 in cardiomyocytes. This specific miRNA, in turn, suppresses the Akt pathway by diminishing the levels of oxysterol-binding protein–related protein 8 (ORP8), a recently identified regulator of insulin activity (Fig. 1) [112]. Myostatin, commonly acknowledged for its potent control over muscle growth and size, is implicated in metabolic processes. Although research indicates a potential correlation between myostatin and insulin resistance, the intricate details of this association remain under investigation [113]. Overall, Serum levels of FST are generally higher in those with T2DM. The underlying process, on the other hand, is still a mystery.

Leukocyte cell-derived chemotaxin-2 (LECT2)

This protein exhibits hormone-like properties and was initially identified as a chemokine influencing the regulation of neutrophil movement [114]. Subsequently, it garnered further characterization as chondromodulin II (CHM2), attributed to its capacity to stimulate proteoglycan synthesis by chondrocytes and facilitate cartilage growth [115]. Substantial progress has been achieved in comprehending its multifaceted roles, spanning liver regeneration, immune system modulation, bone development, neuronal growth, glucose regulation, metabolic syndrome, cancer, and amyloidosis [116]. While hepatocytes constitute the primary source of production and release of LECT2 into the bloodstream, its presence is also discernible in diverse cell types, encompassing vascular endothelial cells, smooth muscle cells, cerebral nerve cells, and adipocytes [117, 118]. LECT2, identified as a hepatokine, has been the subject of research establishing a direct correlation between hepatic LECT2 mRNA levels and body mass index (BMI). This association implies that elevated mRNA levels of hepatic LECT2 are associated with the severity of obesity in humans, potentially leading to insulin resistance in skeletal muscle [119, 120]. Glucose and insulin loading tests on Lect2–/– mice revealed reduced blood glucose levels following glucose or insulin administration. Furthermore, Lect2–/– mice exhibited heightened insulin-stimulated Akt phosphorylation specifically in skeletal muscle, with no discernible impact in the liver or adipose tissue. These observations suggest that the absence of the hepatokine LECT2 enhances insulin sensitivity in rodent skeletal muscle [119]. Moreover, as displayed in Fig. 1, the overproduction of LECT2 in the liver may contribute to JNK phosphorylation, resulting in insulin resistance in the skeletal muscle of obese individuals. However, the precise mechanism underlying how LECT2 facilitates JNK phosphorylation remains incompletely elucidated [120]. Additionally, LECT2 is involved in the body's inflammation response by attaching to cell surface receptors like CD209a, Met, and Tie1. Additionally, in NAFLD, this hepatokine enhances the polarization of M2 macrophages and influences liver inflammation by impacting the JNK signaling pathway (Fig. 2) [121]. In summary, LECT2 emerges as a causative factor in inducing insulin resistance in skeletal muscles.

Hepassocin

Hepassocin, also recognized as hepatocyte-derived fibrinogen-related protein 1 (HFREP1) or fibrinogen-like protein 1, stands out as a specialized factor exerting mitogenic effects, particularly fostering the proliferation of liver cells (in an autocrine manner) [122–124]. Its primary source of secretion is the liver, but noteworthy findings indicate its expression within brown adipose tissues as well. Following liver damage, some signals stimulate an upregulation of its expression in brown adipose tissues [125]. While an investigation observed elevated levels of hepassocin in overweight or obese individuals compared to those with normal weight, the precise nature of the association between hepassocin and obesity remains elusive [126, 127]. As outlined in a study, this hepatokine assumes a pivotal role in the development of NAFLD, contributing to hepatic lipid accumulation through the activation of an ERK1/2-dependent mechanism

