Review

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Hepatokines and adipokines in NASH-related hepatocellular carcinoma

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Summary

The incidence of hepatocellular carcinoma (HCC) is increasing in industrialised societies; this is likely secondary to the increasing burden of non-alcoholic fatty liver disease (NAFLD), its progressive form non-alcoholic steatohepatitis (NASH), and the metabolic syndrome. Cumulative studies suggest that NAFLD-related HCC may also develop in non-cirrhotic livers. However, prognosis and survival do not differ between NAFLD- or virus-associated HCC. Thus, research has increasingly focused on NAFLD-related risk factors to better understand the biology of hepatocarcinogenesis and to develop new diagnostic, preventive, and therapeutic strategies. One important aspect thereof is the role of hepatokines and adipokines in NAFLD/NASH-related HCC. In this review, we compile current data supporting the use of hepatokines and adipokines as potential markers of disease progression in NAFLD or as early markers of NAFLD-related HCC. While much work must be done to elucidate the mechanisms and interactions underlying alterations to hepatokines and adipokines, current data support the possible utility of these factors – in particular, angiopoietin-like proteins, fibroblast growth factors, and apelin – for detection or even as therapeutic targets in NAFLD-related HCC.

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Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide, and the most common primary liver cancer.[1] The incidence of HCC increased by 3.1% per year between 2008 and 2012.[2] Growing epidemiologic evidence indicates an association between non-alcoholic fatty liver disease (NAFLD) and the risk of HCC development. The incidence of HCC among patients with NAFLD is around 0.44 per 1,000 person-years (range: 0.29–0.66).[3]

The pathogenic mechanisms linking NAFLD/non-alcoholic steatohepatitis (NASH) to HCC remain poorly understood (Fig. 1). Although cirrhosis is the major risk factor for HCC development,[4,5] a significant portion of NASH-related HCC develops in livers with no or minimal liver fibrosis.[6] Among individuals without cirrhosis, those with NASH are at a higher risk of HCC than those with other liver diseases.[7] In 500 patients with HCC of various aetiologies, 43% had cirrhosis.[8] In particular, cirrhosis was present in only 23% of NAFLD-related and 21% of NASH-related HCC.[8] We reported that of 162 adults with HCC, cirrhosis was present in 58.3% of those with NAFLD-related HCC; by contrast, cirrhosis was seen in nearly 90% of patients with non-NASH and non-cryptogenic HCC.[9] In a US Veterans Health Administration cohort of 1,500 patients, about 87% had cirrhosis. Among patients with NAFLD-related HCC only 65.4% had evidence of cirrhosis. The risk of developing HCC in a non-cirrhotic liver was increased 5.4-fold for NAFLD and 5-fold for metabolic syndrome (MetS) compared to HCV.[10] In 77 patients with non-viral-associated HCC, 30% of NAFLD-related HCC cases developed in patients with no or minimal fibrosis.[6,11] Collectively, these results suggest that HCC in NAFLD can develop at any stage of hepatic fibrosis,[6,10,11] with 20–50% of NAFLD-related HCC occurring in non-cirrhotic cases. This wide range could be explained by heterogeneous methods and protocols to assure or exclude cirrhosis. Most patients with NAFLD without symptoms do not undergo liver biopsy, leading to a substantial underdiagnosis of compensated cirrhosis.[12] However, given the current understanding of HCC in non-cirrhotic NAFLD, we cannot exclude that the development of HCC may start at early stages of NAFLD.[13–15]

The prevalence of NAFLD has increased worldwide in parallel with the rising tide of obesity, MetS, and type 2 diabetes mellitus (T2DM).[16,17] In MetS-related HCC (MetS-HCC), tumours are often larger and well differentiated compared to non-MetS-HCC (65% *vs.* 28%, p <0.001). While 74% of patients with non-MetS-HCC have bridging fibrosis or cirrhosis (F3-F4), only 35% of patients with MetS-HCC have significant fibrosis (65% non-cirrhotic).[18] In a multicentre study of 1,563 patients

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with HCC, the prevalence of NASH was significantly higher in the MetS-HCC group than the matched HCV-HCC group (25.0% *vs.* 9.4%, $p = 0.004$).[19] 90-day morbidity and liver failure rates were similar in MetS-HCC and HCV-HCC, and were impacted by the presence of cirrhosis, major hepatectomy, and a model for end-stage liver disease (MELD) score of >8, but not by NASH. Overall 5-year survival was significantly higher in the MetS-HCC group (65.6% *vs.* 61.4%, $p = 0.031$).[19,20] Additionally, inflammatory hepatocellular adenoma, which may undergo malignant transformation, is likewise associated with obesity, steatosis and MetS – hence constituting another risk factor for HCC development in non-cirrhotic livers.[6,18,21,22]

Overall, the mechanisms of HCC development in NAFLD remain uncertain and merit in-depth investigation at the molecular level. In this context, hepatokines and adipokines have been gaining much attention in recent years. Herein, we will review the current understanding of how hepatokines and adipokines affect the pathogenesis of NASH-related HCC.

Risk factors and the pathogenesis of NASH and NASH-related HCC

Obesity results from excess calorie uptake due to an unhealthy diet (*i.e.* high calorie diet) and a sedentary lifestyle, combined with the complex interplay between genes and the environment.[16] Obesity-related chronic inflammation is associated with increased proinflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6),[23] and an imbalanced adipokine profile.[24,25] Other effects of obesity include increased reactive oxygen species (ROS), endoplasmic reticulum (ER) stress and activation of NF-κB, resulting in inhibition of apoptosis in the liver.[23,26] ER stress in the liver augments the unfolded protein response, and NOD-like receptor P3 (NLRP3) inflammasome pathway stimulation[27,28] as well as hepatic insulin resistance (IR). These multifactorial effects of obesity not only favour lipid storage and inflammation but also tumour development in the liver. Obesity is generally associated with cancer growth.[29] The increased risk of HCC development observed in obesity probably results from interactions between the aforementioned effects: Prevention of apoptosis, *i.e.* due to ROS and ER stress, can promote tumour cell proliferation,[30,31] while free fatty acid (FFA)-induced and ER-stress-enhanced NLRP3 activation[27,28] results in disrupted insulin signalling and IR.[28]

As described, IR is associated with overweight and obesity and is considered a key pathophysiological mechanism for development of NAFLD, NASH and MetS.[32–35] In patients with IR, increased release of lipids and FFAs from adipose tissue into the blood leads to ectopic fat deposition in the liver and other organs.[36] IR results in continued high blood glucose levels and in T2DM in the long term. NAFLD is independently associated with an increased incidence of T2DM.[37,38] Conversely, T2DM increases the risk of HCC development 2- to 3-fold[39] and IR might be the common underlying risk factor.[40,41]

Obesity and NAFLD are both closely associated with MetS and a complex change of multiple cellular mechanisms, metabolic pathways, and inflammatory activity in adipose tissue and the liver. However, many of these processes cannot currently be utilised for the detection or diagnosis of HCC development in NAFLD.

Do hepatokines and adipokines influence NASH-related HCC?

Liver and adipose tissue release organ-specific cytokines, termed hepatokines and adipokines, with autocrine, paracrine, and endocrine functions. Both hepatokines and adipokines have potent effects on metabolic homeostasis[42] and are candidate biomarkers for the diagnosis or monitoring of metabolic diseases.[43]

Hepatokines play a central role in orchestrating whole-body energy metabolism as the liver adapts their secretion in response to stress signals (IR, T2DM, NASH). Hepatocytes in culture secrete more than 500 proteins.[44,45] However, only few have been studied as hepatokines and only a fraction – such as hepassocin, fetuins A and B and fibroblast growth factor 21 (FGF21) – have been linked to obesity and IR[45] and their role in the development of NAFLD- and NASH-related HCC remains unclear.

It has been established that adipokines play a crucial role in adipogenesis and in obesity-related diseases such as NAFLD.[46] Herein, we aim to provide an overview of the current knowledge on hepatokines (Table 1) and adipokines (Table 2) relevant to NAFLD, and discuss known associations with NASH-related HCC.

Key point

NAFLD is the most common cause of chronic liver disease worldwide. The prevalence of NASH, the severe variant of NAFLD, is rising in parallel with the epidemics of obesity and type 2 diabetes mellitus.

Key point

HCC is a leading cause of cancer-related death in the general population, and it is estimated that the occurrence of NASH-related HCC will increase continually following the still ongoing increase of NAFLD prevalence.

Hepatokines

Angiopoietin-like proteins

Angiopoietin-like proteins (ANGPTLs) are circulating hepatokines that act on angiogenesis, inflammation and carcinogenesis.[47] Specifically, ANGPTL3, -4, -6 and -8 affect lipoprotein metabolism and the regulation of plasma lipid levels – the latter by inhibiting extracellular lipases;[48] ANGPTL1, -2 and -8 have diverse roles in HCC tumorigenesis. To date, the role of the ANGPTLs in NASH-related HCC remains to be elucidated.

In obese patients, fasting was found to decrease serum ANGPTL3 but increase ANGPTL4 levels, and only ANGPTL3 was reduced after a very low calorie diet.[49] ANGPTL3 directly inhibits lipoprotein lipase (LPL).[48] ANGPTL4 is mainly expressed in the liver and adipose tissues, contributes to inhibition of LPL, and regulates triglyceride metabolism.[48,50] In

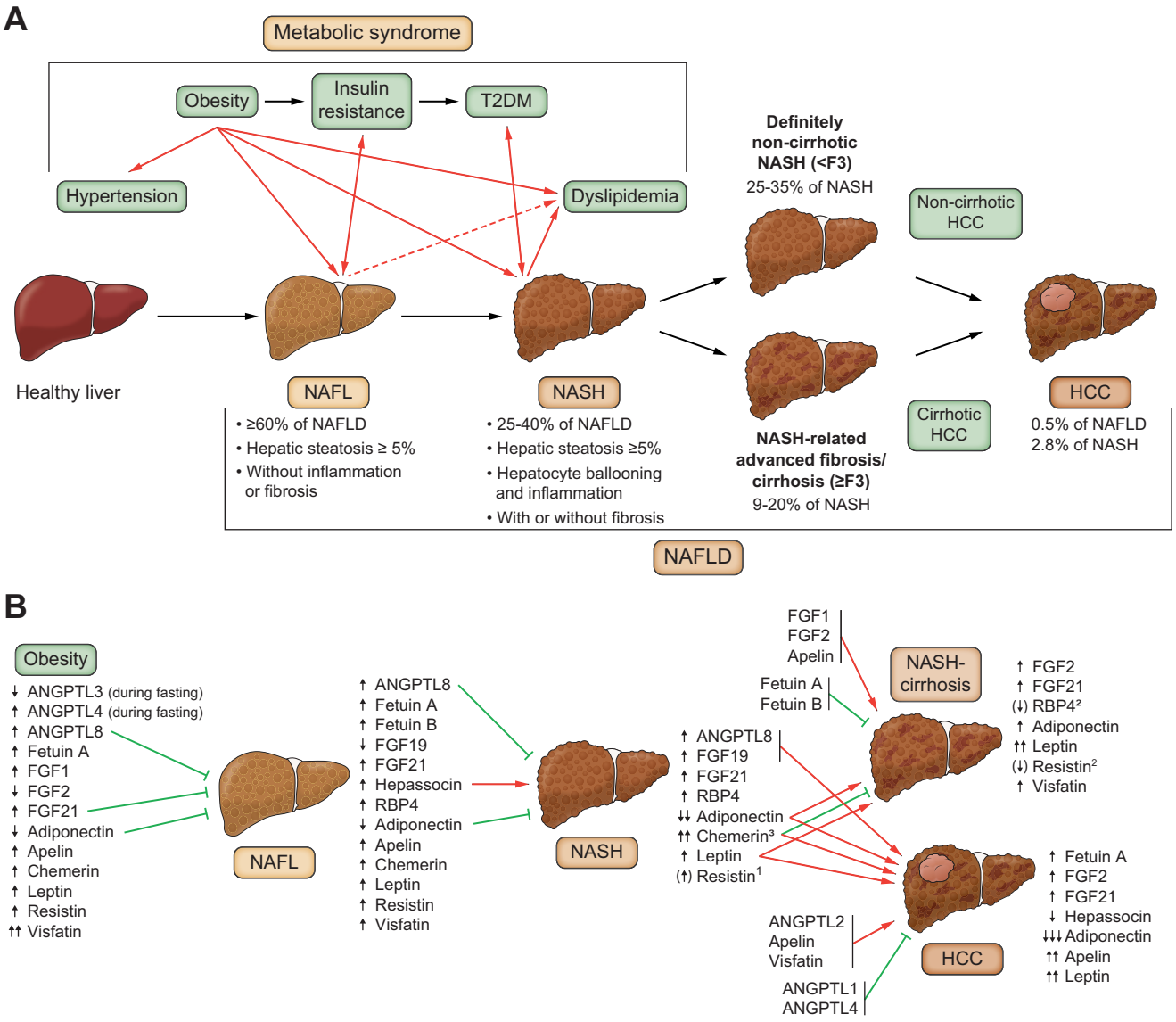

Fig. 1. Associations of obesity and risk factors for NAFLD and NASH-related-HCC with hepatokines and adipokines. (A) Overview of generally known risk factors for NAFLD and NAFLD-related HCC and natural history of NAFLD. Obesity constitutes a risk factor for development of NAFLD, IR, hyperlipidaemia, and hypertension. These are components of the MetS, with NAFLD the hepatic manifestation. NAFLD ranges from simple hepatic steatosis (NAFL) to NASH, which is characterised by the presence of inflammation and hepatocyte ballooning with or without fibrosis. While NAFL is a risk for IR, NASH also constitutes a risk factor for progression from IR to T2DM and *vice versa*. NASH also increases the risk of hyperlipidaemia and hypertension. Approximately 60% of NAFLD cases are NAFL, while NASH occurs in 25–40%. Of patients with NASH, 25–35% develop simple to mild fibrosis. Cirrhosis and cirrhotic HCC are found in 9–20% of patients with NASH. Approximately 0.5% of the patients with NAFLD and 2.8% of the patients with NASH develop HCC.[26] Red arrows indicate a risk for the target condition; black arrows indicate a possible development/progression of the target condition. (B) Known regulations of hepatokines and adipokines during obesity and different stages of NAFLD. Black up-arrow: upregulated in condition; Black down-arrow: downregulated in condition; red arrow: (increased) hepatokine or adipokine facilitates or increases risk of developing target condition; green arrow: (increased) hepatokine or adipokine blocks or reduces risk of developing target condition. ANGPTL, angiopoietin-like protein; FGF, fibroblast growth factor; HCC, hepatocellular carcinoma; IR, insulin resistance; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RBP4, retinol-binding protein 4; T2DM, type 2 diabetes mellitus.

