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Review Article

The role of novel adipokines in hepatocellular carcinoma progression: a mini review

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Abstract: Hepatocellular carcinoma (HCC), which originates from hepatocytes, accounts for the majority of primary liver cancers. Globally, HCC ranks among the most common cancers and is a leading cause of cancer-related deaths. Obesity, a growing health issue worldwide, is increasingly recognized as a critical risk factor for HCC, influenced by both epidemiological and clinical factors. Adipokines, secreted by adipocytes, have been shown to play pivotal roles in the tumor microenvironment, affecting cancer progression, metastasis, and resistance to therapies through various signaling mechanisms. Despite inconsistencies in certain findings, a substantial body of research supports the significant role of adipokines in HCC development. This review focuses on exploring newly identified adipokines and their mechanisms in HCC, with the goal of uncovering potential therapeutic targets for improved management and treatment strategies.

Keywords: Adipokines, hepatocellular carcinoma, tumorigenesis, prognosis

Introduction

Cancer continues to pose a significant global health challenge, with its incidence rate escalating worldwide [1, 2]. By 2025, it is projected that over one million individuals will be diagnosed with cancer annually. Liver cancer stands as one of the predominant malignant tumors, primarily comprising two pathological histological types: hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) [3]. There is increasing evidence that adipose tissue, inflammation, non-alcoholic fatty liver disease (NAFLD), and alcoholic fatty liver disease (AFLD) are closely linked to the risk of HCC occurrence [4-6]. Therefore, maintaining a healthy lifestyle and avoiding hepatocellular carcinoma risk factors are additional strategies for the prevention of HCC [7]. Currently, in blood-based surveillance tests, detection of elevated serum alpha-fetoprotein levels is usually used as an adjunct to liver ultrasonography, but its use as a surveillance test for HCC remains controversial because of its low sensitivity of 40-60% and specificity of 80-90% [8].

Adipocytes function as a crucial endocrine organ, secreting various functional adipokines, peptides, and non-coding RNAs. These act on adipose tissue itself or other distant tissues or organs via autocrine, paracrine, or endocrine mechanisms [9-11]. Adipokines exhibit diverse roles across various cancer types, often influencing cell proliferation, migration, invasion, and metastasis pathways in contradictory ways. This complexity necessitates further research into the role of adipokines in the tumor environment. In recent years, the number of identified adipokines has surged, including adiponectin, resistin, visfatin, apelin, retinol-binding protein-4, serum amyloid A, plasminogen activator inhibitor-1, angiotensinogen, vaspin, omentin, chemerin, and zinc-alpha2-glycoprotein. Pro-inflammatory cytokines produced by macrophage infiltration into white adipose tissue, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are also classified as adipokines [12].

It is widely recognized that metabolic disorders elevate the risk of cancer and its associated

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mortality [13]. Growing evidence indicates that these disorders can also instigate HCC and are linked to its progression [14]. In recent years, the correlation between metabolic syndrome (MS), a cluster of conditions encompassing insulin resistance, obesity, hypertension, and hyperlipidemia, and malignancies has gained significant attention [15]. A comprehensive review and meta-analysis of data on the prevention of future cancer post-bariatric surgery revealed a reduced incidence of subsequent HCC [16]. Several large-scale epidemiological investigations have demonstrated that individuals with overweight and obesity exhibit elevated risks of liver cancer compared to the general populace [17, 18]. Furthermore, patients with obesity not only face an increased likelihood of developing HCC but also a heightened risk of liver cancer-related mortality [17, 19].