[128]. Conversely, a reduction in hepassocin levels correlates with heightened insulin sensitivity, achieved through the modulation of ERK1/2 activity within the liver. This implies that elevated hepassocin concentrations may escalate the susceptibility to insulin resistance and diabetes [129]. Furthermore, hepassocin instigates insulin resistance in skeletal muscle cells through a 396 EGFR/JNK-mediated mechanism [130]. Nevertheless, conflicting perspectives arise from certain studies, challenging the earlier postulates. One investigation suggests a potentially beneficial impact of hepassocin on liver fat accumulation, coupled with a partial mitigation of hepatic apoptosis, fibrosis, and inflammation through the inhibition of oxidative stress. If the liver is injured, an increase in hepassocin in the liver can protect the liver against inflammation, steatosis, fibrosis and cell death. Therefore, the production of inflammatory cytokines such as IL-1β, IL-6, and TNFα increased in the mice where the expression of hepasosin was knocked down (Fig. 2) [121]. This, in turn, proved instrumental in preventing the development of steatohepatitis in mice [131].

Secreted modular calcium-binding protein 1 (SMOC1)

SMOC-1, secreted by hepatocytes, encompasses one N-terminal follistatin-like (FS), one extracellular calcium (EC), two thyroglobulin-like (TY) domains, and a distinctive domain lacking known homologs. Its expression is widespread across diverse tissues, frequently positioning it in proximity to the cell's basement membrane [132, 133]. This hepatokine demonstrates interaction capabilities with laminins [132], C-reactive protein (CRP), fibulin-1, vitronectin [134], transglutaminase 2 [135], and tenascin-C [132, 136]. These interactions substantiate its involvement in integrin-matrix interactions and cell adhesion [137]. Through an acute intraperitoneal injection in mice, SMOC1 demonstrated the capacity to enhance insulin sensitivity and regulate glucose without influencing insulin secretion. The mechanism underlying its favorable glycemic effects involves the inhibition of adenosine 3′,5′-cyclic monophosphate (cAMP)–cAMP-dependent protein kinase (PKA)–cAMP response element–binding protein (CREB) signaling in the liver. Figure 1 depicts, this, in turn, led to a downregulation of gluconeogenic gene expression and a suppression of hepatic glucose production [138]. Additionally, individuals characterized by obesity and insulin resistance exhibited lower circulating levels of SMOC1, with a discernible association with both hepatic and systemic insulin sensitivity [138]. Overall, SMOC1 seems to manifest beneficial effects in the context of T2DM. In addition, SMOC1 is involved in the inflammatory processes of kidney diseases. A prior study showed that interleukin 1 beta reduces the expression of SMOC1 in animal mesangial cells by stimulating the production of nitric oxide (NO). Consequently, blocking the function of nitric oxide synthases results in an elevation of SMOC1 expression, exacerbating inflammation and fibrin deposition in the animal's glomerulus. Furthermore, decreasing SMOC1 expression reduces the activity of the TGF-β signaling pathway, subsequently leading to a decline in the activity and expression of the Smad gene [139].

Insulin-like growth factor 1 (IGF-1)

This hepatokine, referred to as somatomedin C, is a hormone exhibiting structural similarities to insulin and holds pivotal significance in the growth processes during childhood. The liver (hepatocytes) serves as the primary site for IGF-1 synthesis, a response elicited by the stimulation of GH. The majority of IGF-1 is bound to one of six binding proteins (IGF-BP) [140]. IGF-1 exerts a comprehensive influence on systemic body growth, displaying growth-promoting effects across diverse cell types such as skeletal muscle, cartilage, bone, liver, kidney, nerve, skin, hematopoietic, and lung cells. In addition to its insulin-like effects, IGF-1 plays a regulatory role in cellular DNA synthesis [141]. GH engages with the cell-surface GH receptor (GHR), a homodimeric transmembrane protein. As showed in Fig. 1, this interaction initiates signal transduction by recruiting and activating cytosolic Janus Kinase 2 (JAK2) [142].