humans, under physiological conditions such as fasting, cold exposure, and exercise, the fatty acid-activated peroxisome proliferator-activated receptors (PPARs) regulate ANGPTL4 expression.[48,50]

ANGPTL6 (also known as angiopoietin-related growth factor, or AGF) is a hepatocyte-derived circulating factor that inhibits the development of obesity and IR.[51] Serum levels of ANGPTL6 positively correlate with fasting glucose in T2DM,[51,52] and with the intake of vitamin D in obese individuals.[53]

ANGPTL8/betatrophin (also known as HCC associated protein, TD26, or lipasin)[54,55] is expressed primarily in liver and visceral adipose

Table 1. Overview of secreted proteins usually described as hepatokines.

Factor	Known effects	Site(s) of expression	Target site(s)	References
ANGPTL1	• *In vitro* Inhibition of the HGF receptor • *In vitro* suppression of motility and metastasis of hepatoma cells • Serum concentrations inversely correlated to clinical outcome in HCC	Vascularised tissue	Vascular endothelial cells	47,63
ANGPTL2	• Increased expression in HCC and positive correlation with intrahepatic metastasis in HCC	Hepatocytes	Endothelial cells	47,64
ANGPTL3	• Decreased serum concentrations during fasting in obesity • Inhibits lipoprotein lipase	Hepatocytes	Adipocytes	48,49
ANGPTL4	• Increased serum concentrations during fasting in obesity • Low expression in HCC liver tissue compared to non-tumourous tissue • Suppression of tumorigenesis and metastasis in murine HCC models	Liver and adipose tissue	Multiple target cell populations, *i.e.* vascular endothelial cells, adipocytes.	48–50,65
ANGPTL6	• Increased serum ANGPTL6 levels in T2DM and with intake of vitamin D in obesity • Preventing the development of obesity and IR	Hepatocyte-derived circulating factor	Probably multiple target cell types	48,51–53
ANGPTL8	• Increased serum levels associated with the presence of liver steatosis and increased plasma triglyceride levels • Decreased serum levels in the development of MetS • Increased serum levels in IR, in impaired glucose regulation and T2DM • Increased lipogenesis and proliferation in HCC by ANGPTL8 • Increased expression in HCC liver tissue, correlation with tumour size	Liver tissue and VAT	Probably multiple target cell types, including autocrine effects	48,55–59,62
Fetuin-A	• Increased serum levels in obesity, T2DM, MetS, NAFLD • Correlation with liver fibrosis stage in NAFLD	Hepatocytes	Carrier protein (*i.e.* for fatty acids); adipocytes, muscle cells	42,66–68,70,76
Fetuin-B	• Increased serum levels in liver steatosis and T2DM • Negative correlation with non-invasive markers of liver fibrosis in NAFLD	Hepatocytes	Carrier protein; multiple target tissues (*i.e.* neurons, adipocytes, hepatocytes)	75,77
FGF1	• Increased FGF1 levels in obesity	Hepatic stellate cells, adipocytes	Auto-and paracrine targeting of adipocytes; hepatic stellate cells, hepatocytes	82,85
FGF2	• Increased FGF2 levels in obesity • Increased serum FGF2 levels in liver cirrhosis and HCC	Hepatic stellate cells, adipocytes, hepatocytes	Multiple target cell types, *i.e.* hepatic stellate cells	82,85,87
FGF19, FGFR4 and β-Klotho	• Increased FGFR4-mediated signalling and reduced serum FGF19 in NAFLD • Modestly increased serum FGF19 and FGFR4 in NASH patients with advanced ballooning • Increased FGF19 levels in diabetic obese and NASH patients with T2DM remission and NAFLD improvement after sleeve gastrectomy • FGF19 analogue reduces liver fat content in NASH • FGFR4 polymorphisms in patients with cirrhosis and HCC • Increased hepatic FGF19/FGFR4 expressions and serum levels associated with poor outcome in HCC • Increased FGF19/FGFR4 expressions together with EpCam in the progression of fatty liver (NAFLD) to HCC • Increased serum β-Klotho proteins in HCC	Ileum, Liver, adipocytes, possibly cholangiocytes	Mature hepatocytes	90–93,95–97,230,231
FGF21	• Increased serum FGF21 levels in obesity, NAFLD, MetS, and T2DM • Positive correlation between liver FGF21 expression and adiposity, fasting insulin, intrahepatic triglycerides, and negative correlation with HDL cholesterol and BMI • Possible independent risk factor for progression to NASH • Increased serum FGF21 levels in liver cirrhosis and HCC	Liver, adipocytes, pancreas	Adipocytes, hypothalamus	101–104,106
Hepassocin (HPS)	• Increased serum levels in NAFLD and correlation with NAS • Low hepassocin expression in HCC	Liver	T-cells	107,108,114
RBP4	• Controversial results for serum RBP4 and expression levels in NAFLD • Increased liver RBP4 protein expression in fibrosis, high lobular inflammation and NAS in NASH • Increased serum RBP4 levels and expressions in adipocytes in obesity • Decreased serum and hepatic RBP4 levels in liver cirrhosis correlated with reduced hepatic glucose production	Hepatocytes, adipocytes	Retinol delivery to diverse peripheral tissues (*i.e.* retina)	120–128,232,233

Known effects and target sites in metabolic diseases (obesity, IR, T2DM, MetS, NAFLD, NASH) and HCC. ANGPTL, angiopoietin-like protein; FGF, fibroblast growth factor; HCC, hepatocellular carcinoma; IR, insulin resistance; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NAS, NAFLD activity scores; RBP4, retinol-binding protein 4; T2DM, type 2 diabetes mellitus; VAT, visceral adipose tissue.

Table 2. Overview of secreted proteins usually described as adipokines.

Factor	Known effects	Site(s) of expression	Target site(s)	References
Adiponectin	• Decreased serum HMW adiponectin levels in obesity, advanced NAFLD and NASH patients with advanced ballooning, IR, T2DM, cardiovascular disease and MetS • Decreased serum adiponectin levels in HCC • Negative correlation with tumour size in HCC and with higher risk of HCC • Increased adiponectin levels in cirrhotic hepatitis virus infected-HCC patients • Adiponectin serum concentrations are an independent predictor of overall survival in HCC patients	Adipocytes	Hepatocytes, hepatic stellate cells, muscle cells, probably more target cell populations (*i.e.* brain)	78,91,136–142,159–163
Apelin	• Increased serum apelin levels in obesity in NAFLD patients • Apelin contributes to the angiogenesis of liver tissue in NASH • Increased apelin expression in HCC and correlation with tumorigenicity in HCC • Apelin stimulates arteriogenesis in HCC • Increased apelin receptor expression in the presence of microvascular invasion, intrahepatic metastasis, and early recurrence independent of HCC aetiology	Adipocytes	Heart, liver, adipose tissue, gastrointestinal tract, brain, endothelium, osteoblasts	167,168,170,171,173,174
Chemerin	• Association between increased serum chemerin levels and NAS, and with the presence of hepatocyte ballooning and inflammatory activity • Decreased chemerin VAT expression in high NAS score and after weight loss and/or bariatric surgery • Correlation between low serum chemerin levels and hepatic dysfunction, increased mortality in patients with decompensated cirrhosis and ascites • Independent prognostic factor in HCC, but no correlation with recurrence or prognosis in HCC patients • Association between increased serum chemerin with a poor prognosis of HCC	Adipocytes, hepatocytes		178–181,187–192
Leptin	• Increased serum leptin levels in obesity, T2DM, NASH and NAFL, but no significant predictor of NASH *vs.* non-NASH • Increased serum leptin levels in cirrhosis independent of HCC • Increased serum leptin levels are a risk factor for recurrent phase I/II of HCC after curative treatment • Increased serum leptin levels in cirrhotic patients with or without HCC *vs.* controls • Increased serum levels associated with carcinogenesis in obesity	Adipocytes, stomach mucosa, muscle	Multiple target cell populations; Brain (hypothalamus)	25,198–202,208
Resistin	• Increased serum resistin levels in morbidly obese patients and T2DM • Independent risk factor and marker to identify HCV-related cirrhosis *vs.* HCV-related HCC development	Adipose tissue	Hepatocytes	212,213,218
Visfatin	• Increased serum visfatin levels in NAFLD • Increased visfatin liver expression in morbidly obese patients with T2DM. • No correlation between liver visfatin expression, NAS score, and inflammatory stages in obese patients with NAFLD • Association between increased visfatin levels and poor prognosis, stage progression and tumour enlargement in HCC • Increased liver expression in liver fibrosis and cirrhosis • Increased serum visfatin levels in viral-HCC	Adipocytes (VAT and epicardial adipose tissue)	Myocytes, hepatocytes, adipocytes, possibly pancreatic β-cells	220,221,223,225–227

Known effects and target sites in metabolic diseases (obesity, IR, T2DM, MetS, NAFLD, NASH) and HCC. HCC, hepatocellular carcinoma; HMW, high molecular weight; IR, insulin resistance; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NAS, NAFLD activity scores; T2DM, type-2 diabetes mellitus; VAT, visceral adipose tissue.

tissue (VAT), and is associated with liver steatosis and increased plasma triglyceride levels in humans.[55,56] Serum levels of ANGPTL8 are significantly increased in IR[57] and T2DM.[58,59] ANGPTL8 requires ANGPTL3 to act on LPL, while ANGPTL8 alone has no demonstrable effect on LPL.[60] When brown adipose tissue (BAT) is exposed to the cold, overexpression of ANGPTL8 (and decreased ANGPTL4) upregulates LPL activity and triglyceride uptake.[60,61] A significant correlation between decreased serum ANGPTL8 levels and the development of MetS was also observed.[62]

Studies in human tissues and cell lines revealed diverging roles of different ANGPTLs in HCC. For example, ANGPTL1 suppressed Snail family of C2H2-type zinc finger transcription factor *SNAI2* expression, which reduced cancer cell motility and metastasis and competed with hepatocyte growth factor for binding to the MET receptor in HCC cell lines; in addition, ANGPTL1 expression was

inversely correlated with poor clinical outcomes in HCC.[63] ANGPTL2 expression was higher in HCC tissues compared with matched non-cancerous liver tissues, and positively correlated with intrahepatic metastasis in patients with HCC.[64] ANGPTL4 expression was lower in HCC tissue than non-tumorous liver tissue[65] and full-length ANGPTL4-overexpression in mice suppressed HCC tumorigenesis and metastasis.[65] ANGPTL8 was significantly overexpressed in HCC, and ANGPTL8 positively correlated with the tumour size in HCC.[55] Lipogenesis and proliferation in HCC are also increased by ANGPTL8 through its interaction with nuclear sterol regulatory element-binding protein-1 (SREBP-1).[55] Altogether, ANGPTL profiling in patients with NASH could identify patients at risk of HCC but further evaluation in larger studies is required.