Adipose tissue, with its inherent metabolic activity, secretes cytokines known as adipokines. These adipokines can either promote or inhibit hepatocarcinogenesis. They play a crucial role in regulating cell growth, proliferation, the cell cycle, angiogenesis, and tumor growth and metastasis [20]. For instance, substantial evidence suggests that leptin and adiponectin may exacerbate steatohepatitis in patients with viral hepatitis, thereby increasing the likelihood of HCC [21]. Adipokines are believed to facilitate cancer progression by enhancing growth, inflammation, migration, and anti-apoptotic mechanisms, which in turn promote cancer metastasis [22]. Recent studies have revealed that a deficiency in p62 in adipose tissue supports the nutritional supply of cancer cells by inhibiting energy utilization pathways in adipocytes [23]. The systemic and hepatic molecular mechanisms involved in obesity and NAFLD-induced hepatocarcinogenesis, as well as potential early markers of hepatocellular carcinoma, are currently under extensive investigation. Adiponectin and leptin are recognized adipokines that can influence the regulation of liver cancer. Adiponectin induces apoptosis and inhibits hepatic stellate cells, affects Kupffer cell survival, and promotes the transformation to M2 phenotype to release mediators that stimulate M1 macrophage apoptosis [24]. Leptin is reported to stimulate liver cancer cell proliferation and inhibit apoptosis [25]. Leptin induces autophagy through the p53/Foxo3A axis, thereby eliminating cancer cell apoptosis [26]. However, data on the role of certain adipokines in the pathogenesis of HCC in patients with viral hepatitis are contradictory. For example, visfatin is elevated in CHC and HCC patients, but increased visfatin concentration is also associated with reduced necroinflammatory activity in the liver [27, 28]. On the basis of above, we explore and summarize the effects of novel adipokines on HCC in this review (**Table 1**).

Metrnl/meteorin-β/IL-41

Meteorin-like (Metrnl), also known as meteorin-β or IL-41, is a novel secreted protein that shares homology with the neurotrophic factor metrnl, which is also referred to as cometin, subfatin, and interleukin 39. This nomenclature reflects its diverse functions, including neurotrophic action, adipokine activity, and potential roles as a cytokine [29]. Identified as a potential diagnostic marker for hepatocellular carcinoma (HCC), Metrnl exhibits marked upregulation in HCC tissues and high expression in the serum of patients with alpha-fetoprotein (AFP)-negative HCC, demonstrating its diagnostic value [30]. Consequently, Metrnl could serve as a novel serum marker for the diagnosis of AFP-negative HCC.

Immunohistochemistry analysis reveals that high tissue expression of Metrnl correlates with early recurrence, mortality, multiple metastases, and microvascular invasion post-HCC resection, suggesting that Metrnl could be a predictive factor for poor prognosis and malignant progression of HCC [30]. In terms of treatment, Metrnl may modulate the response of liver cancer patients to chemotherapy drugs. It has been shown to mitigate doxorubicin-induced cardiotoxicity without compromising its anticancer effects [31]. Du et al. demonstrated that Metrnl overexpression significantly inhibits the release of pro-inflammatory cytokines TNF and IL-1β, reduces chemokine-dependent inflammatory cell infiltration into the liver, and ameliorates acute hepatitis in mice [32]. In contrast, a study by Liu et al. found reduced serum Metrnl levels in adult non-alcoholic fatty liver disease (NAFLD) patients, suggesting that Metrnl may act as a protective factor in the pathogenesis of NAFLD [33].

Retinol binding protein 4 (RBP4)

RBP4 is a 21 kDa monomeric binding protein crucial for transporting retinol (vitamin A) in the

Table 1. Clinical studies concerning the changes of novel adipokines in HCC patients