In individuals with T2DM, IGFBP1 exhibits an elevation and possesses the capacity to counteract insulin's hypoglycemic effects by inhibiting IGF1 [143]. There exists compelling evidence indicating that insulin resistance, an increased susceptibility to metabolic syndrome and cardiovascular disease, along with diminished plasma levels of IGF1, collectively serve as prognostic indicators for the onset of type 2 diabetes [144–146]. Furthermore, certain studies propose that the modulation of IGF1 significantly influences glucose metabolism in mice subjected to a regular or high-fat diet. For instance, the systemic overexpression of IGFBP1 led to heightened plasma insulin levels, effectively mitigating the hypoglycemic impact of endogenous IGF1. However, this intervention also induced a reduction in insulin-stimulated glucose transport and glycogen synthesis in skeletal muscle, indicative of a subtle degree of insulin resistance [147]. Investigations have also unveiled a reduction in IGF levels among individuals afflicted with NAFLD and obesity [148]. A noteworthy observation arises from mice lacking Stat5a/b specifically in the central nervous system, denoted as Stat5NKO mice. These mice exhibit pronounced obesity, accompanied by insulin resistance, hyperphagia, hyperleptinemia, and a diminished capacity to respond thermally to cold stimuli [149]. In the realm of energy homeostasis regulation, a prominent player is UCP1 within Brown Adipose

Tissue (BAT) activity. Comparative analyses between BAT from AAV-Igf1 mice (subjected to adeno-associated virus (AAV)-mediated delivery of IGF-I cDNA) and control mice (those injected with empty AAV) elucidated a marked augmentation in UCP1 expression, as discerned through Western blotting assays [150].

Robust neuroanatomical and functional evidence substantiates the involvement of the sympathetic nervous system (SNS) in the innervation and regulation of both WAT and BAT, orchestrating processes essential for thermoregulation and the generation of beige adipocytes [151]. The pivotal protein UCP1 in BAT, crucial for initiating thermogenesis in response to dietary and cold stimuli, is subject to control by SNS activity [152]. Intriguingly, the aforementioned findings suggest that the central activity of IGF1 can enhance central sympathetic outflow, consequently influencing UCP1 expression [150]. Beyond its role in improving insulin sensitivity and glucose tolerance, as well as fostering energy expenditure through thermogenesis, central IGF1 is implicated in the regulation of appetite [150]. Notably, administration of IGF1 has been associated with a boosted insulin sensitivity and lowered blood glucose levels in both individuals with T2DM and those without diabetes [150, 153, 154]. Moreover, Obese individuals have enlarged fat cells that, in collaboration with immune cells, elevate the production of pro-inflammatory cytokines like IL-6 and TNF-α. In such cases, the rise in serum IGF1 levels can serve as an anti-inflammatory agent and help regulate the levels of inflammatory factors (Fig. 2) [155].

Growth differentiation factor 15 (GDF15)

The protein secreted by hepatocytes, also known as macrophage inhibitory cytokine-1 (MIC-1), is a constituent of the TGF-β superfamily [9, 156]. In physiological condition, its regulatory influence extends to hematopoietic growth, energy equilibrium, adipose tissue metabolism, somatic growth, bone remodeling, and responsiveness to stress signals [9]. GDF15 assumes a multifaceted role in various pathological conditions, encompassing cancer, cardiometabolic disorders, etc. [9]. While GDF15 is typically absent in reproductive organs, it can be induced in numerous cell types under stress conditions [156]. A critical aspect of its operation is the regulation of energy balance, which is accomplished by increasing energy expenditure and decreasing body weight gain [4].

