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Serum resistin and the risk for hepatocellular carcinoma in diabetic patients

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Abstract

Hepatocellular carcinoma (HCC), the predominant type of liver cancer, is a major contributor to cancer-related fatalities across the globe. Diabetes has been identified as a significant risk factor for HCC, with recent research indicating that the hormone resistin could be involved in the onset and advancement of HCC in diabetic individuals. Resistin is a hormone that is known to be involved in inflammation and insulin resistance. Patients with HCC have been observed to exhibit increased resistin levels, which could be correlated with more severe disease stages and unfavourable prognoses. Nevertheless, the exact processes through which resistin influences the development and progression of HCC in diabetic patients remain unclear. This article aims to examine the existing literature on the possible use of resistin levels as a biomarker for HCC development and monitoring. Furthermore, it reviews the possible pathways of HCC initiation due to elevated resistin and offers new perspectives on comprehending the fundamental mechanisms of HCC in diabetic patients. Gaining a better understanding of these processes may yield valuable insights into HCC's development and progression, as well as identify possible avenues for prevention and therapy.

Key Words: Hepatocellular carcinoma; Resistin; Insulin resistance; Obesity; Diabetes; Liver cancer

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Core Tip: Resistin, a hormone linked to the onset of insulin resistance and diabetes, could be involved in the development and advancement of hepatocellular carcinoma (HCC) in individuals with diabetes. Increased resistin levels have been observed in HCC patients and might be connected to a more severe disease stage and unfavourable prognosis. This review aims to assess the existing literature concerning the possible application of resistin as a biomarker for HCC development and monitoring while

investigating the potential processes through which resistin influences HCC's development and progression in diabetic patients. Gaining a better understanding of these processes may offer valuable insights for the prevention and therapy of this condition.

INTRODUCTION

³ Liver cancer, particularly hepatocellular carcinoma (HCC), poses a significant global health challenge. As the sixth most prevalent cancer and the third leading cause of cancer-related deaths worldwide, it accounts for roughly one million fatalities each year^[1-3]. HCC also ranks as the second primary factor contributing to premature cancer-related deaths^[4], with projections indicating that annual liver cancer diagnoses will exceed one million by 2025^[5]. Moreover, between 2020 and 2040, the number of liver cancer diagnoses is predicted to rise by 55.0%^[6]. Although liver cancer prevalence and mortality have decreased in some East Asian countries, they have escalated in other parts of the world^[7]. HCC represents the most frequent liver cancer variety, comprising 90% of cases^[8]. It is commonly associated with chronic liver diseases (CLD), including viral hepatitis^[9-12], alcoholic liver disease, liver cirrhosis^[13-15] and “non-alcoholic fatty liver disease (NAFLD)”^[16-18]. Because of the increased prevalence of obesity and type 2 diabetes mellitus (T2DM), the incidence of NAFLD and associated consequences, such as “non-alcoholic steatohepatitis (NASH)”, is rapidly increasing. NAFLD is currently the major cause of liver cirrhosis, which in turn, raises the probability of developing HCC^[19]. The development of HCC is influenced by various factors, including oxidative stress^[20], inflammation^[21,22], and insulin resistance (IR)^[22-25].

Diabetes is a chronic metabolic condition characterized by high blood sugar and IR, which is associated with an increased risk of several health complications, including cardiovascular disease, kidney disease, and fatty liver^[26]. The most common form of diabetes, T2DM, is caused primarily by IR. The relationship between diabetes and HCC is complex and multifaceted. On the one hand, diabetes is a risk factor for the development of liver diseases, including liver fibrosis and HCC^[27]. On the other hand,

HCC can lead to diabetes due to IR, impaired glucose tolerance, and liver dysfunction^[28,29].

Resistin, a hormone secreted by both adipocytes and macrophages, and linked to obesity and T2DM, has been connected to HCC development and progression^[30-33]. High levels of resistin have been associated with IR, inflammation, and oxidative stress. All these factors are known risk factors for the development of HCC^[32-34]. Studies have found that high resistin levels are correlated with a greater risk of getting HCC^[30,32,35]. Nevertheless, the mechanisms by which resistin contributes to the initiation and progression of HCC in diabetic patients are not fully understood. Therefore, the purpose of this review is to assess the current literature on the potential use of resistin levels as a biomarker for the development and monitoring of HCC in diabetic patients. Additionally, this review aims to explore resistin's role in HCC pathogenesis among this patient group and provide novel insights into the involved underlying mechanisms. These findings could help identify new targets for preventing and treating HCC in diabetic patients.