Adipokines	Subjects	Sample size		Change In HCC	Promoting(+)/ inhibitory(-) effect of cancer	Prognosis	Study
		HCC	Healthy controls				
Metrnl/IL-41	Human	176	19	Upregulated in HCC tissues	+	The serum IL-41 level was lower in patients with late recurrence (2 years after resection) than in patients with early recurrence and death	Yazhao Li et al., 2024 [30]
RBP4	Human	290	269	Reduction in both liver tissues and serum samples	-	The serum RBP4 level exhibited a negative correlation with overall survival time	Fengjie Wan et al., 2024 [48]
Irisin	Human	36	7	Reduced irisin concentrations	+	Low serum irisin levels are associated with high CCI scores after hepatectomy in HCC patients	Monika Pazgan-Simon et al., 2020 [71]
	Human	69	20	Decline of serum irisin			M Pazgan-Simon et al., 2020 [72]
Vaspin	Human	36	7	Higher concentrations of vaspin	+	Unkown	Monika Pazgan-Simon et al., 2020 [71]
	Human	37	20	Serum vaspin were higher			Walaa Abdelhamed, 2023 [86]
LCN-2	Human	167	106	Levels in HCC sera were higher	-	Blood NGAL levels predict the rate of survival, even in patients presenting with HCC	Lin Du, 2022 [151]
sFRP4	Human	142	33	Serum sFRP-4 levels higher	-	Unkown	Cheng Xu, 2015 [122]
ApoM	Human	36	64	The plasma relative ApoM levels was higher	-	Multivariate COX proportional hazard analysis suggested that high serum AZGP1 level was associated with better survival of HCC patients	Jingting Jiang, 2011 [136]

blood, primarily secreted by the liver [34, 35]. Research has identified RBP4 as a novel adipokine associated with insulin resistance, which may impact glucose homeostasis and induce inflammation in mice [36]. Further studies have linked RBP4 to various metabolic diseases, including type 2 diabetes, hepatic steatosis, and steatohepatitis [37-39], all of which are closely related to primary liver cancer. Additionally, RBP4 levels vary in certain tumors, such as head and neck cancer, ovarian cancer, colorectal cancer, breast cancer, and acute lymphoblastic leukemia [40-45]. Relevant research has demonstrated that serum RBP4 concentration in early HCV-infected patients is inversely proportional to disease severity; as liver fibrosis escalates, serum RBP4 concentration decreases [46, 47].

Research indicates that RBP4 levels in both liver tissue and serum samples from HCC patients are significantly diminished [48, 49]. Moritoshi et al. discovered a strong correlation between low RBP4 expression in HCC tissues and the incidence of HCC. They identified differentially expressed genes associated with chronic viral hepatitis in HCC through differential gene display analysis, revealing insufficient expression of the RBP4 gene in cancer tissues from 12 HCC patients [50]. Consequently, RBP4 holds significant potential as a biomarker due to its substantial diagnostic value, serving as a supplement to AFP in HCC diagnosis. Recently, Li M et al. employed online bioinformatics tools to analyze RBP4, revealing significant downregulation of RBP4 expression in both HCC and cholangiocarcinoma. This downregulation was found to be indicative of poor prognosis for HCC and was closely linked to immune cell infiltration within the tumor microenvironment [51]. Furthermore, studies have demonstrated a significant correlation between serum RBP4 levels in HCC patients and factors such as cirrhosis, tumor size, venous invasion, disease stage, and poor prognosis [15]. Therefore, it is anticipated that RBP4 could be integrated into a combined prognostic model as a prognostic biomarker, significantly enhancing the prognostic efficiency of HCC.

RBP4 expression has also been linked to immune cell infiltration, particularly during inflammation [52]. This protein can stimulate macrophages and $CD4^+$ T cells via the TLR4 and JNK-dependent pathway, resulting in the production of cytokines such as TNF-α, IL-1β, and IL-6 [53, 54]. Consequently, we propose that RBP4 may offer a protective effect against HCC through metabolic regulation and immune cell infiltration. Additionally, it may contribute to the development of precancerous liver lesions via exosome-mediated macrophage activation. Interestingly, RBP4 is inversely correlated with the severity of liver fibrosis. This correlation could be attributed to diminished RBP4 levels, which are involved in the overactivation of hepatic stellate cells and the accumulation of type I collagen in the liver, promoting the progression of liver fibrosis [47, 55], potentially leading to cirrhosis or HCC.