Fetuins A and B

Fetuin-A (also known as α2-HS-glycoprotein) was the first hepatokine shown to be associated with metabolic disease. Serum levels are increased in obesity,[42,66] and it is an early biomarker of NAFLD,[67,68] MetS, IR[69] and T2DM.[70] Fetuin-A was identified as an endogenous Toll-like receptor 4 (TLR4)-ligand in lipid-induced IR.[71] Secretion of fetuin-B by hepatocytes has also been described in liver steatosis and T2DM.[44,45] Hepatic expression of both fetuins A and B increased in hepatic steatosis in humans.[69] However, only weak correlations were observed between hepatic and serum concentrations of fetuins A and B.[69] Human studies have meanwhile established that fetuin-A induces IR in concert with FFA via TLR4.[45,69,72] Most data on fetuin-B derive from *in vitro* or animal studies which show that it may reduce insulin sensitivity but could actually cause glucose intolerance.[72,73] Treatment of HepG2 cells with recombinant fetuin-B increased hepatic lipid accumulation, while loss of fetuin-B inhibited hepatocellular lipid accumulation, improved glucose metabolism,[44,74] and reduced intrahepatic and serum triglyceride contents in mice.[75] Fetuin-B seems to reduce phosphorylation of 5'adenosine monophosphate-activated protein kinase (AMPK) and to inhibit LXR-SREBP1c-dependent lipogenesis, while increasing fatty acid oxidation *in vitro* and *in vivo* in mice.[75] In patients with NAFLD, serum levels of both fetuins A and B negatively correlated with liver fibrosis stage[76] and other markers of liver fibrosis.[77] High serum fetuin-A concentrations were also detected in patients with HCC.[78] Taken together fetuin-A and B seem to negatively affect insulin sensitivity and glucose tolerance, suggesting a role in NAFLD and probably NAFLD-related HCC via IR.

Fibroblast growth factors

Fibroblast growth factors (FGFs) are secreted signalling proteins which regulate energy metabolism.[79] Canonical FGF functions comprise control of cell proliferation, differentiation and survival.[80,81] The FGF family includes 7 subfamilies with 18 secreted FGFs, which interact with 4 tyrosine kinase FGF receptors (FGFRs) via different cofactors.[82] FGFs bind heparin (mainly paracrine FGFs) – except for the FGF19 subfamily (FGF19, FGF21, and FGF23), which requires the Klotho proteins as cofactors (mainly endocrine FGFs).[82,83] Hepatic stellate cells (HSCs) play a pivotal role in liver fibrosis[84] and are activated by neighbouring cells and secreted factors. FGFs produced by HSCs – *i.e.* FGF1, FGF2, FGF7, FGF15, FGF9 – bind FGFRs on hepatocytes.[82] Some FGFs (FGF1, FGF2, FGF7, FGF19, FGF18 and FHF2 [previously known as FGF13]) are also expressed in subcutaneous white adipose tissue (scWAT).[85] The particular functions of FGFs depend on the FGF/FGFRs and the expression of heparin/klotho proteins in target tissue.[83,85,86] Here, we briefly discuss the most relevant FGFs relating to human metabolism and liver disease.

FGF1 and FGF2 are involved in HSC activation.[82] One study mapped the expression and secretion of FGFs in scWAT from non-obese and obese individuals.[85] Apparently only FGF1 is produced in adipocytes and acts as an auto- and paracrine factor. Only the levels of FGF1 and FGF2 significantly differed between non-obese and obese female individuals. While FGF1 expression levels were doubled among obese individuals compared to non-obese controls, FGF2 expression in scWAT was significantly reduced.[85] Serum FGF2 levels were also found to be increased in cirrhosis and HCC.[87]

In the liver and adipocytes, endocrine FGF19 and FGF21 activate FGFR4 and FGFR1c together with cofactor β-Klotho, which is abundantly expressed in hepatocytes. FGF19 and FGF21 control bile acid, lipid and glucose metabolism.[88,89] FGFR4 is predominantly expressed in mature hepatocytes.[90] In a study in humans, serum FGF19 and FGFR4 levels paralleled those of serum bile acids and were significantly increased in patients with NASH and advanced ballooning.[91] In patients with NAFLD, serum concentrations of primary and secondary bile acids were increased as a result of impaired FXR and FGFR4-mediated signalling.[92,93] Recently, a multicentre, randomized, double-blinded, placebo-controlled, phase II trial was performed to test the safety and efficacy of an FGF19 analogue for patients with NASH (NAFLD activity score [NAS] ≥4, fibrosis stage: 1–3; liver fat ≥8%). Twelve weeks of treatment led to a rapid and significant reduction in the amount of liver fat.[94] FGFR4 polymorphisms have also been detected in patients with cirrhosis and HCC[95] and the overexpression of hepatic and serum FGF19/FGFR4 has been associated with poor outcomes in patients with HCC.[93,96,97] This was confirmed by our own group, demonstrating increased serum FGF19 in NASH, NASH-HCC and in particular cirrhotic NASH-HCC.[98] FGF19 was also correlated with alterations

Key point

While a significant number of individuals with NAFLD develops HCC without advanced liver fibrosis or cirrhosis, the underlying mechanisms remain poorly understood.

in bile acids and tumour markers. The β-Klotho proteins are also increased in the serum and livers of patients with HCC as a result of ER stress.[93,97]

The hepatokine FGF21 is a regulator of glucose and lipid homeostasis and a stress response hormone. FGF21 has a positive effect on hepatic steatosis, enhances lipid oxidation, suppresses *de novo* lipogenesis in the liver,[99] and improves IR by inhibiting mTOR.[100] Serum FGF21 levels are significantly increased in overweight/obese patients[101] and in those with NAFLD,[102] MetS,[101] T2DM[103] as well as HCC and cirrhosis.[104] Liver FGF21 expressions were positively correlated with adiposity, fasting insulin and intrahepatic triglycerides,[101,102] but negatively correlated with HDL cholesterol and BMI.[101] Elevated serum FGF21 levels were also independently associated with an increased risk of developing MetS.[101] These results were consistent with a study in obese children with and without NAFLD. Serum FGF21 concentrations were significantly higher in obese children with NAFLD and were positively correlated with steatosis grades (severe *vs.* mild) in biopsies and with the total intrahepatic lipid content assessed by magnetic resonance proton spectroscopy.[105] Serum FGF21 levels positively correlated with NAS and pathological characteristics of NAFLD; patients with advanced NASH could be identified by FGF21 serum levels in combination with cytokeratin-18-M30 antigen, IL-1Ra, pigment epithelium-derived factor and osteoprotegerin.[106] Moreover, hepatic FGF21 protein expression is significantly induced in murine models of hepatocarcinogenesis and during hepatic stress in humans.[104] Increased hepatic FGF21 expression has been observed in stage A HCC, NAFLD, cirrhosis and hepatitis C, so its applicability as a marker for a specific disease could be limited. Further studies on FGF21 and its association with hepatic injury beyond NAFLD and MetS are required.

Hepassocin

Hepassocin (HPS) (also known as hepatocyte-derived fibrinogen-related protein 1) is a hepatokine that is involved in liver regeneration and is induced by the hepatocyte nuclear factor 1α (HNF1α)-regulated IL-6/IL-6R/STAT3 pathway in hepatoma cells *in vitro*.[107] High levels of serum HPS were detected in mice and patients with NAFLD, and levels of HPS correlated with NAS.[108] Serum HPS concentrations also correlated with those of inflammatory cytokines (*e.g.* IL-1b, IL-6, TNF-α) and the expression of lipogenesis-related markers (FASN, ACC, SREBP-1). Hepatic overexpression of HPS induced lipid accumulation through an extracellular signal-regulated kinase 1/2 (ERK1/2)-dependent pathway in mice.[109] Additionally, HPS has been shown to contribute to the development of IR and T2DM through ERK1/2 activation in HPS knock-out mice.[110] HPS expression in BAT and liver was increased following partial hepatectomy in mice[110] and by IL-6 *in vitro*,[107] suggesting a cross talk between the injured liver and adipose tissue.[110] Oleic acid increased HPS expression by activating signal transducer and activator of transcription 3 (STAT3) signalling and inducing IR in HepG2 cells,[111] while palmitic acid induced HPS through p38-modulated binding of C/EBPβ to the HPS promoter in mice.[112] HPS administration protected against liver injury and improved survival in rats with hepatitis.[113] In contrast, liver-specific HPS expression is repressed in HCC cells and patients with HCC,[107,114] likely through a decrease in HNF1α expression.[107,115] It remains to be elucidated if HPS has protective effects on metabolic alterations in the liver and adipocytes in NASH and NASH-related HCC.

Retinol-binding protein 4

Retinol-binding protein 4 (RBP4) is a specific retinol/vitamin A carrier protein belonging to the lipocalin family. This plasma protein is primarily synthesised in the liver but also released from adipose tissue as an adipokine.[116] All-*trans*-retinol binding induces RBP4 secretion, and vitamin A deficiency causes RBP4 accumulation in human liver.[116,117] In turn RBP4 is released upon saturation with retinol. In NAFLD, liver vitamin A homeostasis is disrupted, which may contribute to disease progression.[118] Though the role of RBP4 in NAFLD and IR is controversial, as has been reviewed elsewhere.[119] Some studies found no correlation between liver and plasma RBP4 levels and NAFLD/NASH severity,[120–122] while others detected a correlation between circulating RBP4 levels and NAFLD development.[123,124] In a large prospective study, baseline RBP4 was positively associated with the occurrence of NAFLD, and elevated levels of serum RBP4 were detected in patients with NAFLD.[124,125] In NASH, high hepatic RBP4 protein expression correlated with a moderate to severe fibrosis score (≥F2, with a high NAS score) and high lobular inflammation scores.[126] RBP4 expression by adipocytes may further contribute to IR and T2DM in obesity.[127,128] Both obese-non-diabetic and obese-diabetic patients had 1.9-fold elevated serum RBP4 levels compared to lean controls,[127,128] and serum levels of RBP4 positively correlated with BMI and IR.[128] Conversely other reports showed serum and hepatic RBP4 levels to negatively correlate with liver fibrosis stage.[121] While these results seem inconclusive, they could be explained by the pleiotropic functions of RBP4, the differences among NAFLD disease stages, and the characteristics of the different populations studied. In cirrhosis, RBP4 expression correlated with reduced hepatic glucose production,[129] but not with IR.[121,129–131] Impaired vitamin A homeostasis and deficiency may also be seen in liver fibrosis and cirrhosis.[132]

Collectively, the data suggests that RBP4 could be a marker to distinguish simple steatosis

from NASH with advanced fibrosis/cirrhosis or NASH-related cirrhotic HCC. Further studies controlling for the separate impact of IR and fibrogenesis on RBP4 expression in the liver and adipose tissue are required.

Adipokines

Adiponectin

Adiponectin is a key adipokine with important metabolic functions including glucose regulation, insulin sensitising, and fatty acid oxidation. Adiponectin also has anti-inflammatory, anti-fibrotic, and anti-tumourigenic activities[37,46,133,134] and is an important mediator of FGF21 activity.[135] Circulating levels of adiponectin negatively correlate with BMI and are decreased in patients with advanced NASH, IR, T2DM, and MetS.[91,136–142] High molecular weight (HMW) adiponectin, which is thought to be the most biologically active form, has been associated with IR, cardiovascular diseases, and liver fibrosis in humans.[140,143] HMW adiponectin also inhibits the proliferation of HSCs in part via the AMPK pathway *in vitro*.[140,144,145] A recent systematic review and meta-analysis showed that serum adiponectin levels were decreased in patients with NAFL and NASH compared to controls, and increased in NAFL compared to NASH, independently of BMI, age, gender, and T2DM.[140] By now it is clear that adiponectin serum concentrations are inversely correlated with BMI as well as the severity of NAFLD (NAS), and low adiponectin is associated with hepatic and systemic IR. Increased adipose tissue mass in overweight and obesity, reduced adiponectin, and IR are interconnected, making it difficult to determine if reduced adiponectin has an effect independent from obesity. That said, a few studies demonstrating the effects of low adiponectin on the severity of NAFLD or IR,[146–149] and increased adiponectin levels under pioglitazone treatment (without any weight loss),[150,151] hint to an effect of adiponectin independent of BMI or adipose tissue mass.

In the liver, adiponectin activates the AMPK and PPAR-α pathways, inhibits gluconeogenesis by downregulating gluconeogenesis-related genes (*i.e.* PEPCK, G6P, ACC, FASN, CPT-1), promotes FFA oxidation, and suppresses lipogenesis.[152] Proinflammatory cytokines such as TNF-α and IL-6 inhibit adiponectin levels under conditions of oxidative stress and hypoxia *in vitro* and in mice.[153,154] Conversely adiponectin suppresses TNF-α in adipocytes. Adiponectin also suppresses NF-κB activation, TNF-α, and IL-6 in murine NASH and HCC models and *in vitro*.[155,156] Adiponectin deficiency enhanced high-fat diet (HFD)-induced glucose intolerance and obesity by increasing TNFα and FFA *via* downregulation of PPARα.[157] In addition, hepatic TNF-α expression was significantly increased in adiponectin knock-out mice and, under HFD conditions, adiponectin deficiency enhanced the development of obesity, hyperlipidaemia, steatohepatitis, pericellular fibrosis, and adenoma formation.[158] These results suggest that adiponectin has a protective role in NASH and liver fibrosis[158] by reducing IR.

Among patients with HCC, plasma adiponectin levels were significantly lower than in non-HCC controls and were also negatively correlated with tumour size.[159] In mice, the administration of exogenous adiponectin inhibited liver tumour growth and metastasis.[159] A prospective case-control study showed that levels of circulating adiponectin, leptin, fetuin-A, C-reactive protein, IL-6 and C-peptide were significantly increased in patients with HCC compared to controls. Non-HMW adiponectin, IL-6, C-reactive protein, C-peptide and GLDH were associated with a higher risk of non-viral HCC, independent of established liver cancer risk factors and BMI.[78] Elevated adiponectin and leptin levels were also found among cirrhotic and non-cirrhotic virus infected patients with HCC.[160–162] Serum adiponectin levels correlated with the stage of liver fibrosis,[163] were associated with cirrhosis in patients with chronic liver diseases,[164] and with worsened overall survival in patients with HCC.[160,162,163] These results suggest that serum adiponectin may be a useful parameter to distinguish early stages of NASH (*i.e.*, decreased levels of adiponectin) from more advanced stages such as liver cirrhosis and HCC (*i.e.*, increased adiponectin levels).[91] Still, the role of adiponectin in NASH-related HCC and non-cirrhotic NASH-HCC requires further investigation.