PREVALENCE OF HCC IN DIABETIC PATIENTS

HCC is more prevalent in diabetic individuals than in those without diabetes. A thorough meta-analysis of 42 studies, including 17 case-control and 32 cohort studies, demonstrated that diabetic patients have a 2.31 times higher chance of developing HCC compared to non-diabetics. Furthermore, diabetic individuals experience a 2.43 times higher HCC mortality risk than their non-diabetic counterparts^[36,37]. HCC patients also exhibit a higher prevalence of diabetes, with reported rates between 20% and 70%^[38]. Additionally, a systematic review and meta-analysis of ten studies reported a 70% prevalence of liver cancer among those with elevated fasting blood glucose levels^[39].

Numerous investigations have corroborated the heightened incidence of HCC in diabetic individuals. For instance, a population-based study in Taiwan discovered that diabetic patients had a 2-3 times greater risk of developing HCC than those without diabetes^[40]. Similarly, a prospective cohort study of Chinese men and women in

Singapore found a heightened HCC risk in diabetics^[41]. Furthermore, an Italian hospital-based case-control study involving 224 HCC patients and 389 control subjects determined that the risk of HCC was significantly higher among patients with T2DM, especially those with longer disease durations^[42]. Additionally, a Korean prospective cohort study using the “National Health Insurance Service-Health Screening Cohort” found a hazard ratio of 1.82, indicating an elevated HCC risk in diabetic patients^[43].

Recent research has established that metabolic factors, such as diabetes mellitus, obesity, dyslipidemia, and metabolic syndromes, are substantial risk factors for HCC development^[44,45]. In populations with low viral hepatitis prevalence, the overall influence of metabolic factors on HCC may be more substantial than that of viral hepatitis. A recent multicenter study in China found that 9.3% of hepatitis B virus (HBV)-infected patients undergoing curative resection for HCC had concomitant metabolic syndrome. During a median follow-up of 50.4 mo, patients with metabolic syndrome had worse 5-year overall survival and recurrence-free survival rates, with increased overall recurrence rates, particularly after two years of surgery. Multivariate analyses revealed that metabolic syndrome was an independent risk factor for reduced overall survival and recurrence-free survival following curative resection for HCC. As a result, proper management of metabolic syndrome is essential for preventing post-hepatectomy recurrence. This information further emphasizes the importance of implementing a more rigorous surveillance program for recurrence in HBV-infected patients with concurrent metabolic syndrome, in addition to routine antiviral therapy^[46].

POTENTIAL MECHANISMS AND RISK FACTORS FOR HCC IN DIABETIC PATIENTS

The elevated incidence of HCC in diabetic patients is attributable to a multitude of factors, such as IR, chronic inflammation, the administration of antidiabetic medications, and the progression of NAFLD and NASH^[47-50]. IR and diminished glucose tolerance in diabetic individuals can result in hepatic fat accumulation, thereby

promoting the onset of NAFLD^[51,52]. NAFLD has been linked to a heightened risk of liver fibrosis and HCC^[18,53,54]. Furthermore, the prevalence of diabetes has been recognized as a risk factor for the emergence of NASH and its subsequent progression to cirrhosis and HCC^[50].

NAFLD is a multifaceted condition that can advance to severe fibrosis, cirrhosis, liver failure, and HCC^[55]. In the United States, NAFLD contributes to roughly 20% of HCC cases and is associated with an increased risk of HCC development, especially in patients with metabolic syndrome, specific ethnic groups, and hepatic siderosis. The incidence of HCC in NASH-related cirrhosis varies considerably, ranging from 2.4% over seven years to 12.8% over three years, with some patients developing HCC *de novo* as a result of NASH^[55]. Patients with T2DM have a higher risk of developing severe manifestations of NAFLD, such as cirrhosis and HCC^[56-58].

The coexistence of diabetes and NASH may contribute to the elevated prevalence of HCC in diabetic individuals. A recent study found that the global burden of NASH-related liver cancer, attributable to increased fasting plasma glucose levels, has significantly risen over the past three decades, particularly in “low- and middle-income countries”. Consequently, effective prevention and management of high fasting plasma glucose levels are vital for reducing the worldwide burden of NASH-related liver cancer^[59].

Besides NAFLD and NASH, other diabetes-associated complications may also contribute to the heightened HCC risk in diabetic patients. Such patients are more prone to chronic kidney disease, leading to the accumulation of uremic toxins and oxidative stress-both implicated in HCC development^[60,61]. Diabetic patients are also more prone to hypertension^[62], which has been linked to a higher HCC risk in some studies^[44,63,64].

The consumption of antidiabetic medications, for instance, insulin and metformin, may also influence the HCC risk in diabetic patients^[49]. Some studies suggest that IR and hyperinsulinemia could promote HCC development, potentially increasing the risk of HCC with insulin therapy^[64-67]. Conversely, metformin has shown protective effects

against HCC development in some studies, possibly due to its antineoplastic, anti-inflammatory, and antifibrotic properties^[42,64,68-70].

Hyperglycemia and hyperinsulinemia are believed to promote HCC development and progression^[71,72]. These conditions can activate various signaling pathways, such as the insulin-like growth factor-1 (IGF-1) pathway, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), mitogen-activated protein kinase (MAPK), and mTOR pathway, all involved in HCC development and progression^[73-77].