Irisin

Irisin, the ectodomain of fibronectin type III domain-containing protein 5 (FNDC5) [56-58], was initially identified in skeletal muscle [59]. However, it has been demonstrated to be ubiquitous, with hepatocytes, Kupffer cells, and sinusoidal endothelial cells also capable of producing it, albeit in small quantities. The role of irisin in the liver remains unclear [60]. Studies have shown a significant decrease in irisin expression in subjects with steatohepatitis [61, 62] and in mice models of liver injury induced by ischemia-reperfusion (I/R) [63, 64]. Long-term exercise-induced irisin or supplementation with exogenous recombinant irisin (r-irisin) has been found to protect against non-alcoholic fatty liver disease (NAFLD) [65, 66], hepatic glucose disorder [67, 68], and I/R-induced liver injury [69]. These findings suggest a potential role for irisin in myokine-hepatokine crosstalk [70].

Studies have indicated that serum irisin levels in patients with HCC are diminished, particularly in those with advanced disease grades, and are also negatively correlated with the severity of liver dysfunction [71, 72]. However, a study by Aydin et al. did not detect a significant change in irisin protein in HCC tissues [73]. In contrast, Melania et al. demonstrated that plasma irisin levels were reduced in HCC patients [74]. Furthermore, a recent study suggested that the liver could be a target tissue for irisin and may contribute to its metabolic clearance in conjunction with the kidney [75]. Given that irisin is primarily expressed in skeletal

muscle, and that muscle loss progresses as liver disease severity increases, this could potentially explain the reduction in irisin concentration observed in patients with cirrhosis and HCC [76].

A study indicated that, among HCC patients undergoing hepatectomy, the AFP level in the group with low serum irisin was over 14 times higher than that in the group with high serum irisin [77]. Furthermore, a preoperatively low serum irisin level was significantly correlated with a high CCI score post-hepatectomy. Consequently, irisin could be utilized in conjunction with AFP for the diagnosis of HCC, and preoperative serum irisin levels could serve as a predictor of the overall risk of postoperative complications.

A recent study demonstrated that exercise-induced irisin competitively inhibits the binding of myeloid differentiation factor 2 (MD2) and Toll-like receptor 4 by forming a complex with MD2 in hepatocytes, thereby suppressing the inflammatory response [78]. The mRNA expression of SCD-1, NOTCH1, tumor necrosis factor-α, and interleukin-6 is elevated in the livers of HCC patients. Overexpression of FNDC5/irisin in HCC-liver tissues correlates with genes involved in adipogenesis, inflammation, and cancer mediators, suggesting that this hormone may have a protective effect on liver injury [74]. However, elevated levels of irisin may significantly increase cell proliferation, invasion, and migration ability by partially activating the PI3K/AKT pathway, indicating its protective role in hepatocellular carcinoma cells. This may promote liver cancer progression and reduce sensitivity to chemotherapy [79]. On the other hand, it has also been shown that irisin may improve insulin resistance, thereby reducing the risk of developing HCC in patients with viral hepatitis [80-82].

Vaspin

The novel adipokine vaspin, also known as Visceral Adipose Tissue-Derived Serine Protease Inhibitor, was initially identified in obese OLETF rats [83]. Primarily expressed in visceral adipose tissue, vaspin enhances glucose tolerance and insulin sensitivity while simultaneously reducing the production of proinflammatory cytokines. Research indicates that serum vaspin levels decrease in patients with non-advanced liver fibrosis due to chronic hepatitis C (CHC), and an increase in vaspin levels correlates with the progression of liver fibrosis [84]. The heightened expression of vaspin in patients with pronounced fibrosis may serve as a compensatory mechanism, offering protection against further liver injury and fibrosis progression. This hypothesis is supported by observations that vaspin can suppress the expression of leptin, TNF-α, and resistin [85]. However, in a study conducted by Monika et al., vaspin concentration was significantly elevated in HCC patients compared to healthy controls, yet it did not emerge as a significant predictor of HCC [71]. Furthermore, it has been determined that the notable increase in serum vaspin levels in HCC patients is associated with tumor staging, suggesting its potential as a biomarker for HCC [86].