In mice with MIC-1/GDF15-induced anorexia/cachexia syndrome, glucose, insulin, and IGF-1 levels were lower [157]. In the context of NAFLD and other chronic liver disorders, there is a proportional elevation of GDF15 levels corresponding to disease severity and the presence of steatotic hepatitis. The augmentation of GDF15, either through overexpression or the introduction of recombinant GDF15, proves efficacious in ameliorating NAFLD and mitigating obesity [158]. In the milieu of obesity, the activation of p53 in adipose tissue contributes to the secretion of pro-inflammatory cytokines, insulin resistance, and the onset of diabetes. Concurrently, it mediates the expression of GDF15 within adipose tissue [159]. Also, in cases of insulin resistance or obesity, the integrative stress pathway and mitochondrial unfolded protein response (UPR) become active, resulting in the attachment of CHOP and ATF4 to the promoter region, this in turn triggers the transcription of GDF15 [160]. As well as, GDF-15 is intricately involved in lipid catabolism, heat generation, and oxidative metabolism. Its presence demonstrates a preventive effect against obesity and insulin resistance arising from dietary or genetic factors. In humans, there is a direct correlation between the expression of the GDF15 gene and the expression of genes associated with inflammation. It is also plausible that GDF15 may be linked to chronic low-grade inflammation, although the precise molecular mechanism for this connection has not yet been determined. When obese mice were given GDF15 antibody, there was an increase in inflammatory markers such as IL-6, CD-68, Tnf, monocyte chemoattractant protein-1 (Mcp1), and F480 in adipose tissue (Fig. 2). However, more research is needed to fully understand the relationship between GDF15 and inflammatory factors. Consequently, GDF15 emerges as a promising therapeutic target for addressing obesity and insulin resistance [161].

Lipocalin-13 (LCN13)

The lipocalin family encompasses a diverse array of small secreted proteins, typically comprising 160–180 amino acids and featuring an N-terminal signal peptide. LCN13 is produced in various tissues such as the hepatocytes, epididymis, pancreas, and skeletal muscle, and it is released into the blood circulation [162]. The distinctive biological activity exhibited by LCN family members is intricately linked to their capacity to selectively bind to diminutive hydrophobic molecules, including phospholipids, fatty acids, steroids, retinol, and pheromones. Research has illuminated the expansive role of LCN family members in governing chemical communication, reproduction, immunological responses, and the progression of cancer in rats. Recent revelations underscore the newfound significance of LCNs in modulating food metabolism and insulin sensitivity among individuals grappling with obesity. Among these, LCN13 stands out, being released into the circulation of mice and expressed by various organs such as the liver, pancreas, epididymis, and skeletal muscle [163]. Notably, LCN13 levels exhibit an inverse correlation with obesity,

and interventions involving LCN13 in mice afflicted with hereditary or diet-induced obesity have demonstrated a reversal of LCN13 deficiency. This reversal, in turn, leads to improvements in insulin resistance, glucose intolerance, hepatic steatosis, hyperglycemia, and hyperinsulinemia. Mechanistically, LCN13 directly impedes hepatic lipogenesis and gluconeogenesis in hepatocytes, while concurrently promoting fatty acid β-oxidation. LCN13 also enhances adipocytes' responsiveness to insulin. A thorough exploration of the underlying processes contributing to LCN13's anti-diabetic and anti-steatotic effects is currently a subject of discourse [163].

Concerning glucose metabolism, the expression and secretion patterns of LCN13 in mice exhibit variability in response to alterations in metabolic conditions. There is an inconsistency in LCN13 expression, which diminishes in the context of obesity. Mice subject to genetic (db/db) or high-fat diet (HFD) conditions display a substantial reduction in circulating LCN13 levels, contributing to the progression of obesity. Remarkably, hepatic LCN13 operates in an autocrine/paracrine manner, exerting inhibitory effects on glucose synthesis within the liver. Even in the absence of insulin, LCN13 facilitates glucose absorption in adipocytes while concurrently suppressing glucose synthesis and the expression of key gluconeogenic genes, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, in primary hepatocytes. These observations suggest an alternate, insulin-independent mechanism through which LCN13 modulates glucose metabolism [164].