Hyperinsulinemia can increase hepatic growth hormone receptor expression, leading to IGF-1 release and the activation of growth factor-like activity on hepatocytes. Insulin and IGF-1 inhibit cell proliferation and apoptosis, increasing the risk of HCC^[78]. High glucose levels can also contribute to HCC development by generating advanced glycosylation end products, which activate inflammatory signaling pathways and produce reactive oxygen species that promote HCC development. IR might directly hasten the development of HCC by promoting the formation of new blood vessels in the liver^[79,80].

Moreover, dyslipidemia, which is common in diabetic patients, may have a role in HCC initiation and progression^[81,82]. Dyslipidemia can cause lipid accumulation in the liver, leading to liver damage and inflammation that promote HCC development^[83]. Research has demonstrated a strong correlation between reduced total cholesterol levels and a heightened likelihood of HCC development^[84-87]. Additionally, diabetic patients who exhibit high triglyceride levels and low high-density lipoprotein cholesterol levels, a pattern often seen in dyslipidemia, have been identified as being at a greater risk for HCC. However, the correlation between the levels of high-density lipoprotein cholesterol with HCC remains uncertain^[85,88].

Furthermore, diabetic patients may experience weakened immune systems^[89,90], which could increase the risk of developing chronic HBV or hepatitis C virus (HCV) infections, both of which are significant risk factors for HCC^[91-95]. Although the connection between DM and HCC risk appears to be stronger in HCV than HBV, a United States study involving 52671 HCV-liver cirrhosis patients (including 7605 HCC

cases) did not find a significant association between DM and HCC risk^[96]. Moreover, immunosuppressive medications prescribed to manage diabetes-related complications, such as kidney and pancreas transplants, might also contribute to an elevated risk of HCC development^[97-99].

Overall, the increased prevalence of HCC in diabetic patients is due to a combination of factors outlined in Figure 1. Further research is necessary to comprehensively understand the mechanisms linking diabetes and HCC and to devise effective strategies for preventing and treating HCC in diabetic patients.

DIAGNOSIS AND MANAGEMENT OF HCC IN DIABETIC PATIENTS

Early detection of HCC is crucial for successful treatment. Although HCC can be diagnosed early in 30%-60% of cases, recurrences can still affect up to 80% of patients within five years, even after receiving curative treatments^[100].

Screening for HCC in diabetic patients is challenging due to the high prevalence of coexisting liver illnesses such as NAFLD and NASH, and there is currently a lack of effective methods to monitor NAFLD-related HCC^[101]. Although guidelines recommend regular HCC surveillance for high-risk individuals, which involves at least once every six months of liver ultrasonography and serum alpha-fetoprotein monitoring^[102-106], the insidious onset of HCC often leads to late detection. Consequently, it is crucial to establish effective monitoring strategies and ensure early diagnosis and treatment to enhance patient outcomes.

The lack of official guidelines for NAFLD-related HCC diagnosis criteria results in clinical symptoms being the primary diagnostic tool, which can lead to late detection of the disease. Patients with NAFLD-related cirrhosis are considered high-risk subgroups for HCC, and ultrasonography is the primary surveillance test^[107-109]. Imaging modalities such as ultrasound, computed tomography, and magnetic resonance imaging are commonly used for HCC screening in diabetic patients, and diagnostic accuracy can be improved by combining different imaging techniques^[108-110].

The management of HCC in diabetic patients requires a multidisciplinary approach that considers the potential interactions between diabetes medications and cancer treatments, as well as their impact on glycaemic control^[49,111-113]. Although surgical removal of the tumour and liver transplant are curative treatments for HCC, they may not be suitable for all diabetic patients due to the higher risk of surgical complications in this population. Furthermore, diabetic individuals with HCC are more likely to have advanced illnesses at the time of diagnosis, which may limit the effectiveness of these treatments^[107-109].

Until recently, Sorafenib was the only medication approved by the United States Food and Drug Administration (FDA) for advanced HCC. Multi-kinase inhibitors like cabozantinib and ramucirumab have been approved as second-line treatments since 2017^[114-116]. Nivolumab^[117] and pembrolizumab^[118], the checkpoint inhibitors have either received FDA approval or are currently being investigated. However, systemic therapies may pose significant challenges in managing side effects in patients with cirrhosis^[119]. Moreover, the high cost of approved medications makes their usage difficult in low-income countries^[120]. Thus, HCC prevention in high-risk individuals could be a viable alternative to HCC treatment since identifying high-risk individuals is possible, and the survival rates after diagnosis are low. Local therapies such as radiofrequency ablation, percutaneous ethanol injections, and transarterial chemoembolization (TACE) are available options for early-stage HCC^[121-125]. Among these options, TACE is commonly used as a treatment approach. TACE involves the direct delivery of chemotherapy drugs into the blood vessels that supply the tumour, followed by the injection of embolic agents to obstruct the tumour's blood flow. This targeted approach allows for the direct impact on the tumour while minimizing the systemic effects of chemotherapy. TACE is often recommended for patients with early-stage HCC who are not suitable candidates for surgery or liver transplantation. Additionally, it can serve as a bridge therapy prior to other definitive treatments or as a palliative measure to reduce tumor size and alleviate symptoms^[124,125]. Systemic therapy with chemotherapy, targeted therapy, or immunotherapy may be used for

advanced-stage HCC, but the choice of treatment should consider the potential interactions with diabetes medications and their impact on glycaemic control^[126-128].