Vaspin exhibits anti-apoptotic effects in various cell types, including ovarian cells, osteoblasts, macrophages, aortic endothelial cells, hepatocellular carcinoma cells, and cardiomyocytes. It has also been found to promote the proliferation of normal and cancerous ovarian cells, preadipocytes, hepatocellular carcinoma cells, and bone mesenchymal stem cells [87]. Several mechanisms have been proposed to elucidate how vaspin can facilitate tumor development, including insulin resistance, stimulation of growth in cells with malignant potential, and prevention of apoptosis through cellular pathways [88].

Lipocalin 2 (LCN-2)

Lipocalin-2 (LCN-2), also known as neutrophil gelatinase-associated lipocalin (NGAL), is a small, secreted protein and iron-binding glycoprotein that is significantly upregulated during the progression of severe cancers [89]. Multiple in vivo and in vitro studies have consistently reported elevated LCN-2 levels in the tissues and serum of hepatocellular carcinoma (HCC) patients compared to healthy individuals [90]. Moreover, LCN-2 is highly expressed in human HCC tissues and in the livers of various mouse models of HCC, triggered by factors such as inflammation or genotoxicity [91-93].

Recent findings suggest that blood LCN-2 levels serve as a reliable prognostic marker for survival in chronic liver disease complicated by HCC [94]. The upregulation of LCN-2 and its

receptor, LCN2R (also known as solute carrier family 22 member 17, SLC22A17), in HCC has been proposed as a prognostic indicator for overall survival [95]. Additionally, studies have shown that LCN-2 is primarily produced by damaged tumor AFP-positive hepatocytes, inflammatory infiltration, and hepatic progenitor cells, highlighting its potential use alongside AFP in HCC diagnosis [96]. Notably, LCN-2 levels above 225 ng/ml offer superior diagnostic accuracy compared to AFP, especially in distinguishing HCC from cirrhosis [97].

LCN-2 has also been found to inhibit the proliferation, invasion, and metastasis of HCC, positioning it as a potential metastatic suppressor and therapeutic target [98-100]. Furthermore, its overexpression induces apoptosis in HCC cells through mitochondrial activity, further reinforcing its therapeutic potential [99]. LCN-2 has been reported to negatively regulate the epithelial-mesenchymal transition (EMT) in HCC cells, suggesting its role in suppressing metastasis warrants further investigation [101].

Comprehensive studies have confirmed the crucial role of LCN-2 in HCC progression, with its expression validated in clinical samples, including patient serum and tumor tissues. Targeting LCN-2 therapeutically has shown strong antitumor effects, such as inhibiting angiogenesis, enhancing sensitivity to sorafenib, and promoting natural killer cell cytotoxicity [102]. In terms of signaling pathways, LCN-2 regulates EMT at least partially via the EGF (or TGF-β1)/LCN2/Twist1 axis [98]. Additionally, LCN-2-induced cell migration has been linked to activation of the Met/FAK cascade [103]. The apoptotic characteristics induced by LCN-2 include the cleavage of caspase-9, -8, -3, and PARP proteins, along with a reduction in mitochondrial membrane potential (MMP). It also downregulates Bcl-2 and upregulates Bax expression, contributing to apoptosis. Importantly, treatment with a neutralizing antibody significantly diminished LCN-2-induced apoptosis, suggesting that LCN-2 overexpression could effectively induce apoptosis in HCC cells, making it a promising therapeutic strategy [99].

In summary, LCN-2 plays a pivotal role in the pathogenesis and progression of HCC. Its elevated expression in HCC tissues and serum, along with its multifaceted role in inhibiting metastasis, promoting apoptosis, and influencing key signaling pathways, underscores its potential as both a diagnostic and therapeutic target in HCC. Further research is essential to fully explore LCN-2's clinical applications and therapeutic implications.