Apelin

Apelin is an adipokine which is regulated by TNF-α and by insulin in human adipocytes *in vitro*.[165,166] Apelin contributes to the angiogenesis of liver tissue in NASH at early stages[167] and seems to stimulate arteriogenesis in HCC in both humans and mice.[168] In addition, apelin promotes hepatic fibrosis through ERK signalling in the human HSC cell line LX-2.[169] In patients with NAFLD, serum apelin levels (with apelin-13 being the main form circulating in plasma) were significantly higher in obese patients.[170,171] Plasma apelin-13 (13 aa), an active fragment of pre-proprotein apelin (77 aa), reduces the expression of lipogenic SREBP-1c and increases lipolytic PPARα expression.[172]

In patients with HCC, apelin is further overexpressed and promotes HCC tumorigenesis.[173,174] Evaluation of apelin and apelin receptor (APJR) expression in 288 curatively resected HCCs revealed that high APJR expression was significantly associated with the presence of microvascular invasion, intrahepatic metastasis, and early recurrence independent of HCC aetiology.[173] In HCC, Wnt/β-catenin signalling induces apelin expression, which correlates with upregulation of phospho-Akt and phospho-glycogen synthase kinase 3 β (GSK3β), thereby accelerating cell cycle progression and inhibiting apoptosis.[174] However,

Key point

As organ-specific cytokines with autocrine, paracrine, and endocrine functions, hepatokines and adipokines are important players in the crosstalk between liver and adipose tissue and the pathophysiology of NAFLD and NASH-related HCC with or without cirrhosis.

the mechanistic role of apelin in NASH-related HCC as well as cirrhotic *vs.* non-cirrhotic HCC remains unclear.

Chemerin

Chemerin, an adipokine as well as hepatokine, is associated with obesity and MetS.[175–177] Increased circulating chemerin levels were significantly associated with NAS and with hepatocyte ballooning and inflammatory activity,[178–180] while chemerin expression in VAT was negatively associated with NAS.[181] Insulin regulates circulating and adipocyte chemerin levels, which can be decreased by treatment with metformin.[182] Serum levels of chemerin are significantly reduced after weight loss and/or bariatric surgery.[183] Chemerin also induces FGF21 expression in primary human hepatocyte cultures[184] and, along with adiponectin and fatty acid binding protein 4 (FABP4), levels of serum chemerin exhibited strong associations with components of MetS.[185] However, results regarding hepatic chemerin levels remain controversial: while some studies showed that the hepatic expression of chemerin is decreased in patients[184] and mouse models of NASH,[186] others reported significantly elevated hepatic mRNA and protein levels of chemerin as well as circulating chemerin levels, and that these positively correlated with BMI, hepatocyte ballooning, and the degree of hepatic steatosis.[180,187–189] This apparent discrepancy may be related to differences in the patient cohorts but requires clarification in sufficiently powered studies.

In patients with HCC, there is a significant correlation between low hepatic and serum chemerin and poor prognosis.[190,191] Low serum chemerin levels correlate with hepatic dysfunction and increased mortality in patients with decompensated cirrhosis and ascites.[192] Serum chemerin negatively correlates with composite scores of disease severity (Child-Pugh score, MELD and CLIF-SOFA) in patients with mixed aetiologies.[191,192] To date, no human study has shown an impact of chemerin in NASH-related HCC. In a single study in mice, no changes in serum and/or hepatic chemerin levels were found in NASH-related HCC compared to NASH.[187] Thus, there is considerable need for experimental and clinical research on the role of chemerin in NASH-related HCC as well as on its role in cirrhotic and non-cirrhotic HCC.

Leptin

Leptin is a regulator of appetite and energy expenditure; it is probably the most prominent adipokine, having been widely studied for many years.[193] By acting on the hypothalamus, leptin decreases appetite and increases energy expenditure via sympathetic stimulation of several tissues.[194] A recent review by Izquierdo *et al.* summarised current knowledge on leptin and leptin resistance in obesity[195] and Adolph *et al.* reviewed the role of leptin in NAFLD-related HCC.[46] Thus, we provide only a short overview of the recent studies focused on leptin in NAFLD and HCC with or without cirrhosis.

Obesity increases the expression and serum levels of leptin, and leptin gene mutations result in obesity in mice and humans.[196,197] According to a systematic review and meta-analysis by Polyzos *et al.*,[198] higher circulating leptin levels were seen in NAFL and NASH compared to healthy controls, and in NASH when compared to NAFL. Increased serum leptin levels also correlated with increased NAFLD severity,[198] and a recent study further showed that obesity and T2DM were associated with increased leptin and decreased adiponectin serum levels in patients with coronary artery disease.[199] In addition, higher protein expression of leptin and IL-6 in subcutaneous adipose tissue has been observed in male patients with coronary artery disease.[199]

In patients with HCC, serum leptin levels are increased and leptin expression significantly correlates with tumour proliferation.[200] Moreover, increased serum leptin levels were found to be a risk factor for recurrent stage I/II of HCC after curative treatment.[25] Serum leptin levels are significantly increased in cirrhotic patients independently of the presence of HCC[201] and are not associated with the development of HCC in cirrhosis.[201,202] However, leptin has a direct effect on HSCs by increasing collagen gene expression and stimulating activation of Stat3 in activated HSCs.[203] Therefore, it has been suggested that leptin contributes to the progression of liver fibrosis in NASH.[204] Moreover, high circulating leptin induces NADPH oxidase-NF-κB activation and causes miR21-mediated SMAD7 inhibition which increases transforming growth factor-β signalling and fibrogenesis in experimental and human NASH.[205] Leptin has oncogenic potential and stimulates the proliferation, tumour invasiveness and migration of HCC cell lines[200,206] and cholangiocarcinoma cells *in vitro*,[207] while adiponectin antagonises the oncogenic activity of leptin in HCC.[200] In addition, normal and malignant cholangiocytes express leptin and both long and short isoforms of leptin receptors.[199,207] Increased serum leptin levels seem to be associated with carcinogenesis in obesity.[208]

Taken together, in patients with obesity and NAFLD, high serum leptin concentrations seem to be associated with adverse disease course (fibrogenesis and HCC development) as well as adverse outcomes. New strategies to utilise leptin as a marker for HCC development in NAFLD or even as a therapeutic target in this setting should be developed.

Resistin

Resistin is an adipokine related to inflammatory responses by NF-κB-dependent stimulation of

Key point

Hepatokines and adipokines, in particular ANGPTLs, FGFs, and apelin, are promising candidates to improve detection, diagnosis and treatment of NAFLD-related HCC.

proinflammatory cytokines such as IL-1, IL-6, IL-12, and TNF-α.[209–211] In humans, resistin seems to be synthesised mostly by mononuclear cells within and outside the adipose tissue.[210] Previously, circulating resistin was found to be significantly elevated in morbidly obese (BMI >49) patients[212] and those with T2DM[213] when compared with healthy donors, but systemic resistin levels did not correlate with IR.[214] A more recent study did not find any significant correlation between resistin levels and BMI.[214] While the comparison of serum resistin levels in patients with different NAFLD stages from various studies was inconsistent,[210] more recent studies showed that serum, liver and VAT resistin levels were decreased in patients with NAFLD after laparoscopic sleeve gastrectomy.[215,216] Interestingly, liver resistin expression significantly correlated with NAS and the adipocyte size as well as VAT inflammation.[216] In patients with NASH, the serum levels of resistin also showed an inverse correlation with the stage of fibrosis.[217] High resistin levels (>12 ng/ml) were associated with HCV-related cirrhosis and are considered an independent risk factor for the development of HCV-related HCC.[218] However, the role of resistin in NASH-related HCC has not yet been investigated.

Visfatin

Visfatin (also known as nicotinamide phosphoribosyl transferase or Nampt), is an adipokine highly expressed in epicardial adipose tissue of male patients with coronary artery disease.[199,219] Plasma visfatin levels are significantly elevated in patients with NAFLD compared to healthy controls,[220,221] and it has been suggested that plasma visfatin concentrations might predict the presence of portal inflammation in patients with NAFLD.[222] However, in NAFLD, visfatin expression did not correlate with the NAS score and inflammatory stages, while visfatin expression was significantly higher among patients with fibrosis than non-fibrotic controls, and even more pronounced in advanced fibrosis.[223] Additionally, hepatic visfatin expression was increased in morbidly obese patients with T2DM.[223] However, according to a recent long-term follow-up study in a German population, visfatin levels did not correlate with the presence or absence of NAFLD at baseline, while there was a strong correlation between serum visfatin levels and leukocyte numbers, which indicates a potential proinflammatory role for visfatin.[224]

Increased visfatin is associated with poor prognosis in patients with HCC,[225,226] which is underlined by its association with HCC progression.[227] Significantly increased visfatin expression was also seen in patients with cirrhosis compared to controls.[226] While increased plasma visfatin levels were found in HCC due to viral hepatitis,[228] there is not yet conclusive evidence for a role of visfatin in NASH-related HCC.

Specific role of hepatokines and adipokines in non-cirrhotic NASH-related HCC and clinical applicability

Up to now, very few studies have specifically addressed the question of how a particular hepatokine or adipokine is involved in HCC development in non-cirrhotic NASH, although we can derive information on this topic from the data we have compiled. The serum levels and hepatic expression of FGF2, FGF21 and leptin are increased in cirrhosis and HCC. Adiponectin is usually reduced in obesity and even more so in NAFLD and NASH, but seems to increase again during fibrogenesis.[161] Very low adiponectin levels have been found in HCC, however high serum adiponectin in HCC is associated with poor survival (in HCV patients). Thus, it is not currently possible to differentiate between the effects of these factors on fibrogenesis/cirrhosis and HCC development. This is also the case for angiopoietins, hepassocin, apelin, resistin and visfatin, which are either similarly regulated in fibrogenesis/cirrhosis and HCC, or for which there are insufficient data to unravel their effect on the development of cirrhosis and HCC in NAFLD. In contrast, FGF19 seems to be on the one hand inversely correlated with fibrosis stage in patients with alcohol-related liver disease[229] and on the other hand associated with increased HCC risk and poor outcome. A well-designed prospective study in patients with NAFLD-related HCC, with and without cirrhosis, would be needed to clarify the contribution of known hepatokines and adipokines to HCC development in non-cirrhotic NAFLD.

The same is valid for the diagnostic and even more so for the therapeutic application of hepatokines and adipokines. The effect sizes of changes in serum concentrations during NAFLD and HCC are probably too small for a single factor to be used as a diagnostic marker for HCC. However, when measured sequentially over the course of NAFLD, individual changes to a set of hepatokines and adipokines could possibly assist in the identification of those at risk or in the process of developing HCC. For example, reductions in serum concentrations of ANGPTL1 and 4, and hepassocin, in association with a pronounced fall in adiponectin level might suggest HCC development. Meanwhile, increases in the level of serum fetuin-A, FGF2, 19, 21, in association with an even greater increase in serum apelin and leptin levels could indicate HCC development. The combination of suppressed adiponectin but elevated chemerin and visfatin levels could portend a poor prognosis in NAFLD-related HCC. Overall, there is still insufficient evidence to utilise the potential of hepatokines and adipokines in clinical practice.

Conclusion

The incidence of NAFLD-related HCC has increased in parallel with the obesity pandemic and the subsequent rise in NAFLD prevalence. Better screening and diagnostic approaches are required to compensate for the expected increase in NAFLD-related HCC cases, while novel therapeutic options are warranted. Hepatokines and adipokines have potential as markers of disease progression in NAFLD or even as early markers for HCC development in this setting. In particular, increases in serum ANGPTL1, 2, and 8, FGF2, 19, and 21, apelin, chemerin, leptin, and visfatin have been associated either with HCC development or a poor prognosis in NAFLD-related HCC. Conversely, reduced serum concentrations of ANGPTL4, hepassocin, and adiponectin were observed in NAFLD-related HCC. These observations provide hope for the possible development of an NAFLD-HCC detection panel based on a combination of hepatokines and adipokines. Deeper understanding of the underlying mechanisms responsible for increases or decreases in these factors in HCC development might even uncover novel preventive or therapeutic strategies.