PREVENTION STRATEGIES FOR HCC IN DIABETIC PATIENTS

Preventing HCC development in diabetic patients is a crucial objective of diabetes management. Lifestyle adjustments, such as weight loss, exercise, and dietary changes, can enhance glycaemic control, diminish the risk of developing NAFLD and NASH, which are vital risk factors for HCC^[101,109,111], and also minimize the risk of HCC^[102,109,129]. Regular HCC screening for diabetic patients can facilitate early detection of the disease when curative therapies are more likely to succeed. The American Association for the Study of Liver Diseases recommends that diabetic patients with cirrhosis and advanced fibrosis undergo ultrasound screening every six months for HCC^[107].

In addition, antidiabetic drugs may also aid in preventing HCC development in diabetic patients. Metformin, in particular, has demonstrated a protective effect against HCC development in some studies, potentially because of its anti-neoplastic, anti-inflammatory, and anti-fibrotic effects^[49,64,68-70]. However, the use of other antidiabetic medications like insulin may raise the risk of HCC, though further investigation is necessary to completely comprehend the association between diabetes medications and HCC risk^[67].

RESISTIN AS A POTENTIAL BIOMARKER FOR HCC: INSIGHTS INTO ITS ROLE IN HCC DEVELOPMENT AND DIAGNOSIS

The timely diagnosis and detection of HCC is crucial for improving patient outcomes, which has led to an increased interest in identifying biomarkers for early detection. Resistin has emerged as a promising candidate in this regard. First identified in 2001, resistin is a hormone that is implicated in IR and is characterized by its pro-inflammatory properties. Resistin is predominantly synthesized by adipocytes in rodents. In contrast, in humans, while adipocytes have the capacity to synthesize

resistin, the hormone is primarily produced by immune cells called macrophages, which are integral to immune responses and inflammation. The presence of resistin in human serum typically ranges within a physiological concentration of 7-22 ng/mL^[130]. The *RETN* gene encodes resistin protein, which is also known as “adipocyte-specific secretory factor, Fizz3, RSTN, or cysteine-rich protein 1”^[131-134].

Resistin contributes to IR by inducing persistent low-grade inflammation associated with obesity-induced macrophage infiltration in adipose tissues. Furthermore, resistin promotes p38 MAPK signaling, altering insulin signaling, modulating the cellular oxidative stress response, and enhancing cells proliferation by increasing the production of various inflammatory molecules such as interleukin (IL)-1 β , IL-6, IL-8, IL-12, and tumor necrosis factor-alpha (TNF- α)^[34,135-137]. Elevated resistin expression has been associated with inflammation, autoimmune illnesses, metabolic diseases, and malignant conditions, suggesting that it could be a reliable biomarker for HCC diagnosis, early detection, and prognosis^[131,132,138,139].

Several clinical studies have investigated the potential of resistin as a diagnostic and prognostic biomarker for HCC^[33,140-142]. Studies have shown that resistin is expressed in HCC tissue and is involved in the progression of HCC through its effects on cell proliferation, apoptosis, invasion, and angiogenesis^[138,143-145]. Serum resistin levels have been found to be positively correlated with tumour size, TNM stage, and vascular invasion, highlighting that resistin might be a helpful HCC predictive biomarker^[32]. Moreover, resistin has been assessed as a diagnostic biomarker for HCC in combination with other biomarkers, such as alpha-fetoprotein and des-gamma-carboxy prothrombin. The combination has been reported to exhibit higher diagnostic accuracy compared to any of the biomarkers alone^[32,146,147].

Yagmur *et al*^[139] investigated the clinical significance of resistin in CLD by measuring serum resistin levels in 82 CLD patients and 76 age and gender-matched healthy controls, and monitoring the patients for six years. The study found that resistin levels were significantly higher in liver cirrhosis patients compared to the healthy controls, with levels increasing as cirrhosis advanced. Resistin levels also showed a positive

correlation with insulin secretion, a negative correlation with insulin sensitivity, and associations with inflammatory markers and clinical complications. The study concluded that patients with higher resistin levels had increased mortality within six years, suggesting that resistin could be a useful clinical biomarker for evaluating liver cirrhosis and its potential link to IR in patients with severe liver disease^[140].