Neuregulin 4 (NRG4)

Neuregulin 4 (NRG4), a member of the epidermal growth factor (EGF) family, binds to and activates the receptor tyrosine kinase of Erb-B2 Receptor Tyrosine Kinase 4 (ErbB4) [104]. This secreted factor, originating from adipose tissue, influences liver function, thereby maintaining metabolic health in mice [105-107]. A reduction in adipose NRG4 expression and plasma levels correlates with human obesity, insulin resistance, and non-alcoholic fatty liver disease (NAFLD) [107-110]. Furthermore, NRG4 plays a significant role in the initiation and progression of various cancers, including prostate cancer, breast cancer, and gastrointestinal malignant lymphoma [111-113].

Woo Sun Rou et al. demonstrated that Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2) and NRG4 serve as independent prognostic indicators for tumor recurrence. Moreover, the combined assessment of serum levels of ERBB2, NRG4, and mitogen-inducible gene 6 (MIG6) offers a more accurate prediction of mortality in HCC patients compared to AFP [114]. Downregulation of NRG4 expression has been observed in HCC [115]. Emerging evidence suggests a novel role for NRG4 in regulating the liver immune microenvironment and the development of NASH-associated HCC. Several RNA sequencing and single-cell transcriptomic studies have revealed that NRG4 deficiency promotes the induction of NASH-associated macrophages (NAMs) and exacerbates intrahepatic $CD8^+$ T cell exhaustion following diet-induced NASH in mice. Conversely, transgenic or recombinant adeno-associated virus (AAV)-mediated overexpression of NRG4 inhibits NAM marker expression and genes associated with T cell exhaustion. Thus, NRG4 may function as a hormone checkpoint to suppress tumor-prone immune features [115].

Previous research has shown that the cellular receptor ErbB4 for NRG4 is present on macrophages and mediates NRG4's effects on macrophage survival and function [116, 117].

Interestingly, liver-specific ErbB4 knockout mice exhibit increased susceptibility to liver injury and diethylnitrosamine (DEN)-induced HCC [118]. The expression of ERBB4 is frequently diminished in cancers and cancer cell lines [119], further supporting a potential tumor-suppressive role for NRG4-ERBB4 signaling.

In conclusion, the ability of NRG4 to influence multiple aspects of liver biology, including hepatic lipid metabolism, hepatocyte injury, and the immune microenvironment, strongly suggests that this hormone pathway may serve as an attractive target for therapeutic intervention in NASH-associated HCC.

Secreted frizzled-related protein 4 (sFRP4)

sFRP4, a member of the secreted frizzled-related protein (SFRP) family, contains a cysteine-rich domain that resembles the putative Wnt binding site of coiled-coil proteins [120]. Several studies have identified sFRP4 as a tumor suppressor in various cancers [121]. Xu et al. reported that sFRP4 levels were significantly upregulated in the serum of HCC patients, and combining sFRP4 with AFP enhanced the diagnostic accuracy for HCC [122].

In approximately 30% of HCC patients, the Wnt/β-catenin signaling pathway is overactivated [123]. sFRP4 can regulate this pathway by directly binding to Wnt ligands, thereby preventing their interaction with Wnt receptors [124, 125]. Overexpression of sFRP4 increases glycogen synthase kinase-3β (GSK-3β) expression and decreases β-catenin levels, indicating that sFRP4 inhibits the Wnt/β-catenin signaling cascade [126]. As a result, sFRP4 suppresses the malignant behavior of HCC cells by blocking this pathway, suggesting that it plays a negative regulatory role in HCC carcinogenesis. Therefore, sFRP4 holds potential as a therapeutic target for HCC treatment.