Abbreviations

ACC, acetyl-CoA carboxylase; AMPK, 5'adenosine monophosphate-activated protein kinase; ANGPTLs, angiopoietin-like proteins; APJR, apelin receptor; BAT, brown adipose tissue; CLIF-SOFA, chronic liver failure – sequential organ failure assessment; ER, endoplasmic reticulum; ERK (MAPK1), extracellular signal-regulated kinase; FASN, fatty acid synthase; FFA, free fatty acid; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; Gsk3b, glycogen synthase kinase 3 β; HCC, hepatocellular carcinoma; HFD, high-fat diet; HMW, high molecular weight; HNF1α, hepatocyte nuclear factor 1α; HPS, hepassocin; HSC, hepatic stellate cell; IL, interleukin; IR, insulin resistance; LPL, lipoprotein lipase; LXR, liver X receptor; MELD, model for end-stage liver disease; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; NLRP3, NOD-like receptor P3; PPARs, peroxisome proliferator-activated receptors; RBP4, retinol-binding protein 4; ROS, reactive oxygen species; sc, subcutaneous; SREBP-1c, sterol regulatory element-binding protein-1c; STAT3, signal transducer and activator of transcription 3; TLR4, Toll-like receptor 4; TNF-α, tumour necrosis factor-α; T2DM, type-2 diabetes mellitus; VAT, visceral adipose tissue; WAT, white adipose tissue.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

O.K. researched the data for the article and contributed to writing the article. AC supervised the manuscript. All authors contributed to critical reviewing and editing of the manuscript before submission.

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Supplementary data

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References

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[1] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–357.

[2] Ryerson AB, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer 2016;122:1312–1337.

[3] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.

[4] Ghouri YA, Mian I, Rowe JH. Review of hepatocellular carcinoma: epidemiology, etiology, and carcinogenesis. J Carcinog 2017;16:1.

[5] Zhang DY, Friedman SL. Fibrosis-dependent mechanisms of hepatocarcinogenesis. Hepatology 2012;56:769–775.

[6] Mezale D, Strumfa I, Vanags A, Mezals M, Fridrihsone I, Strumfs B, et al. Non-alcoholic steatohepatitis, liver cirrhosis and hepatocellular carcinoma: the molecular pathways | IntechOpen. Liver Cirrhosis 2018. https://doi.org/10.5772/intechopen.68771.

[7] Stine JG, Wentworth BJ, Zimmet A, Rinella ME, Loomba R, Caldwell SH, et al. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. Aliment Pharmacol Ther 2018;48:696–703.

[8] **Nakagawa S**, **Wei L**, **Song WM**, Higashi T, Ghoshal S, Kim RS, et al. Molecular liver cancer prevention in cirrhosis by organ transcriptome analysis and lysophosphatidic acid pathway inhibition. Cancer Cell 2016;30:879–890.

[9] Ertle J, Dechêne A, Sowa J-P, Penndorf V, Herzer K, Kaiser G, et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. Int J Cancer 2011;128:2436–2443.

[10] Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2016;14:124–131.e1.

[11] Kimura T, Kobayashi A, Tanaka N, Sano K, Komatsu M, Fujimori N, et al. Clinicopathological characteristics of non-B non-C hepatocellular carcinoma without past hepatitis B virus infection. Hepatol Res 2017;47:405–418.

[12] Canbay A, Kachru N, Haas JS, Sowa J-P, Meise D, Ozbay AB. Patterns and predictors of mortality and disease progression among patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2020;52:1185–1194.
[13] Cholankeril G, Patel R, Khurana S, Satapathy SK. Hepatocellular carcinoma in non-alcoholic steatohepatitis: current knowledge and implications for management. World J Hepatol 2017;9:533–543.
[14] Perumpail RB, Liu A, Wong RJ, Ahmed A, Harrison SA. Pathogenesis of hepatocarcinogenesis in non-cirrhotic nonalcoholic fatty liver disease: potential mechanistic pathways. World J Hepatol 2015;7:2384–2388.
[15] Best J, Bechmann LP, Sowa J-P, Sydor S, Dechêne A, Pflanz K, et al. GALAD score detects early hepatocellular carcinoma in an international cohort of patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2020;18:728–735.e4.
[16] Apovian CM. The obesity epidemic–understanding the disease and the treatment. N Engl J Med 2016;374:177–179.
[17] Polyzos SA, Kountouras J, Mantzoros CS. Adipose tissue, obesity and non-alcoholic fatty liver disease. Minerva Endocrinol 2017;42:92–108.
[18] Paradis V, Zalinski S, Chelbi E, Guedj N, Degos F, Vilgrain V, et al. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. Hepatology 2009;49:851–859.
[19] Viganò L, Conci S, Cescon M, Fava C, Capelli P, D'Errico A, et al. Liver resection for hepatocellular carcinoma in patients with metabolic syndrome: a multicenter matched analysis with HCV-related HCC. J Hepatol 2015;63:93–101.
[20] Cauchy F, Zalinski S, Dokmak S, Fuks D, Farges O, Castera L, et al. Surgical treatment of hepatocellular carcinoma associated with the metabolic syndrome. Br J Surg 2013;100:113–121.
[21] Farges O, Ferreira N, Dokmak S, Belghiti J, Bedossa P, Paradis V. Changing trends in malignant transformation of hepatocellular adenoma. Gut 2011;60:85–89.
[22] Guzman G, Brunt EM, Petrovic LM, Chejfec G, Layden TJ, Cotler SJ. Does nonalcoholic fatty liver disease predispose patients to hepatocellular carcinoma in the absence of cirrhosis? Arch Pathol Lab Med 2008;132:1761–1766.
[23] Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology 2010;51:1820–1832.
[24] Shin E, Yu Y-D, Kim D-S, Won NH. Adiponectin receptor expression predicts favorable prognosis in cases of hepatocellular carcinoma. Pathol Oncol Res 2014;20:667–675.
[25] Watanabe N, Takai K, Imai K, Shimizu M, Naiki T, Nagaki M, et al. Increased levels of serum leptin are a risk factor for the recurrence of stage I/II hepatocellular carcinoma after curative treatment. J Clin Biochem Nutr 2011;49:153–158.
[26] Shen C, Zhao C-Y, Zhang R, Qiao L. Obesity-related hepatocellular carcinoma: roles of risk factors altered in obesity. Front Biosci (Landmark Ed) 2012;17:2356–2370.
[27] Ringseis R, Eder K, Mooren FC, Krüger K. Metabolic signals and innate immune activation in obesity and exercise. Exerc Immunol Rev 2015;21:58–68.
[28] Wen H, Gris D, Lei Y, Jha S, Zhang L, Huang MT-H, et al. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat Immunol 2011;12:408–415.
[29] Handelsman Y, Leroith D, Bloomgarden ZT, Dagogo-Jack S, Einhorn D, Garber AJ, et al. Diabetes and cancer–an AACE/ACE consensus statement. Endocr Pract 2013;19:675–693.
[30] Jialal I, Kaur H, Devaraj S. Toll-like receptor status in obesity and metabolic syndrome: a translational perspective. J Clin Endocrinol Metab 2014;99:39–48.
[31] Engin AB. Adipocyte-macrophage cross-talk in obesity. Adv Exp Med Biol 2017;960:327–343.
[32] Najjar SM, Russo L. CEACAM1 loss links inflammation to insulin resistance in obesity and non-alcoholic steatohepatitis (NASH). Semin Immunopathol 2014;36:55–71.
[33] Nolan CJ, Prentki M. Insulin resistance and insulin hypersecretion in the metabolic syndrome and type 2 diabetes: time for a conceptual framework shift. Diab Vasc Dis Res 2019;16:118–127.
[34] Arcopinto M, Schiavo A, Salzano A, Bossone E, D'Assante R, Marsico F, et al. Metabolic syndrome in heart failure: friend or foe? Heart Fail Clin 2019;15:349–358.
[35] Tagi VM, Giannini C, Chiarelli F. Insulin resistance in children. Front Endocrinol (Lausanne) 2019;10:342.
[36] **Marchisello S**, **Di Pino A**, Scicali R, Urbano F, Piro S, Purrello F, et al. Pathophysiological, molecular and therapeutic issues of nonalcoholic fatty liver disease: an overview. Int J Mol Sci 2019;20:1948.
[37] Valenti L, Bugianesi E, Pajvani U, Targher G. Nonalcoholic fatty liver disease: cause or consequence of type 2 diabetes? Liver Int 2016;36:1563–1579.
[38] **Li Y**, **Wang J**, Tang Y, Han X, Liu B, Hu H, et al. Bidirectional association between nonalcoholic fatty liver disease and type 2 diabetes in Chinese population: evidence from the Dongfeng-Tongji cohort study. PLoS One 2017;12:e0174291.
[39] Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. Gut 2005;54:533–539.
[40] Mantovani A, Targher G. Type 2 diabetes mellitus and risk of hepatocellular carcinoma: spotlight on nonalcoholic fatty liver disease. Ann Transl Med 2017;5:270.
[41] Kim JH, Sinn DH, Gwak G-Y, Kang W, Paik Y-H, Choi MS, et al. Insulin resistance and the risk of hepatocellular carcinoma in chronic hepatitis B patients. J Gastroenterol Hepatol 2017;32:1100–1106.
[42] Stefan N, Häring H-U. The role of hepatokines in metabolism. Nat Rev Endocrinol 2013;9:144–152.
[43] Iroz A, Couty J-P, Postic C. Hepatokines: unlocking the multi-organ network in metabolic diseases. Diabetologia 2015;58:1699–1703.
[44] Meex RC, Hoy AJ, Morris A, Brown RD, Lo JCY, Burke M, et al. Fetuin B is a secreted hepatocyte factor linking steatosis to impaired glucose metabolism. Cell Metab 2015;22:1078–1089.
[45] Meex RCR, Watt MJ. Hepatokines: linking nonalcoholic fatty liver disease and insulin resistance. Nat Rev Endocrinol 2017;13:509–520.
[46] Adolph TE, Grander C, Grabherr F, Tilg H. Adipokines and non-alcoholic fatty liver disease: multiple interactions. Int J Mol Sci 2017;18:1649.
[47] Carbone C, Piro G, Merz V, Simionato F, Santoro R, Zecchetto C, et al. Angiopoietin-like proteins in angiogenesis, inflammation and cancer. Int J Mol Sci 2018;19:431.
[48] Dijk W, Kersten S. Regulation of lipid metabolism by angiopoietin-like proteins. Curr Opin Lipidol 2016;27:249–256.
[49] Cinkajzlová A, Mráz M, Lacinová Z, Kloučková J, Kaválková P, Kratochvílová H, et al. Angiopoietin-like protein 3 and 4 in obesity, type 2 diabetes mellitus, and malnutrition: the effect of weight reduction and realimentation. Nutr Diabetes 2018;8:21.
[50] **Mandard S**, **Zandbergen F**, van Straten E, Wahli W, Kuipers F, Müller M, et al. The fasting-induced adipose factor/angiopoietin-like protein 4 is physically associated with lipoproteins and governs plasma lipid levels and adiposity. J Biol Chem 2006;281:934–944.
[51] Oike Y, Akao M, Yasunaga K, Yamauchi T, Morisada T, Ito Y, et al. Angiopoietin-related growth factor antagonizes obesity and insulin resistance. Nat Med 2005;11:400–408.
[52] **Ebert T**, **Bachmann A**, Lössner U, Kratzsch J, Blüher M, Stumvoll M, et al. Serum levels of angiopoietin-related growth factor in diabetes mellitus and chronic hemodialysis. Metab Clin Exp 2009;58:547–551.
[53] Daneshzad E, Farsad-Naeimi A, Heshmati J, Mirzaei K, Maghbooli Z, Keshavarz S-A. The association between dietary antioxidants and adipokines level among obese women. Diabetes Metab Syndr 2019;13:1369–1373.
[54] Dong X-Y, Pang X-W, Yu S-T, Su Y-R, Wang H-C, Yin Y-H, et al. Identification of genes differentially expressed in human hepatocellular carcinoma by a modified suppression subtractive hybridization method. Int J Cancer 2004;112:239–248.
[55] Wang C, Tong Y, Wen Y, Cai J, Guo H, Huang L, et al. Hepatocellular carcinoma-associated protein TD26 interacts and enhances sterol regulatory element-binding protein 1 activity to promote tumor cell proliferation and growth. Hepatology 2018;68:1833–1850.
[56] von Loeffelholz C, Pfeiffer AFH, Lock JF, Lieske S, Döcke S, Murahovschi V, et al. ANGPTL8 (betatrophin) is expressed in visceral adipose tissue and relates to human hepatic steatosis in two independent clinical collectives. Horm Metab Res 2017;49:343–349.
[57] **Xu J**, **Lin Y**, Zhou H, Zhao L, Xiang G. The correlation between circulating betatrophin and insulin resistance in general population: a meta-analysis. Horm Metab Res 2017;49:760–771.
[58] Yin Y, Ding X, Peng L, Hou Y, Ling Y, Gu M, et al. Increased serum ANGPTL8 concentrations in patients with prediabetes and type 2 diabetes. J Diabetes Res 2017;2017:8293207.