Da Silva *et al*^[141] conducted a prospective cohort study to investigate potential factors associated with adiponectin and resistin levels in cirrhosis patients and their clinical significance. The study involved 122 cirrhosis patients from an outpatient clinic and a control group of 30 healthy subjects. The study found that patients with cirrhosis had higher adiponectin and resistin levels compared to the control group. Adiponectin levels, but not resistin well established levels, were significantly associated with the severity of liver dysfunction and a worse prognosis in patients with alcoholic liver disease, suggesting a potential role as a prognostic biomarker^[142].

A recently published systematic review and meta-analysis investigated the correlation between serum resistin levels and NAFLD in adults. The review comprised 28 studies that included 4088 participants, which were analyzed using meta-analysis techniques. The study findings indicated that patients with NAFLD had considerably higher serum resistin levels when compared to healthy individuals. In contrast, patients with NASH had lower serum resistin levels than healthy controls. No significant difference was observed in serum resistin levels between patients with NAFLD and healthy controls or between patients with NAFLD and NASH. The study also suggested that serum resistin may be a potential biomarker for predicting the risk of developing NAFLD, a known risk factor for HCC, and could also differentiate between NAFLD and NASH. However, further research is necessary to support these findings and to comprehend the underlying mechanisms of this association^[148].

EVALUATION OF RESISTIN AS A DIAGNOSTIC AND PROGNOSTIC BIOMARKER FOR HCC: INSIGHTS FROM CLINICAL STUDIES

A thorough search was executed on PubMed and Google Scholar databases, employing a set of keywords including “resistin and HCC”, “resistin and hepatocellular carcinoma”, “resistin and liver cancer”, “resistin as a biomarker for hepatocellular carcinoma”, and “resistin and hepatic cancer” with the objective of identifying research that investigates the role of resistin as a biomarker specifically for HCC. The search yielded four studies that delved into the clinical utility of resistin in the diagnosis and prognosis of HCC. The ensuing compilation of studies is presented in a chronological fashion, commencing with the pioneering study conducted in 2014 and culminating with the latest research from 2022.

Elbedewy *et al*^[30] conducted a study to investigate whether serum resistin and IR could be considered as risk factors for HCC in HCV-cirrhotic patients with T2DM. The study involved 50 adult patients with HCV infection who were categorized into three groups based on their HCC status, and were subjected to routine tests for DM, HCV, liver cirrhosis, and HCC. The results revealed that patients with HCC and diabetes (group I) had significantly higher levels of homeostasis model assessment-IR (HOMA-IR) and resistin than diabetic patients with cirrhosis (group II) and control subjects (group III). The study concluded that HOMA-IR and serum resistin could potentially serve as novel biomarkers to identify HCV-cirrhotic patients with T2DM who are at a greater risk of developing HCC^[30].

Furthermore, a prospective case-control study was conducted by Elsayed *et al*^[33] to investigate the implications of IR and serum resistin as possible risk factors for HCC among individuals with HCV-related liver cirrhosis. The study involved 200 patients with HCV-related liver cirrhosis (100 with HCC and 100 without HCC) as well as 50 healthy controls. The study found that patients with HCC had significantly higher levels of resistin and HOMA-IR than cirrhotic patients and healthy controls. Patients with resistin levels more than or equal to 12 ng/mL and HOMA-IR values higher than or equal to 4 were 1.6 times more likely to experience HCC. These data imply that HOMA as well as serum resistin, may be useful in identifying HCV-cirrhotic individuals at high risk of developing HCC^[33].

Mohamed *et al*^[32] conducted a study to evaluate the potential of serum resistin levels as a biomarker for assessing response to therapy in individuals with hepatic cirrhosis and HCC. The study included 50 patients with HCV-related cirrhosis, 30 of whom had HCC and the remaining 20 did not. Patients with HCC had higher levels of serum resistin, which showed strong positive correlations with hepatic focal lesions, portal vein invasion, total bilirubin, international normalized ratio, and model of end-stage liver disease score. After one month of HCC intervention, serum resistin levels were significantly lower than before the intervention. These findings suggest that serum resistin could be used as a reliable biomarker for evaluating treatment response in HCC patients^[32].

More recently, Ashour *et al*^[31] conducted a case-control study to investigate the relationship between serum resistin levels and HCC in patients with liver cirrhosis. The study included 80 cirrhotic patients (40 with HCC and 40 without HCC). The results showed that serum resistin levels were significantly higher in the HCC group compared to the control group, with a strong positive correlation between resistin and total cholesterol and low-density lipoprotein. Additionally, the study found that resistin levels could be used as a diagnostic marker for HCC, with a sensitivity of 90% and specificity of 95% at a cutoff value of > 13.7 ng/mL. These findings support the use of serum resistin levels as a diagnostic biomarker for HCC in patients with liver cirrhosis^[31]. Table 1 provides a summary of the above-mentioned studies.