Shifting focus to lipid metabolism, there is a plausible mechanism suggesting that LCN13 plays a preventive role in obesity-related hepatic steatosis. This preventive action is primarily achieved through the enhancement of fatty acid β-oxidation and the concurrent reduction of lipogenesis within the liver (Fig. 1). LCN13 and its analogs exhibit therapeutic potential for the treatment of T2DM and NAFLD, owing to their dual properties of anti-steatosis and anti-diabetic effects [163]. It is hypothesized that LCN13 orchestrates lipid metabolism by upregulating the expression of carnitine palmitoyltransferase-1α (CPT1α) in the liver, while concurrently downregulating the expression of key lipogenic genes such as PPARγ and carbohydrate response element binding protein (ChREBP) (Fig. 1). This dual regulation serves to mitigate lipogenesis and augment fatty acid β-oxidation [165]. In the context of obese mice, LCN13 demonstrates a notable reduction in hepatic steatosis without a concomitant impact on adiposity, suggesting a preferential inhibition of lipogenesis and promotion of fatty acid oxidation specifically within hepatocytes, as opposed to adipocytes. Additionally, LCN13 directly facilitates glucose absorption by adipocytes through pathways that are both insulin-dependent and insulin-independent [164]. Although the level of LCN13 expression through the effect of Akt S473 phosphorylation and Glut4 expression can affect the insulin signaling pathway in the liver and skeletal muscles, its effect on the expression of inflammatory cytokines has not been observed [166].

Tsukushi (TSK)

TSK, secreted by hepatocytes, stands as an atypical member within the small leucine-rich proteoglycan family, exerting regulatory influence over developmental processes in diverse organisms [167]. TSK has been associated with the process of neurogenesis, the formation of the anterior commissure, the development of the eyes and inner ear, as well as bone growth and maintaining liver homeostasis [168]. This hepatokine, induced by both obesity and exposure to cold conditions, emerges as a significant player in the orchestration of physiological responses. The prevalence of liver steatosis, commonly associated with obesity and acute cold exposure, exhibits a high correlation with circulating TSK levels in various mouse models. Intriguingly, both inflammation and endoplasmic reticulum stress, implicated in excessive hepatic lipid accumulation, serve as stimulants for the expression of TSK in the liver [169]. A study by Wang et al. has demonstrated that the deletion of TSK amplifies sympathetic innervation and thermogenesis in BAT, contributing to a protective effect against diet-induced obesity and an enhancement in glucose regulation in mice [170]. TSK deficiency also heightens adrenergic action and augments thermogenic stimulation in brown fat by promoting the phosphorylation of hormone-sensitive lipase (HSL) and Protein Kinase A (PKA) substrates [171].

The interplay between Tsk and inflammation has been elucidated, with Lipopolysaccharide (LPS), a component of gram-negative bacteria, demonstrating an ability to elevate TSK levels in mice. This observation suggests a direct link between inflammation and the induction of Tsk expression [172]. Notably, deficiency in TSK has been associated with an increase in protein levels of UCP1 [169]. Liver cells respond to proinflammatory cytokines, such as TNF-α, IL-1β, and IFN-γ, collectively promoting the transcription of TSK [169]. The initial surge in TSK levels may serve a protective role in stressed liver cells by mitigating cholesterol influx into the liver. However, the prolonged elevation of TSK observed in conditions like obesity and NAFLD raises concerns about its potential contribution to atherosclerosis, potentially attributed to the chronic constriction of reverse cholesterol transport [172].

Adropin

Hepatocytes and brain are two of the many tissues that express adropin, a small peptide with 76 amino acids. Its presence has been noted in proteins of the pancreas, heart, blood vessels, and kidneys as well [173–175]. This peptide exhibits a decrease in response to heightened lipid availability in the liver. Furthermore, individuals with obesity and T2DM manifest a decline in serum adropin levels [5]. Mouse hepatic steatosis reduces energy homeostasis-associated gene (ENHO) gene expression, which encodes adropin [176]. Conversely, in hepatic steatosis induced by a lipid-rich diet, an upregulation of adropin expression is observed [177]. An intriguing observation reveals a positive correlation between adropin and phosphoenolpyruvate carboxykinase 1 (PCK1), a pivotal regulatory point in gluconeogenesis [178]. In addition, Adropin is used as a therapeutic stimulus to increase glucose tolerance and insulin sensitivity in rats induced by high-fat diet [179]. Furthermore, aside from its involvement in the body's metabolic processes, adropin also has a function in reducing inflammatory factors in diabetes. Adropin is able to prevent the attachment of THP1 monocytes to Human Umbilical Vein Endothelial Cells (HUVEC) cells by affecting the TNF-α signaling pathway, thus exhibiting its anti-inflammatory properties (Fig. 2) [180].