[59] **Wang S**, **Hong X**, Tu Z, Yuan G. Angiopoietin-like protein 8: an attractive biomarker for the evaluation of subjects with insulin resistance and related disorders. Diabetes Res Clin Pract 2017;133:168–177.
[60] Kovrov O, Kristensen KK, Larsson E, Ploug M, Olivecrona G. On the mechanism of angiopoietin-like protein 8 for control of lipoprotein lipase activity. J Lipid Res 2019;60:783–793.
[61] **Fu Z**, **Yao F**, Abou-Samra AB, Zhang R. Lipasin, thermoregulated in brown fat, is a novel but atypical member of the angiopoietin-like protein family. Biochem Biophys Res Commun 2013;430:1126–1131.
[62] Wang H, Lai Y, Han C, Liu A, Fan C, Wang H, et al. The effects of serum ANGPTL8/betatrophin on the risk of developing the metabolic syndrome – a prospective study. Scientific Rep 2016;6:28431.
[63] Chen H-A, Kuo T-C, Tseng C-F, Ma J-T, Yang S-T, Yen C-J, et al. Angiopoietin-like protein 1 antagonizes MET receptor activity to repress sorafenib resistance and cancer stemness in hepatocellular carcinoma. Hepatology 2016;64:1637–1651.
[64] Gao L, Ge C, Fang T, Zhao F, Chen T, Yao M, et al. ANGPTL2 promotes tumor metastasis in hepatocellular carcinoma. J Gastroenterol Hepatol 2015;30:396–404.
[65] Ng KT-P, Xu A, Cheng Q, Guo DY, Lim ZX-H, Sun CK-W, et al. Clinical relevance and therapeutic potential of angiopoietin-like protein 4 in hepatocellular carcinoma. Mol Cancer 2014;13:196.
[66] von Loeffelholz C, Horn P, Birkenfeld AL, Claus RA, Metzing BU, Döcke S, et al. Fetuin A is a predictor of liver fat in preoperative patients with nonalcoholic fatty liver disease. J Invest Surg 2016;29:266–274.
[67] **Huang Y**, **Huang X**, Ding L, Wang P, Peng K, Chen Y, et al. Serum fetuin-A associated with fatty liver index, early indicator of nonalcoholic fatty liver disease: a strobe-compliant article. Medicine (Baltimore) 2015;94:e1517.
[68] **Kahraman A**, **Sowa J-P**, Schlattjan M, Sydor S, Pronadl M, Wree A, et al. Fetuin-A mRNA expression is elevated in NASH compared with NAFL patients. Clin Sci 2013;125:391–400.
[69] Peter A, Kovarova M, Staiger H, Machann J, Schick F, Königsrainer A, et al. The hepatokines fetuin-A and fetuin-B are upregulated in the state of hepatic steatosis and may differently impact on glucose homeostasis in humans. Am J Physiol Endocrinol Metab 2018;314:E266–E273.
[70] Iroz A, Couty J-P, Postic C. Hepatokines: unlocking the multi-organ network in metabolic diseases. Diabetologia 2015;58:1699–1703.
[71] Pal D, Dasgupta S, Kundu R, Maitra S, Das G, Mukhopadhyay S, et al. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. Nat Med 2012;18:1279–1285.
[72] Lonardo A, Lugari S, Ballestri S, Nascimbeni F, Baldelli E, Maurantonio M. A round trip from nonalcoholic fatty liver disease to diabetes: molecular targets to the rescue? Acta Diabetol 2019;56:385–396.
[73] Best JD, Kahn SE, Ader M, Watanabe RM, Ni TC, Bergman RN. Role of glucose effectiveness in the determination of glucose tolerance. Diabetes Care 1996;19:1018–1030.
[74] Šeda O, Cahová M, Míková I, Šedová L, Daňková H, Heczková M, et al. Hepatic gene expression profiles differentiate steatotic and non-steatotic grafts in liver transplant recipients. Front Endocrinol (Lausanne) 2019;10:270.
[75] **Zhou W**, **Yang J**, **Zhu J**, Wang Y, Wu Y, Xu L, et al. Fetuin B aggravates liver X receptor-mediated hepatic steatosis through AMPK in HepG2 cells and mice. Am J Transl Res 2019;11:1498–1509.
[76] Sato M, Kamada Y, Takeda Y, Kida S, Ohara Y, Fujii H, et al. Fetuin-A negatively correlates with liver and vascular fibrosis in nonalcoholic fatty liver disease subjects. Liver Int 2015;35:925–935.
[77] Ebert T, Linder N, Schaudinn A, Busse H, Berger J, Lichtinghagen R, et al. Association of fetuin B with markers of liver fibrosis in nonalcoholic fatty liver disease. Endocrine 2017;58:246–252.
[78] Aleksandrova K, Boeing H, Nöthlings U, Jenab M, Fedirko V, Kaaks R, et al. Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. Hepatology 2014;60:858–871.
[79] Nies VJM, Sancar G, Liu W, van Zutphen T, Struik D, Yu RT, et al. Fibroblast growth factor signaling in metabolic regulation. Front Endocrinol (Lausanne) 2015;6:193.
[80] Ornitz DM, Itoh N. The fibroblast growth factor signaling pathway. Wiley Interdiscip Rev Dev Biol 2015;4:215–266.
[81] Wilkie AO, Morriss-Kay GM, Jones EY, Heath JK. Functions of fibroblast growth factors and their receptors. Curr Biol 1995;5:500–507.
[82] Schumacher JD, Guo GL. Regulation of hepatic stellate cells and fibrogenesis by fibroblast growth factors. Biomed Res Int 2016;2016:8323747.
[83] Goetz R, Beenken A, Ibrahimi OA, Kalinina J, Olsen SK, Eliseenkova AV, et al. Molecular insights into the klotho-dependent, endocrine mode of action of fibroblast growth factor 19 subfamily members. Mol Cell Biol 2007;27:3417–3428.
[84] **Wang J-N**, **Li L**, **Li L-Y**, Yan Q, Li J, Xu T. Emerging role and therapeutic implication of Wnt signaling pathways in liver fibrosis. Gene 2018;674:57–69.
[85] Mejhert N, Galitzky J, Pettersson AT, Bambace C, Blomqvist L, Bouloumié A, et al. Mapping of the fibroblast growth factors in human white adipose tissue. J Clin Endocrinol Metab 2010;95:2451–2457.
[86] Dailey L, Ambrosetti D, Mansukhani A, Basilico C. Mechanisms underlying differential responses to FGF signaling. Cytokine Growth Factor Rev 2005;16:233–247.
[87] Jin-no K, Tanimizu M, Hyodo I, Kurimoto F, Yamashita T. Plasma level of basic fibroblast growth factor increases with progression of chronic liver disease. J Gastroenterol 1997;32:119–121.
[88] **Luo Y**, **Yang C**, Lu W, Xie R, Jin C, Huang P, et al. Metabolic regulator βKlotho interacts with fibroblast growth factor receptor 4 (FGFR4) to induce apoptosis and inhibit tumor cell proliferation. J Biol Chem 2010;285:30069–30078.
[89] Kurosu H, Choi M, Ogawa Y, Dickson AS, Goetz R, Eliseenkova AV, et al. Tissue-specific expression of βKlotho and fibroblast growth factor (FGF) receptor isoforms determines metabolic activity of FGF19 and FGF21. J Biol Chem 2007;282:26687–26695.
[90] Kan M, Wu X, Wang F, McKeehan WL. Specificity for fibroblast growth factors determined by heparan sulfate in a binary complex with the receptor kinase. J Biol Chem 1999;274:15947–15952.
[91] Bechmann LP, Kocabayoglu P, Sowa J-P, Sydor S, Best J, Schlattjan M, et al. Free fatty acids repress small heterodimer partner (SHP) activation and adiponectin counteracts bile acid-induced liver injury in superobese patients with nonalcoholic steatohepatitis. Hepatology 2013;57:1394–1406.
[92] Jiao N, Baker SS, Chapa-Rodriguez A, Liu W, Nugent CA, Tsompana M, et al. Suppressed hepatic bile acid signalling despite elevated production of primary and secondary bile acids in NAFLD. Gut 2018;67:1881–1891.
[93] **Li Y**, **Zhang W**, Doughtie A, Cui G, Li X, Pandit H, et al. Up-regulation of fibroblast growth factor 19 and its receptor associates with progression from fatty liver to hepatocellular carcinoma. Oncotarget 2016;7:52329–52339.
[94] Harrison SA, Rinella ME, Abdelmalek MF, Trotter JF, Paredes AH, Arnold HL, et al. NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2018;391:1174–1185.
[95] Sheu M-J, Hsieh M-J, Chiang W-L, Yang S-F, Lee H-L, Lee L-M, et al. Fibroblast growth factor receptor 4 polymorphism is associated with liver cirrhosis in hepatocarcinoma. PLoS One 2015;10:e0122961.
[96] Hyeon J, Ahn S, Lee JJ, Song DH, Park C-K. Expression of fibroblast growth factor 19 is associated with recurrence and poor prognosis of hepatocellular carcinoma. Dig Dis Sci 2013;58:1916–1922.
[97] Miura S, Mitsuhashi N, Shimizu H, Kimura F, Yoshidome H, Otsuka M, et al. Fibroblast growth factor 19 expression correlates with tumor progression and poorer prognosis of hepatocellular carcinoma. BMC Cancer 2012;12:56.
[98] Sydor S, Best J, Messerschmidt I, Manka P, Vilchez-Vargas R, Brodesser S, et al. Altered microbiota diversity and bile acid signaling in cirrhotic and noncirrhotic NASH-HCC. Clin Transl Gastroenterol 2020;11:e00131.
[99] Coskun T, Bina HA, Schneider MA, Dunbar JD, Hu CC, Chen Y, et al. Fibroblast growth factor 21 corrects obesity in mice. Endocrinology 2008;149:6018–6027.
[100] Xu J, Lloyd DJ, Hale C, Stanislaus S, Chen M, Sivits G, et al. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. Diabetes 2009;58:250–259.
[101] Zhang X, Yeung DCY, Karpisek M, Stejskal D, Zhou Z-G, Liu F, et al. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes 2008;57:1246–1253.
[102] **Li H**, **Fang Q**, Gao F, Fan J, Zhou J, Wang X, et al. Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride. J Hepatol 2010;53:934–940.
[103] Hong ES, Lim C, Choi HY, Lee YK, Ku EJ, Moon JH, et al. Plasma fibroblast growth factor 21 levels increase with ectopic fat accumulation and its receptor levels are decreased in the visceral fat of patients with type 2 diabetes. BMJ Open Diabetes Res Care 2019;7:e000776.
[104] Yang C, Lu W, Lin T, You P, Ye M, Huang Y, et al. Activation of Liver FGF21 in hepatocarcinogenesis and during hepatic stress. BMC Gastroenterol 2013;13:67.