POTENTIAL MECHANISMS OF HCC INDUCTION BY ELEVATED RESISTIN LEVELS

Resistin has been implicated in cancer development through various signaling pathways. Among these, the toll-like receptor 4 (TLR4), PI3K, and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκβ) pathways are particularly noteworthy. These signaling cascades are instrumental in modulating various cellular processes that are crucial for cancer development and progression. In the context of different cancer types, these signaling pathways have been demonstrated to play an imperative role in

fostering cellular proliferation. Notably, specific pathways are often selectively associated with distinct types of cancer. For instance, the AKT pathway, a downstream effector of PI3K, has been predominantly associated with prostate cancer, serving as a key regulator in promoting cell survival and growth^[149]. Conversely, lung cancer demonstrates a more complex network of signaling pathways. Among these, PI3K, NFκβ, epidermal growth factor receptor, and TLR4 have been implicated^[150]. These pathways collaboratively contribute to the progression of lung cancer through mechanisms such as cell proliferation, angiogenesis, and resistance to apoptosis.

Additionally, melanoma, a malignancy of melanocytes, has been found to be under the influence of distinct signaling axes, such as the phosphorylated AKT and Caveolin-1, which are critical in dictating the course of the disease^[151].

Resistin's influence extends beyond these pathways; it has been implicated in the activation of the IL-6 dependent signal transducer and activator of transcription 3 (STAT3) signaling pathway^[152,153]. This pathway is especially noteworthy in breast cancer progression. Moreover, resistin has been linked to the progression of ovarian cancer through the modulation of microRNAs, such as "miR let-7a, miR-200c, and miR-186"^[154].

Diving deeper into the IL-6/STAT3 axis, this signaling pathway has been linked with various aspects of cancer biology, including tumor progression, metastasis, and therapy resistance in diverse cancer types such as breast, colorectal, and HCC. The crux of this axis lies in the overexpression of IL-6 and the consequent hyperactivation of STAT3, a combination frequently associated with a grim prognosis. Resistin further exacerbates this by promoting the secretion of pro-inflammatory cytokines like IL-6, which activates STAT3. This sets into motion an autocrine loop intensifying STAT3 signaling, leading to aggressive tumor behavior^[153,155,156].

Intriguingly, Resistin dons yet another hat - that of a potential tumor suppressor. It has been shown to induce cell cycle arrest in colon cancer cells through the upregulation of suppressor of cytokine signaling 3 (SOCS3)^[157]. SOCS3, part of the SOCS protein family, is integral in curbing cytokine signaling. This implies that resistin may play a

role in keeping the proliferation of colon cancer cells in check, revealing its context-dependent pleiotropic nature. In summary, resistin orchestrates a plethora of pathways, including the activation of pro-inflammatory cytokines, fostering angiogenesis, modulating insulin signaling, and influencing cell proliferation and survival^[155,156,158]. Its context-dependent roles in both promoting and potentially suppressing tumors accentuate the complexity of resistin's function in cancer. This warrants a nuanced understanding and approach in considering resistin as a potential target for therapeutic interventions.

Resistin's role in proinflammatory cytokine activation

The role of resistin in activating proinflammatory cytokines has been well-established in various studies. These cytokines, including TNF- α , IL-6, and monocyte chemoattractant protein-1 are crucial in inflammation, cell proliferation, and apoptosis, all of which contribute to HCC development and progression^[159-163].

Resistin has been demonstrated to directly stimulate TNF- α and IL-6 production in macrophages by binding to TLR4 and initiating downstream signaling pathways, such as NF- κ B^[164,165]. The activation of the NF- κ B pathway results in the transcription of proinflammatory cytokines, perpetuating chronic inflammation associated with an increased risk of HCC^[166].

In addition to direct stimulation, resistin activates other inflammatory pathways, notably the c-Jun N-terminal kinase and STAT3 pathways^[167-170]. These pathways contribute to the production of proinflammatory cytokines and are implicated in the pathogenesis of HCC^[168,169,171]. Moreover, resistin-induced cytokines have been linked to hepatic stellate cell activation, subsequently leading to liver fibrosis and cirrhosis, both of which are significant precursors to HCC^[172-174]. In this regard, resistin's activation of proinflammatory cytokines serves as a vital connection between resistin and the development of HCC in diabetic patients.

Resistin and the modulation of immune responses

In addition to resistin's proinflammatory effect, resistin has been implicated in macrophage activation and polarization of tumor-associated macrophages towards the M2 phenotype^[175]. M2 macrophages are characterized by their pro-tumorigenic properties, such as promoting angiogenesis, immunosuppression, and tissue remodeling, which further advance HCC progression^[176].