Activins

Activins, members of the TGFβ superfamily, constitute a diverse group of proteins with multifaceted effects on various tissues. Traditionally perceived as heterogeneous, these proteins consist of multiple βA and βB subunits interconnected by disulfide bridges. Their pivotal role in the formation of gonadal follicles was initially discerned. Recent investigations have unveiled two additional subunits, namely βE and βC, characterized by sequences akin to their classical counterparts. Intriguingly, despite their initial association with gonads, it has been established that the hepatocytes serves as the primary source of activins [181, 182]. This protein instigates a cascade of signaling events by binding to the Activin A receptors type I (ActRI) and type II (ActRII), characterized as serine-threonine kinases. These signals subsequently culminate in the activation of genes with diverse functionalities [183].

In 2023, Liu and colleagues uncovered that the expression of Activin A in the liver led to a decrease in inflammation, expansion of hematopoietic stem cells, reduction of liver steatosis, decreased fat accumulation and lower levels of circulating cholesterol. These findings suggested that these effects collectively contribute to the observed protection against atherosclerosis and metabolic related diseases [184]. Moreover, in murine models, the analysis of activin E mRNA levels within hepatocytes' cytosol suggests a plausible involvement in both exacerbating insulin resistance associated with obesity and facilitating thermogenesis in brown adipose tissue [185]. In a study, it has been shown that overexpression of hepatic activin E led to the activation of thermogenesis by upregulating Ucp1 in both white and brown adipose tissues. Furthermore, hepatic activin E-transgenic mice showed enhanced insulin sensitivity. Additionally, experiments conducted in vitro indicated that activin E directly promoted the expression of Ucp1 and FGF21, potentially through the mediation of transforming growth factor-b or activin type I receptors [186]. Within this gene cohort, UCP1 holds significance, encoding uncoupler proteins that induce the leakage of hydrogen ions into the mitochondrial space, consequently generating heat within the targeted cell and tissue. Another noteworthy gene in this category is FGF21, contributing to the growth and specialization of brown adipocytes [187]. During fasting, the protein level of FGF21 is elevated, with its suppression attributed to the absence of an insulin receptor [188]. In contrast, there is an observed elevation in the level of activin E in mice experiencing obesity due to a high-fat diet [6].

Additionally, a prior study explored the inflammatory function of Activin in umbilical vein endothelial cells. As depicted in Fig. 2, the findings indicated that this hepatokine impacts the expression of chemokines and inflammatory cytokines by influencing NF-κB and MAPK signaling pathways. As a result, it exerts an anti-inflammatory effect against TNF-α in these cells [189].

Selenoproteins

Selenocysteine, an amino acid implicated in oxidation-reduction processes, is found in selenoprotein P [190, 191], which is primarily secreted from the hepatocytes in mammals, selenoprotein P may also be released into the bloodstream by the testis and brain tissue [192]. In addition, Selenoprotein S is involved in different metabolic conditions in the body, including insulin resistance, diabetes, and obesity. When selenoprotein S is not expressed in liver cells, it can worsen obesity and lead to reduced insulin sensitivity and glucose tolerance [193]. Human studies suggest a positive correlation between SELENOP and NAFLD [194]. The expression of this protein escalates in response to endoplasmic reticulum stress and the activation of the JNK protein. Furthermore, SELENOP synthesis is triggered by the activation of AMPK, which can be achieved by the use of anti-inflammatory or insulin-sensitizing medications (Fig. 1) [195, 196]. In the context of T2DM, there is an observed elevation in the mRNA level of SELENOP. In-vitro investigations indicate that SELENOP dysregulates glucose metabolism [197, 198]. While selenoprotein-S is involved

in controlling the release of inflammatory cytokines, selenoprotein-P functions as a regulator of homeostasis and a transporter of Se from the liver to other tissues in the body [199, 200].