[105] Flisiak-Jackiewicz M, Bobrus-Chociej A, Wasilewska N, Tarasow E, Wojtkowska M, Lebensztejn DM. Can hepatokines be regarded as novel non-invasive serum biomarkers of intrahepatic lipid content in obese children? Adv Med Sci 2019;64:280–284.
[106] **Yang M**, **Xu D**, Liu Y, Guo X, Li W, Guo C, et al. Combined serum biomarkers in non-invasive diagnosis of non-alcoholic steatohepatitis. PLoS ONE 2015;10:e0131664.
[107] **Yu H-T**, **Yu M**, Li C-Y, Zhan Y-Q, Xu W-X, Li Y-H, et al. Specific expression and regulation of hepassocin in the liver and down-regulation of the correlation of HNF1alpha with decreased levels of hepassocin in human hepatocellular carcinoma. J Biol Chem 2009;284:13335–13347.
[108] Abdelmoemen G, Khodeir SA, Zaki AN, Kassab M, Abou-Saif S, Abd-Elsalam S. Overexpression of hepassocin in diabetic patients with nonalcoholic fatty liver disease may facilitate increased hepatic lipid accumulation. Endocr Metab Immune Disord Drug Targets 2019;19:185–188.
[109] **Wu H-T**, **Lu F-H**, Ou H-Y, Su Y-C, Hung H-C, Wu J-S, et al. The role of hepassocin in the development of non-alcoholic fatty liver disease. J Hepatol 2013;59:1065–1072.
[110] **Demchev V**, **Malana G**, Vangala D, Stoll J, Desai A, Kang HW, et al. Targeted deletion of fibrinogen like protein 1 reveals a novel role in energy substrate utilization. PLoS ONE 2013;8:e58084.
[111] Cheng K-P, Ou H-Y, Hung H-C, Li C-H, Fan K-C, Wu J-S, et al. Unsaturated fatty acids increase the expression of hepassocin through a signal transducer and activator of transcription 3-dependent pathway in HepG2 cells. Lipids 2018;53:863–869.
[112] Jung TW, Chung YH, Kim H-C, Abd El-Aty AM, Jeong JH. Hyperlipidemia-induced hepassocin in the liver contributes to insulin resistance in skeletal muscle. Mol Cell Endocrinol 2018;470:26–33.
[113] Li C-Y, Cao C-Z, Xu W-X, Cao M-M, Yang F, Dong L, et al. Recombinant human hepassocin stimulates proliferation of hepatocytes in vivo and improves survival in rats with fulminant hepatic failure. Gut 2010;59:817–826.
[114] Yan J, Yu Y, Wang N, Chang Y, Ying H, Liu W, et al. LFIRE-1/HFREP-1, a liver-specific gene, is frequently downregulated and has growth suppressor activity in hepatocellular carcinoma. Oncogene 2004;23:1939–1949.
[115] Ni Q, Ding K, Wang K-Q, He J, Yin C, Shi J, et al. Deletion of HNF1α in hepatocytes results in fatty liver-related hepatocellular carcinoma in mice. FEBS Lett 2017;591:1947–1957.
[116] Perduca M, Nicolis S, Mannucci B, Galliano M, Monaco HL. Human plasma retinol-binding protein (RBP4) is also a fatty acid-binding protein. Biochim Biophys Acta Mol Cell Biol Lipids 2018;1863:458–466.
[117] Ronne H, Ocklind C, Wiman K, Rask L, Obrink B, Peterson PA. Ligand-dependent regulation of intracellular protein transport: effect of vitamin a on the secretion of the retinol-binding protein. J Cell Biol 1983;96:907–910.
[118] Zhong G, Kirkwood J, Won K-J, Tjota N, Jeong H, Isoherranen N. Characterization of vitamin A metabolome in human livers with and without nonalcoholic fatty liver disease. J Pharmacol Exp Ther 2019;370:92–103.
[119] Kotnik P, Fischer-Posovszky P, Wabitsch M. RBP4: a controversial adipokine. Eur J Endocrinol 2011;165:703–711.
[120] Kashyap SR, Diab DL, Baker AR, Yerian L, Bajaj H, Gray-McGuire C, et al. Triglyceride levels and not adipokine concentrations are closely related to severity of nonalcoholic fatty liver disease in an obesity surgery cohort. Obesity (Silver Spring) 2009;17:1696–1701.
[121] Alkhouri N, Lopez R, Berk M, Feldstein AE. Serum retinol-binding protein 4 levels in patients with nonalcoholic fatty liver disease. J Clin Gastroenterol 2009;43:985–989.
[122] Milner K-L, van der Poorten D, Xu A, Bugianesi E, Kench JG, Lam KSL, et al. Adipocyte fatty acid binding protein levels relate to inflammation and fibrosis in nonalcoholic fatty liver disease. Hepatology 2009;49:1926–1934.
[123] Liu Y, Mu D, Chen H, Li D, Song J, Zhong Y, et al. Retinol-binding protein 4 induces hepatic mitochondrial dysfunction and promotes hepatic steatosis. J Clin Endocrinol Metab 2016;101:4338–4348.
[124] Wang X, Chen X, Zhang H, Pang J, Lin J, Xu X, et al. Circulating retinol-binding protein 4 is associated with the development and regression of non-alcoholic fatty liver disease. Diabetes Metab 2020;46:119–128.
[125] Seo JA, Kim NH, Park SY, Kim HY, Ryu OH, Lee KW, et al. Serum retinol-binding protein 4 levels are elevated in non-alcoholic fatty liver disease. Clin Endocrinol (Oxf) 2008;68:555–560.
[126] **Petta S**, **Tripodo C**, Grimaudo S, Cabibi D, Cammà C, Di Cristina A, et al. High liver RBP4 protein content is associated with histological features in patients with genotype 1 chronic hepatitis C and with nonalcoholic steatohepatitis. Dig Liver Dis 2011;43:404–410.
[127] Graham TE, Yang Q, Blüher M, Hammarstedt A, Ciaraldi TP, Henry RR, et al. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N Engl J Med 2006;354:2552–2563.
[128] Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 2005;436:356–362.
[129] Bahr MJ, Boeker KHW, Manns MP, Tietge UJF. Decreased hepatic RBP4 secretion is correlated with reduced hepatic glucose production but is not associated with insulin resistance in patients with liver cirrhosis. Clin Endocrinol (Oxf) 2009;70:60–65.
[130] Schina M, Koskinas J, Tiniakos D, Hadziyannis E, Savvas S, Karamanos B, et al. Circulating and liver tissue levels of retinol-binding protein-4 in non-alcoholic fatty liver disease. Hepatol Res 2009;39:972–978.
[131] Nobili V, Alkhouri N, Alisi A, Ottino S, Lopez R, Manco M, et al. Retinol-binding protein 4: a promising circulating marker of liver damage in pediatric nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:575–579.
[132] Saeed A, Dullaart RPF, Schreuder TCMA, Blokzijl H, Faber KN. Disturbed vitamin A metabolism in non-alcoholic fatty liver disease (NAFLD). Nutrients 2017;10:29.
[133] Carbone F, La Rocca C, Matarese G. Immunological functions of leptin and adiponectin. Biochimie 2012;94:2082–2088.
[134] Wree A, Kahraman A, Gerken G, Canbay A. Obesity affects the liver - the link between adipocytes and hepatocytes. Digestion 2011;83:124–133.
[135] Holland WL, Adams AC, Brozinick JT, Bui HH, Miyauchi Y, Kusminski CM, et al. An FGF21-adiponectin-ceramide axis controls energy expenditure and insulin action in mice. Cell Metab 2013;17:790–797.
[136] Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, et al. Adiponectin as a biomarker of the metabolic syndrome. Circ J 2004;68:975–981.
[137] Nannipieri M, Cecchetti F, Anselmino M, Mancini E, Marchetti G, Bonotti A, et al. Pattern of expression of adiponectin receptors in human liver and its relation to nonalcoholic steatohepatitis. OBES SURG 2008;19:467.
[138] Lesmana CR, Lesmana LA, Akbar N, Gani RA, Simandjuntak W, Oemardi M, et al. Clinical picture, insulin resistance, and adipocytokines profiles of nonalcoholic steatohepatitis (NASH) patients in Indonesia. Acta Med Indonesiana 2009;41:6–10.
[139] Li S, Shin HJ, Ding EL, Dam RM van. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2009;302:179–188.
[140] Polyzos SA, Toulis KA, Goulis DG, Zavos C, Kountouras J. Serum total adiponectin in nonalcoholic fatty liver disease: a systematic review and meta-analysis. Metabolism 2011;60:313–326.
[141] Kälsch J, Bechmann LP, Heider D, Best J, Manka P, Kälsch H, et al. Normal liver enzymes are correlated with severity of metabolic syndrome in a large population based cohort. Sci Rep 2015;5:13058.
[142] **Canbay A**, **Kälsch J**, Neumann U, Rau M, Hohenester S, Baba HA, et al. Non-invasive assessment of NAFLD as systemic disease-A machine learning perspective. PLoS One 2019;14:e0214436.
[143] Ziemke F, Mantzoros CS. Adiponectin in insulin resistance: lessons from translational research. Am J Clin Nutr 2010;91:258S–261S.
[144] Gamberi T, Magherini F, Modesti A, Fiaschi T. Adiponectin signaling pathways in liver diseases. Biomedicines 2018;6:52.
[145] Adachi M, Brenner DA. High molecular weight adiponectin inhibits proliferation of hepatic stellate cells via activation of adenosine monophosphate–activated protein kinase. Hepatology 2008;47:677–685.
[146] Hanley AJG, Bowden D, Wagenknecht LE, Balasubramanyam A, Langfeld C, Saad MF, et al. Associations of adiponectin with body fat distribution and insulin sensitivity in nondiabetic hispanics and African-Americans. J Clin Endocrinol Metab 2007;92:2665–2671.
[147] Vaidya A, Williams JS, Forman JP. The independent association between 25-hydroxyvitamin D and adiponectin and its relation with BMI in two large cohorts: the NHS and the HPFS. Obesity (Silver Spring) 2012;20:186–191.
[148] Wree A, Schlattjan M, Bechmann LP, Claudel T, Sowa J-P, Stojakovic T, et al. Adipocyte cell size, free fatty acids and apolipoproteins are associated with non-alcoholic liver injury progression in severely obese patients. Metab Clin Exp 2014;63:1542–1552.
[149] Gariballa S, Alkaabi J, Yasin J, Al Essa A. Total adiponectin in overweight and obese subjects and its response to visceral fat loss. BMC Endocr Disord 2019;19:55.

[150] Bril F, Maximos M, Portillo-Sanchez P, Biernacki D, Lomonaco R, Subbarayan S, et al. Relationship of vitamin D with insulin resistance and disease severity in non-alcoholic steatohepatitis. J Hepatol 2015;62:405–411.

[151] Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med 2016;165:305–315.

[152] Polyzos SA, Kountouras J, Zavos C, Tsiaousi E. The role of adiponectin in the pathogenesis and treatment of non-alcoholic fatty liver disease. Diabetes Obes Metab 2010;12:365–383.

[153] Wree A, Mayer A, Westphal S, Beilfuss A, Canbay A, Schick RR, et al. Adipokine expression in brown and white adipocytes in response to hypoxia. J Endocrinol Invest 2012;35:522–527.

[154] Hosogai N, Fukuhara A, Oshima K, Miyata Y, Tanaka S, Segawa K, et al. Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. Diabetes 2007;56:901–911.

[155] Al-Gayyar MMH, Abbas A, Hamdan AM. Chemopreventive and hepatoprotective roles of adiponectin (SULF2 inhibitor) in hepatocelluar carcinoma. Biol Chem 2016;397:257–267.

[156] Man K, Ng KTP, Xu A, Cheng Q, Lo CM, Xiao JW, et al. Suppression of liver tumor growth and metastasis by adiponectin in nude mice through inhibition of tumor angiogenesis and downregulation of Rho kinase/IFN-inducible protein 10/matrix metalloproteinase 9 signaling. Clin Cancer Res 2010;16:967–977.

[157] Guo R, Zhang Y, Turdi S, Ren J. Adiponectin knockout accentuates high fat diet-induced obesity and cardiac dysfunction: role of autophagy. Biochim Biophys Acta 2013;1832:1136–1148.

[158] Asano T, Watanabe K, Kubota N, Gunji T, Omata M, Kadowaki T, et al. Adiponectin knockout mice on high fat diet develop fibrosing steatohepatitis. J Gastroenterol Hepatol 2009;24:1669–1676.

[159] Saxena NK, Fu PP, Nagalingam A, Wang J, Handy J, Cohen C, et al. Adiponectin modulates C-jun N-terminal kinase and mammalian target of rapamycin and inhibits hepatocellular carcinoma. Gastroenterology 2010;139:1762–1773. 1773.e1-5.

[160] Sadik NAE-H, Ahmed A, Ahmed S. The significance of serum levels of adiponectin, leptin, and hyaluronic acid in hepatocellular carcinoma of cirrhotic and noncirrhotic patients. Hum Exp Toxicol 2012;31:311–321.

[161] da Silva TE, Costa-Silva M, Correa CG, Denardin G, Alencar MLA, Coelho MSPH, et al. Clinical significance of serum adiponectin and resistin levels in liver cirrhosis. Ann Hepatol 2018;17:286–299.

[162] Shen J, Yeh C-C, Wang Q, Gurvich I, Siegel AB, Santella RM. Plasma adiponectin and hepatocellular carcinoma survival among patients without liver transplantation. Anticancer Res 2016;36:5307–5314.

[163] Siegel AB, Goyal A, Salomao M, Wang S, Lee V, Hsu C, et al. Serum adiponectin is associated with worsened overall survival in a prospective cohort of hepatocellular carcinoma patients. Oncology 2015;88:57–68.

[164] Tacke F, Wüstefeld T, Horn R, Luedde T, Srinivas Rao A, Manns MP, et al. High adiponectin in chronic liver disease and cholestasis suggests biliary route of adiponectin excretion in vivo. J Hepatol 2005;42:666–673.

[165] Daviaud D, Boucher J, Gesta S, Dray C, Guigne C, Quilliot D, et al. TNFalpha up-regulates apelin expression in human and mouse adipose tissue. FASEB J 2006;20:1528–1530.

[166] Boucher J, Masri B, Daviaud D, Gesta S, Guigné C, Mazzucotelli A, et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology 2005;146:1764–1771.

[167] Ando W, Yokomori H, Otori K, Oda M. The apelin receptor APJ in hematopoietic stem cells/progenitor cells in the early stage of non-alcoholic steatohepatitis. J Clin Med Res 2017;9:809–811.

[168] Muto J, Shirabe K, Yoshizumi T, Ikegami T, Aishima S, Ishigami K, et al. The apelin-APJ system induces tumor arteriogenesis in hepatocellular carcinoma. Anticancer Res 2014;34:5313–5320.

[169] Wang Y, Song J, Bian H, Bo J, Lv S, Pan W, et al. Apelin promotes hepatic fibrosis through ERK signaling in LX-2 cells. Mol Cell Biochem 2019;460:205–215.

[170] Montazerifar F, Bakhshipour AR, Karajibani M, Torki Z, Dashipour AR. Serum omentin-1, vaspin, and apelin levels and central obesity in patients with nonalcoholic fatty liver disease. J Res Med Sci 2017;22:70.

[171] Ercin CN, Dogru T, Tapan S, Kara M, Haymana C, Karadurmus N, et al. Plasma apelin levels in subjects with nonalcoholic fatty liver disease. Metab Clin Exp 2010;59:977–981.

[172] Huang J, Kang S, Park S-J, Im D-S. Apelin protects against liver X receptor-mediated steatosis through AMPK and PPARα in human and mouse hepatocytes. Cell Signal 2017;39:84–94.

[173] Lee T, Park C-K, Ha SY. Prognostic role of apelin receptor expression in hepatocellular carcinoma treated with curative surgical resection. Anticancer Res 2019;39:3025–3031.

[174] Chen H, Wong C-C, Liu D, Go MYY, Wu B, Peng S, et al. APLN promotes hepatocellular carcinoma through activating PI3K/Akt pathway and is a druggable target. Theranostics 2019;9:5246–5260.

[175] Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, et al. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology 2007;148:4687–4694.