Additionally, resistin has been implicated in the modulation of the immune response through increased expression of the macrophage inflammatory protein- α (MIP- α), a chemokine also known as CC chemokine ligand 3^[177]. It is a small signaling protein secreted by various immune cells, including macrophages, T cells, and dendritic cells. MIP- α plays a crucial role in immune response modulation by attracting and activating leukocytes, particularly monocytes and neutrophils, to the site of inflammation or infection. This chemokine is involved in various biological processes, including inflammation, immune cell activation, and the regulation of cell migration during an immune response. MIP- α has also been implicated in the progression of certain diseases, such as autoimmune disorders, chronic inflammatory conditions, and even cancer, due to its ability to modulate immune responses^[178]. Furthermore, resistin has been reported to modulate the function of other immune cell populations, including natural killer cells and T lymphocytes, impairing their antitumor activities and allowing HCC tumor evasion^[179,180]. Taken together, these findings highlight the multifaceted role of resistin in HCC pathogenesis through the modulation of the immune responses and tumour microenvironment.

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Resistin and promotion of angiogenesis

Angiogenesis, the formation of new blood vessels from existing ones, is a pivotal process in tumor growth, invasion, and metastasis. Resistin promotes angiogenesis through various mechanisms, including the upregulation of vascular endothelial growth factor (VEGF), activation of the hypoxia-inducible factor-1 α (HIF-1 α) pathway, and modulation of other signaling pathways^[181-184].

VEGF, which spurs endothelial cell proliferation, migration, and survival, is crucial for angiogenesis^[185]. Studies have demonstrated that resistin boosts VEGF expression in different cell types, including cancer cells^[186,187]. In a study by Tsai *et al*^[178], resistin was found to upregulate VEGF expression in osteosarcoma *via* the activation of NFκβ signaling^[181]. Furthermore, Chen *et al*^[179] demonstrated that resistin enhanced VEGF formation in human chondrosarcoma cells through a PI3K/AKT-dependent mechanism^[182]. Elevated VEGF expression in HCC tissue has been associated with a worse prognosis^[188,189].

Resistin can also contribute to angiogenesis by stimulating the HIF-1α pathway^[190]. Under hypoxic conditions, HIF-1α is stabilized and translocated to the nucleus, where it binds to hypoxia-response elements and promotes the transcription of various genes, including VEGF^[191]. It has been demonstrated that resistin increased HIF-1α expression in human adipocytes under hypoxia, leading to enhanced VEGF expression^[182].

Resistin's impact on insulin signaling

Insulin signaling is critical for maintaining glucose homeostasis and is often disrupted in diabetes, obesity, and cancer. Resistin has been implicated in modulating insulin signaling, contributing to IR and affecting HCC development in diabetic patients^[158].

Resistin has been demonstrated to disrupt insulin-driven glucose uptake in peripheral tissues like adipose tissue and skeletal muscle by interfering with insulin signaling^[192,193]. Fu *et al*^[191] found that resistin inhibited insulin-induced glucose uptake in 3T3-L1 adipocytes by reducing the activity of glucose transporters^[194]. Similar results were observed in skeletal muscle cells, where resistin impaired insulin-stimulated glucose uptake by decreasing IRS-1-associated PI3K activity^[195].

Resistin has been shown to affect liver glucose metabolism by enhancing hepatic gluconeogenesis^[196]. In a study by Rajala *et al*^[193], resistin administration in mice led to elevated liver glucose production and hyperglycemia. The researchers suggested that this effect occurs *via* activating the cAMP-protein kinase A pathway.

In L6 rat myotubes, resistin overexpression was shown to hinder insulin-mediated glucose uptake without altering glucose transporter type 4 (GLUT4) translocation, GLUT1 expression, or IRS signaling^[197]. Moreover, resistin or RELM β infusion in adult male Sprague Dawley rats led to hepatic IR, characterized by increased hepatic glucose production *via* AMP-activated protein kinase^[198]. Lastly, resistin treatment in rat hepatocytes and mice with liver-specific resistin expression resulted in impaired hepatic insulin action by reducing phosphorylation of GSK3 β at serine 9. This observation was made in a study conducted on C57BL/6 J mice^[199].

The modulation of insulin signaling by resistin may indirectly contribute to HCC development by exacerbating hyperinsulinemia and IR in diabetic patients. Hyperinsulinemia has been associated with an increased risk of HCC, as insulin can promote cell proliferation and survival through the activation of mitogenic signaling pathways, such as the PI3K/Akt and Ras/MAPK pathways^[200,201]. Furthermore, IR may lead to chronic inflammation and liver damage, which can promote HCC development^[202,203]. Hence, resistin modulates insulin signaling by impairing insulin-stimulated glucose uptake and promoting hepatic gluconeogenesis. These effects may indirectly contribute to HCC development in diabetic patients by exacerbating hyperinsulinemia, IR, and inflammation.