Apolipoprotein M (ApoM)

The majority of ApoM is found in high-density lipoprotein (HDL), with smaller amounts present in low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and chylomicrons (CM) [127]. Only about 5% of HDL particles and less than 2% of LDL particles contain ApoM, with a significant correlation observed between ApoM levels and HDL concentrations [128, 129]. Research has shown that ApoM can be modulated by various inflammatory factors, such as platelet-activating factor (PAF) and lipopolysaccharides [130-134].

Through suppression subtractive hybridization and cDNA microarray analysis, elevated ApoM expression was observed in HCC samples [135]. However, further studies revealed that HCC tissues have a reduced capacity to synthesize ApoM compared to adjacent non-tumor tissues, suggesting that the increased ApoM levels primarily originate from the surrounding non-tumorous areas [136]. Additionally, plasma ApoM levels in HCC patients were found to be higher than those in healthy individuals but lower than those in patients with chronic hepatitis or cirrhosis. These variations may be linked to immune system abnormalities or other underlying factors [137].

Bai et al. demonstrated that deletion of the ApoM gene in mice exposed to N-nitrosodiethylamine accelerated liver cancer development, highlighting ApoM's antitumor role in HCC progression [138]. Xu et al. found that PAF significantly increased ApoM mRNA levels in HepG2 cell cultures, suggesting that the elevated ApoM levels in HCC patients may be mediated through PAF-induced inflammatory responses [139]. Furthermore, inhibiting ApoM gene expression selectively regulated phosphofructokinase liver type (PFKL) via the transcription factor SREBF1, enhancing PFKL promoter activity. This likely explains the significant increase in proliferation, migration, and invasion observed in hepatoma cells with ApoM knockdown [140]. Reduced ApoM expression has also been shown to promote hepatic lipid accumulation by inhibiting autophagy in hepatocytes [141]. Overexpression of ApoM was found to downregulate MUC1 (a gene associated with ferroptosis suppression) by upregulating miR-4489, which disrupted the GSH-GPX4 antiferroptotic mechanism, thereby inhibiting hepatoma cell progression [142].

Zinc-alpha2-glycoprotein (AZGP1)

AZGP1, a 42 kDa soluble secreted protein, exhibits structural homology and similar amino acid sequences to proteins of the major histocompatibility complex class I family [143]. Previously identified as an anti-inflammatory