[176] Bozaoglu K, Segal D, Shields KA, Cummings N, Curran JE, Comuzzie AG, et al. Chemerin is associated with metabolic syndrome phenotypes in a Mexican-American population. J Clin Endocrinol Metab 2009;94:3085–3088.

[177] Parlee SD, Ernst MC, Muruganandan S, Sinal CJ, Goralski KB. Serum chemerin levels vary with time of day and are modified by obesity and tumor necrosis factor-α. Endocrinology 2010;151:2590–2602.

[178] Kukla M, Zwirska-Korczala K, Hartleb M, Waluga M, Chwist A, Kajor M, et al. Serum chemerin and vaspin in non-alcoholic fatty liver disease. Scand J Gastroenterol 2010;45:235–242.

[179] Yilmaz Y, Yonal O, Kurt R, Alahdab YO, Eren F, Ozdogan O, et al. Serum levels of omentin, chemerin and adipsin in patients with biopsy-proven nonalcoholic fatty liver disease. Scand J Gastroenterol 2011;46:91–97.

[180] Kajor M, Kukla M, Waluga M, Liszka Ł, Dyaczyński M, Kowalski G, et al. Hepatic chemerin mRNA in morbidly obese patients with nonalcoholic fatty liver disease. Pol J Pathol 2017;68:117–127.

[181] Bekaert M, Ouwens DM, Hörbelt T, Van de Velde F, Fahlbusch P, Herzfeld de Wiza D, et al. Reduced expression of chemerin in visceral adipose tissue associates with hepatic steatosis in patients with obesity. Obesity (Silver Spring) 2016;24:2544–2552.

[182] Tan BK, Chen J, Farhatullah S, Adya R, Kaur J, Heutling D, et al. Insulin and metformin regulate circulating and adipose tissue chemerin. Diabetes 2009;58:1971–1977.

[183] Sell H, Divoux A, Poitou C, Basdevant A, Bouillot J-L, Bedossa P, et al. Chemerin correlates with markers for fatty liver in morbidly obese patients and strongly decreases after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 2010;95:2892–2896.

[184] Pohl R, Haberl EM, Rein-Fischboeck L, Zimny S, Neumann M, Aslanidis C, et al. Hepatic chemerin mRNA expression is reduced in human nonalcoholic steatohepatitis. Eur J Clin Invest 2017;47:7–18.

[185] **Ebert T**, **Gebhardt C**, Scholz M, Wohland T, Schleinitz D, Fasshauer M, et al. Relationship between 12 adipocytokines and distinct components of the metabolic syndrome. J Clin Endocrinol Metab 2018;103:1015–1023.

[186] Deng Y, Wang H, Lu Y, Liu S, Zhang Q, Huang J, et al. Identification of chemerin as a novel FXR target gene down-regulated in the progression of nonalcoholic steatohepatitis. Endocrinology 2013;154:1794–1801.

[187] Haberl EM, Pohl R, Rein-Fischboeck L, Feder S, Sinal CJ, Buechler C. Chemerin in a mouse model of non-alcoholic steatohepatitis and hepatocarcinogenesis. Anticancer Res 2018;38:2649–2657.

[188] Krautbauer S, Wanninger J, Eisinger K, Hader Y, Beck M, Kopp A, et al. Chemerin is highly expressed in hepatocytes and is induced in non-alcoholic steatohepatitis liver. Exp Mol Pathol 2013;95:199–205.

[189] Döcke S, Lock JF, Birkenfeld AL, Hoppe S, Lieske S, Rieger A, et al. Elevated hepatic chemerin mRNA expression in human non-alcoholic fatty liver disease. Eur J Endocrinol 2013;169:547–557.

[190] Lin W, Chen Y-L, Jiang L, Chen J-K. Reduced expression of chemerin is associated with a poor prognosis and a lowed infiltration of both dendritic cells and natural killer cells in human hepatocellular carcinoma. Clin Lab 2011;57:879–885.

[191] Imai K, Takai K, Hanai T, Shiraki M, Suzuki Y, Hayashi H, et al. Impact of serum chemerin levels on liver functional reserves and platelet counts in patients with hepatocellular carcinoma. Int J Mol Sci 2014;15:11294–11306.

[192] Horn P, von Loeffelholz C, Forkert F, Stengel S, Reuken P, Aschenbach R, et al. Low circulating chemerin levels correlate with hepatic dysfunction and increased mortality in decompensated liver cirrhosis. Sci Rep 2018;8:9242.

[193] Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995;269:543–546.

[194] Jéquier E. Leptin signaling, adiposity, and energy balance. Ann N Y Acad Sci 2002;967:379–388.

[195] **Izquierdo AG**, **Crujeiras AB**, Casanueva FF, Carreira MC. Leptin, obesity, and leptin resistance: where are we 25 years later? Nutrients 2019;11:2704.

[196] Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997;387:903–908.
[197] Kamada Y, Takehara T, Hayashi N. Adipocytokines and liver disease. J Gastroenterol 2008;43:811–822.
[198] Polyzos SA, Aronis KN, Kountouras J, Raptis DD, Vasiloglou MF, Mantzoros CS. Circulating leptin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Diabetologia 2016;59:30–43.
[199] Toczylowski K, Hirnle T, Harasiuk D, Zabielski P, Lewczuk A, Dmitruk I, et al. Plasma concentration and expression of adipokines in epicardial and subcutaneous adipose tissue are associated with impaired left ventricular filling pattern. J Transl Med 2019;17:310.
[200] Sharma D, Wang J, Fu PP, Sharma S, Nagalingam A, Mells J, et al. Adiponectin antagonizes the oncogenic actions of leptin in hepatocellular carcinogenesis. Hepatology 2010;52:1713–1722.
[201] Wang Y-Y, Lin S-Y. Leptin in relation to hepatocellular carcinoma in patients with liver cirrhosis. Horm Res 2003;60:185–190.
[202] Andrighetto LV, Poziomyck AK. Serum leptin levens and hepatocellular carcinoma: review article. Arq Bras Cir Dig 2016;29:276–278.
[203] Saxena NK, Ikeda K, Rockey DC, Friedman SL, Anania FA. Leptin in hepatic fibrosis: evidence for increased collagen production in stellate cells and lean littermates of ob/ob mice. Hepatology 2002;35:762–771.
[204] Noureddin M, Rinella ME. Nonalcoholic fatty liver disease, diabetes, obesity, and hepatocellular carcinoma. Clin Liver Dis 2015;19:361–379.
[205] Dattaroy D, Pourhoseini S, Das S, Alhasson F, Seth RK, Nagarkatti M, et al. Micro-RNA 21 inhibition of SMAD7 enhances fibrogenesis via leptin-mediated NADPH oxidase in experimental and human nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol 2015;308:G298–G312.
[206] Saxena NK, Sharma D, Ding X, Lin S, Marra F, Merlin D, et al. Concomitant activation of the JAK/STAT, PI3K/AKT, and ERK signaling is involved in leptin-mediated promotion of invasion and migration of hepatocellular carcinoma cells. Cancer Res 2007;67:2497–2507.
[207] Fava G, Alpini G, Rychlicki C, Saccomanno S, DeMorrow S, Trozzi L, et al. Leptin enhances cholangiocarcinoma cell growth. Cancer Res 2008;68:6752–6761.
[208] Garofalo C, Surmacz E. Leptin and cancer. J Cell Physiol 2006;207:12–22.
[209] **Silswal N**, **Singh AK**, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. Biochem Biophys Res Commun 2005;334:1092–1101.
[210] Filková M, Haluzík M, Gay S, Senolt L. The role of resistin as a regulator of inflammation: implications for various human pathologies. Clin Immunol 2009;133:157–170.
[211] Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol 2005;174:5789–5795.
[212] Degawa-Yamauchi M, Bovenkerk JE, Juliar BE, Watson W, Kerr K, Jones R, et al. Serum resistin (FIZZ3) protein is increased in obese humans. J Clin Endocrinol Metab 2003;88:5452–5455.
[213] McTernan PG, Fisher FM, Valsamakis G, Chetty R, Harte A, McTernan CL, et al. Resistin and type 2 diabetes: regulation of resistin expression by insulin and rosiglitazone and the effects of recombinant resistin on lipid and glucose metabolism in human differentiated adipocytes. J Clin Endocrinol Metab 2003;88:6098–6106.
[214] Parreño Caparrós E, Illán Gómez F, Gonzálvez Ortega M, Orea Soler I, Pérez Paredes M, Lozano Almela ML, et al. Resistin in morbidly obese patients before and after gastric bypass surgery. Nutr Hosp 2017;34:1333–1337.
[215] Salman AA, Sultan AAEA, Abdallah A, Abdelsalam A, Mikhail HMS, Tourky M, et al. Effect of weight loss induced by laparoscopic sleeve gastrectomy on liver histology and serum adipokine levels. J Gastroenterol Hepatol 2020;35:1769–1773.
[216] **Franchitto A**, **Carpino G**, Alisi A, De Peppo F, Overi D, De Stefanis C, et al. The contribution of the adipose tissue-liver Axis in pediatric patients with nonalcoholic fatty liver disease after laparoscopic sleeve gastrectomy. J Pediatr 2020;216:117–127.e2.
[217] D'Incao RB, Tovo CV, Mattevi VS, Borges DO, Ulbrich JM, Coral GP, et al. Adipokine levels versus hepatic histopathology in bariatric surgery patients. Obes Surg 2017;27:2151–2158.
[218] Elsayed EY, Mosalam NA, Mohamed NR. Resistin and insulin resistance: a link between inflammation and hepatocarcinogenesis. Asian Pac J Cancer Prev 2015;16:7139–7142.
[219] Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H, et al. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. J Immunol 2007;178:1748–1758.
[220] Akbal E, Koçak E, Taş A, Yüksel E, Köklü S. Visfatin levels in nonalcoholic fatty liver disease. J Clin Lab Anal 2012;26:115–119.
[221] Amirkalali B, Sohrabi MR, Esrafily A, Jalali M, Gholami A, Hosseinzadeh P, et al. Association between nicotinamide phosphoribosyltransferase and de novo lipogenesis in nonalcoholic fatty liver disease. Med Princ Pract 2017;26:251–257.
[222] Aller R, de Luis DA, Izaola O, Sagrado MG, Conde R, Velasco MC, et al. Influence of visfatin on histopathological changes of non-alcoholic fatty liver disease. Dig Dis Sci 2009;54:1772–1777.
[223] Kukla M, Ciupińska-Kajor M, Kajor M, Wyleżoł M, Żwirska-Korczala K, Hartleb M, et al. Liver visfatin expression in morbidly obese patients with nonalcoholic fatty liver disease undergoing bariatric surgery. Pol J Pathol 2010;61:147–153.
[224] Johannsen K, Flechtner-Mors M, Kratzer W, Koenig W, Boehm BO, Schmidberger J, et al. Association between visfatin and hepatic steatosis in the general population during long-term follow-up. Horm Metab Res 2019;51:602–607.
[225] **Wu Z**, **Sun Y**, Huang Y, Zhu S, Feng Y, Ye H, et al. Genetic variant in visfatin gene promoter contributes to reduced risk of hepatocellular carcinoma in a Chinese population. Oncotarget 2016;7:77968–77977.
[226] **Sun Y**, **Zhu S**, **Wu Z**, Huang Y, Liu C, Tang S, et al. Elevated serum visfatin levels are associated with poor prognosis of hepatocellular carcinoma. Oncotarget 2017;8:23427–23435.
[227] Ninomiya S, Shimizu M, Imai K, Takai K, Shiraki M, Hara T, et al. Possible role of visfatin in hepatoma progression and the effects of branched-chain amino acids on visfatin-induced proliferation in human hepatoma cells. Cancer Prev Res (Phila) 2011;4:2092–2100.
[228] Tsai I-T, Wang C-P, Yu T-H, Lu Y-C, Lin C-W, Lu L-F, et al. Circulating visfatin level is associated with hepatocellular carcinoma in chronic hepatitis B or C virus infection. Cytokine 2017;90:54–59.
[229] **Brandl K**, **Hartmann P**, Jih LJ, Pizzo DP, Argemi J, Ventura-Cots M, et al. Dysregulation of serum bile acids and FGF19 in alcoholic hepatitis. J Hepatol 2018;69:396–405.
[230] **Huang H-H**, **Lee W-J**, Chen S-C, Chen T-F, Lee S-D, Chen C-Y. Bile acid and fibroblast growth factor 19 regulation in obese diabetics, and non-alcoholic fatty liver disease after sleeve gastrectomy. J Clin Med 2019;8:815.
[231] Zhou Z, Chen H, Ju H, Sun M. Circulating retinol binding protein 4 levels in nonalcoholic fatty liver disease: a systematic review and meta-analysis. Lipids Health Dis 2017;16:180.
[232] Terra X, Auguet T, Broch M, Sabench F, Hernández M, Pastor RM, et al. Retinol binding protein-4 circulating levels were higher in nonalcoholic fatty liver disease vs. histologically normal liver from morbidly obese women. Obesity (Silver Spring) 2013;21:170–177.
[233] Yagmur E, Weiskirchen R, Gressner AM, Trautwein C, Tacke F. Insulin resistance in liver cirrhosis is not associated with circulating retinol-binding protein 4. Diabetes Care 2007;30:1168–1172.