Hepcidin

Hepcidin, the primary regulator of iron homeostasis in the body, is a polypeptide hormone that primarily originates from liver hepatocytes. Hepcidin acts as an iron regulator by affecting the transfer of iron to the plasma through the action of ferroportin, reducing the amount of iron absorption from the diet and increasing cellular iron storage [201, 202]. Iron metabolism is one of the factors that influences the functioning of the endocrine system. Ferroptosis, a form of iron-dependent cell death, leads to insulin resistance in fat, liver, and muscle cells, and also reduces insulin secretion in pancreatic β cells [203]. Dysregulation of hepcidin leads to various metabolic diseases such as obesity, type 2 diabetes, and insulin resistance. Additionally, the plasma concentration of hepcidin changes in acute and chronic inflammatory conditions, and by affecting macrophages, it leads to the release of inflammatory cytokines [201, 202].

Iron metabolism plays a crucial role in blood glucose homeostasis through its effects on fat metabolism, insulin secretion, and liver metabolism [203]. Uncontrolled iron metabolism in adipose tissue and increased liver ferroptosis can lead to the development of diabetes and insulin resistance, respectively [203]. Previous studies have shown that individuals with T2DM tend to have higher levels of hepcidin compared to those without the condition [201, 204]. Additionally, inactivation of the hepcidin-coding gene in liver cells results in the activation of Akt and glycogen synthase kinase-3β (GSK3β) in the insulin signaling pathway [205]. Protein kinase Akt, by activating GSK3β and increasing the expression of GLUT4, leads to enhanced glucose uptake by cells and a reduction in insulin resistance [206, 207]. Increased iron levels can also lead to elevated blood glucose, fasting insulin, and hepatic ferroptosis. Through the JAK2/STAT3 signaling pathway, this can then result in the activation of SOCS-1 and the development of insulin resistance [208, 209]. Considering that hepcidin is an acute-phase reactant, the inflammation associated with T2DM can lead to increased secretion of IL-6 and activin-B (Act-B), which in turn stimulate the synthesis of hepcidin in the liver via the STAT3 signaling pathway [204].

Lipopolysaccharide binding protein

Lipopolysaccharide binding protein (LBP) is an acute-phase protein that plays a crucial role in the lipopolysaccharide (LPS) transport cascade. LBP is primarily produced by hepatocytes and, to a lesser extent, in non-hepatic tissues such as intestinal epithelial cells, lungs, and gum tissue, also, it is present in low amounts in the blood circulation. During the acute-phase response to infection and inflammation, LBP's concentration increases 10 to 20 times compared to its baseline level [210, 211].

Lipopolysaccharide is a pathogenic factor found in the outer membrane of Gram-negative bacteria, commonly known as endotoxin [211]. Since lipopolysaccharide primarily exerts its endotoxic effects by activating the innate immune system, it is not inherently toxic [212]. However, the entry and increased level of lipopolysaccharide in the bloodstream can lead to a condition called endotoxemia, which can occur due to unhealthy eating habits or digestive disorders (derived from the intestinal microbiome). This endotoxemia can cause disorders such as metabolic endotoxemia (even in healthy individuals) and chronically contribute to inflammation-related disorders, including cardiovascular diseases, liver diseases, insulin resistance, metabolic syndromes, obesity, and diabetes [213].

LBP plays a crucial role in the LPS-to-TLR4 signaling cascade. LBP can form high-affinity complexes with LPS and then bind to CD14. LPS interacts with the LRR13-LRR15 region of TLR4, gets transferred from CD14 to MD2, and leads to signal generation, thereby greatly enhancing the host's response to extracellular LPS [214]. Activation of the TLR4 pathway triggers the production of pro-inflammatory cytokines, such as TNF-α and IL-6. These pro-inflammatory cytokines can contribute to insulin resistance by interfering with insulin signaling pathways [215].