Resistin's induction of matrix metalloproteinases

Matrix metalloproteinases (MMPs) are enzymes responsible for the breakdown of extracellular matrix components, thereby aiding tumour invasion and metastasis^[204]. Resistin has been found to increase MMP expression in various cell types, including endothelial cells and cancer cells^[136,205]. In a study by Di Simone *et al*^[203], resistin was shown to stimulate MMP-2 production in human endothelial cells, potentially contributing to angiogenesis and tumour invasion^[206]. Similarly, Huang *et al*^[207] demonstrated that resistin increased MMP-2 and MMP-9 expression in human colorectal cancer cells. Furthermore, a study by Tsai *et al*^[178] revealed that resistin

enhanced MMP-2 expression *via* the activation of the AMPK/p38 signaling pathway and downregulation of miR-519d, contributing to chondrosarcoma metastasis^[208].

Moreover, resistin has been implicated in the promotion of HCC metastasis through the upregulation of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, both of which are critical mediators of cancer cell adhesion and migration. Evidence suggests that resistin stimulates the expression of these adhesion molecules in endothelial cells^[209], thereby facilitating the adhesion and transendothelial migration of HCC cells. Taken together, the available evidence suggests that resistin contributes to HCC progression and metastasis through multiple mechanisms, including the promotion of angiogenesis, upregulation of VEGF, activation of the HIF-1 α pathway, induction of MMP expression, and increased expression of cell adhesion molecules.

Promotion of cell proliferation and survival by resistin

Resistin has been associated with the enhancement of cell proliferation as well as survival in various cell types, including cancer cells, which can contribute to HCC development and progression in diabetic patients. This is achieved through the activation of mitogenic signaling pathways like PI3K/AKT and MAPK/ERK^[135,140,183,207,208]. These pathways have been found to mediate cell proliferation and HCC progression^[210,211]. Additionally, resistin promotes cell survival by upregulating anti-apoptotic proteins like Bcl-2 and Bcl-xL^[145]. For instance, a study by Pang *et al*^[144] demonstrated that resistin increased Bcl-2 expression in human myeloma cell lines, contributing to improved cell survival and resistance to chemotherapy, potentially through the activation of the NF κ B signaling pathway.

Moreover, resistin impacts cell cycle regulation. Research revealed that resistin increased the expression of cyclin D1 in colon cancer patients^[157]. Cyclin D1 is integral for cell cycle progression, particularly for the transition from the G1 to S phase. This upregulation of cyclin D1 was suggested to be a result of SOCS 3 upregulation, mediated by the activation of the ERK signaling pathway^[157].

Overall, resistin contributes to cell proliferation and survival through various mechanisms, including the activation of mitogenic signaling pathways, induction of anti-apoptotic proteins, and modulation of cell cycle regulation. Figure 2 provides a schematic representation of the mechanisms through which resistin influences the development and metastasis of HCC.

CONCLUSION

Resistin, an adipokine implicated in obesity and IR, plays a crucial role in promoting HCC development and progression in diabetic patients. There is evidence supporting the potential use of resistin as a biomarker for HCC in diabetic patients. The potential mechanisms through which resistin promotes HCC include the activation of proinflammatory cytokines, promotion of angiogenesis, modulation of insulin signaling, and enhancement of cell proliferation and survival. These diverse effects highlight the need for further research to better understand the complex interplay between resistin and HCC development in diabetic patients.

Limitations

This review, while offering a comprehensive overview of resistin's role in HCC development among diabetic patients, possesses several limitations. First, the scope is bound to the literature available at the time, which may not encompass recent developments. Additionally, the multifaceted molecular mechanisms discussed are highly complex, and there may be aspects not extensively covered here. It is also imperative to differentiate between correlation and causation, as the review addresses associations but does not confirm causal relationships. Furthermore, the generalizability of the conclusion is uncertain, as genetic diversity, lifestyle factors, and additional health conditions could affect the interplay between resistin and HCC in different populations. Lastly, the reliance on studies that might contain biases or have their own limitations could inadvertently influence the conclusion drawn in this review.

Recognizing these limitations is vital for a well-rounded understanding and highlights the importance of further studies.

Future studies

Future studies should focus on identifying novel molecular targets for therapeutic intervention and developing strategies to counteract the deleterious effects of resistin on HCC development and progression. Understanding the molecular mechanisms underlying resistin's role in HCC could lead to the development of novel diagnostic and therapeutic strategies for the management of HCC in diabetic patients. Additionally, the development of effective therapies targeting resistin and its associated signaling pathways may help mitigate the risk of HCC in diabetic patients, especially those with obesity and IR. Further research is required to assess the effectiveness and safety of such therapeutic strategies in preclinical and clinical settings.

Moreover, given the complexity of the molecular mechanisms underlying resistin's role in HCC, a multidisciplinary approach involving collaboration between experts in endocrinology, oncology, and molecular biology is essential for advancing our understanding of this complex relationship. This collaborative effort may help identify potential biomarkers for early detection and prognosis of HCC in diabetic patients and facilitate the development of personalized medicine approaches.

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