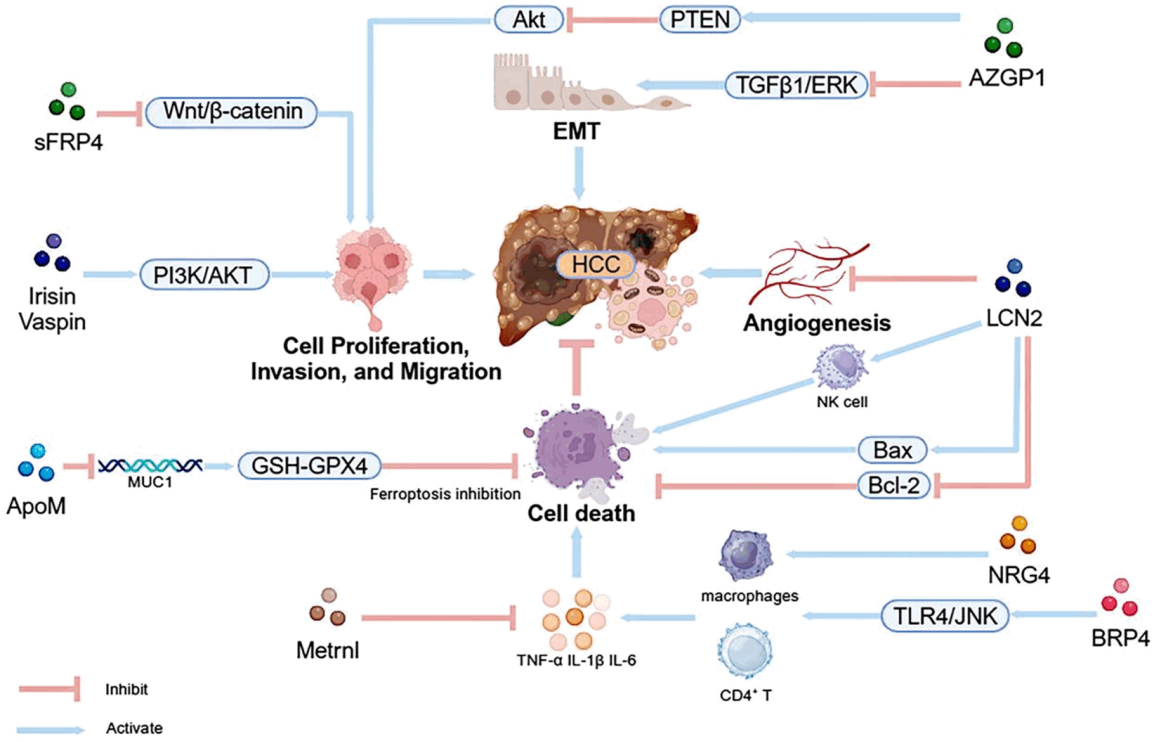

Figure 1. The pathways through which novel adipokines affect HCC. Novel adipokines exert their influence on hepatocellular carcinoma (HCC) development primarily by dysregulating key signaling cascades, including the Wnt/β-catenin, PI3K/AKT, PTEN/AKT, and TGFβ1/ERK pathways. These cascades, in turn, modulate cellular processes such as proliferation, invasion, migration, epithelial-mesenchymal transition (EMT), angiogenesis, and apoptosis, often through the interplay with immune signaling pathways.

adipokine with the ability to inhibit tumor development [12], AZGP1 is also linked to cancer cachexia due to its high amino acid sequence homology with lipid mobilization factors derived from tumors [144]. In mouse models, where AZGP1 is produced, it stimulates lipolysis in adipocytes, resulting in cachexia [145].

AZGP1 has been identified as a suppressor of HCC cell invasion, functioning by obstructing TGF-β-mediated epithelial-mesenchymal transition (EMT) [146]. This study revealed that the transcription factor Ikaros and histone deacetylation modulate AZGP1 expression in HCC. Additionally, a correlation was observed between the downregulation of AZGP1 in HCC serum samples and patient prognosis. Furthermore, AZGP1 was found to inhibit cell migration and invasion by regulating the PTEN/Akt and CD44s pathways in HCC [147]. Research conducted by Bingyi Lin et al. indicated that the suppression of LINC00844 expression significantly contributes to the pathogenesis and pathophysiology of HCC by promoting the AZGP1-mediated TGFβ1-ERK pathway, leading to HCC recurrence and adverse survival outcomes [148]. Similarly, Ming-Yi Xu et al. discovered that a deficiency in AZGP1 can trigger TGFβ1-ERK2 signaling-induced EMT, disrupt energy metabolism, decrease cell proliferation and induce apoptosis, activate survival signals, and promote invasion [149].

Conclusion

Compared to AFP, certain novel adipokines demonstrate enhanced sensitivity and specificity in predicting the onset of HCC, offering significant potential for clinical application. However, current research on these adipokines in relation to HCC is limited, and the mechanisms of most of these factors remain unclear. Existing studies suggest that these adipokines primarily influence HCC progression by modulating mechanisms related to growth, inflammation, migration, and apoptosis, as well as through pathways such as insulin resistance, which can either promote or protect liver cancer cells (**Figure 1**). The prognosis for HCC patients remains poor due to the tumor's high

propensity for metastasis and its poor response to drug treatments [150]. Therefore, identifying metastatic factors and elucidating the molecular mechanisms related to metastatic progression have become critical challenges. A deeper exploration of the mechanistic pathways involving adipokines could aid in the development of novel therapeutic drugs, providing promising targets for HCC treatment.

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Disclosure of conflict of interest

None.

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