LBP is involved in the metabolism of lipids, particularly triglycerides and high-density lipoprotein (HDL) cholesterol. Clinical studies on metabolic endotoxemia in obese patients have shown that the serum level of LPS increases with a high-fat diet. As a result, obesity is considered a state of low-grade chronic inflammation [216, 217]. The signaling cascade initiated by the binding of LBP to LPS leads to an inflammatory response and modulation of lipid metabolism. These changes in lipid metabolism can affect insulin sensitivity and contribute to insulin resistance [87, 210, 218].

Conclusion

Recent investigations posit that the disorder in hepatokines significantly contributes to the genesis of insulin resistance and inflammation culminating in the onset of T2DM. In the context of this study, we scrutinized various hepatokines and explored their impacts on insulin resistance and inflammation. It is evident that the involvement of hepatokines stems from their modulation of key metabolic mechanisms,

including lipogenesis, lipolysis, and the transfer of lipoproteins, insulin-dependent sugar metabolism and the modulation of inflammatory pathways. Briefly, fetuin-A facilitates the development of lipid-induced insulin resistance through its role as an endogenous ligand for TLR-4. FGF21 mitigates inflammation in diabetes by impeding the nuclear translocation of NF-κB in adipocytes and adipose tissue under insulin-resistant conditions, concurrently augmenting glucose metabolism. Moreover, the overproduction of LECT2 in the liver may contribute to JNK phosphorylation, resulting in insulin resistance in the skeletal muscle of obese individuals. ANGPTL6 enhances AMPK and boosts insulin signaling in muscle. Additionally, it suppresses gluconeogenesis by inhibiting the expression of the G6P gene. Furthermore, ANGPTL8 may enhance insulin sensitivity by directly affecting Akt phosphorylation. More importantly, Follistatin possesses the potential to influence insulin resistance and inflammation by virtue of its interaction with members of the TGF-β family. Also, Hepassocin assumes a pivotal role in the development of NAFLD, contributing to hepatic lipid accumulation through the activation of an ERK1/2-dependent mechanism. Furthermore, hepassocin instigates insulin resistance in skeletal muscle cells through a 396 EGFR/JNK-mediated mechanism. SMOC1 demonstrated the capacity to enhance insulin sensitivity and regulate glucose, as well. The mechanism underlying its favorable glycemic effects involves the inhibition of adenosine 3′,5′-cyclic monophosphate (cAMP)–cAMP-dependent protein kinase (PKA)–cAMP response element–binding protein (CREB) signaling in the liver. This, in turn, led to a downregulation of gluconeogenic gene expression and a suppression of hepatic glucose production. Intriguingly, the central activity of IGF1 can enhance central sympathetic outflow, consequently influencing UCP1 expression. Beyond its role in improving insulin sensitivity and glucose tolerance, as well as fostering energy expenditure through thermogenesis, central IGF1 is implicated in the regulation of appetite. In addition, LCN13 orchestrates lipid metabolism by upregulating the expression of CPT1α in the liver, while concurrently downregulating the expression of key lipogenic genes such as PPARγ and ChREBP. Liver cells respond to pro-inflammatory cytokines, such as TNF-α, IL-1β, and IFN-γ, collectively promoting the transcription of TSK. The initial surge in TSK levels may serve a protective role in stressed liver cells by mitigating cholesterol influx into the liver. An intriguing observation reveals a positive correlation between adropin and phosphoenolpyruvate carboxykinase 1 (PCK1), a pivotal regulatory point in gluconeogenesis. The prospect is optimistic that harnessing the potential of hepatokines and manipulating the pertinent pathways through the use of agonists and antagonists could pave the way for enhancing human health and advancing the treatment of T2DM and fatty liver disease. In addition, research in the field of hepatokines may help for the pathomechanism-based clustering of insulin resistance in some diseases to better implement precision medicine in clinical practice [18]. However, more complementary studies are needed in this regard.

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Author contributions RA and XM were involved in designing the study. Searching were conducted and results were interpreted by RA, YJ, MD and XM. The initial draft of the manuscript was written by VS, AA, NJ, FS and FA. The manuscript was then edited by RA and MD. All authors reviewed and endorsed the final version of the manuscript.

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