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# Role of insulin-like growth factor/receptor signaling in hepatocellular carcinoma

**Running Head: IGF/IGFR signaling in HCC**

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**Abstract**
Hepatocellular carcinoma (HCC) is one of the most common and deadly forms of liver cancer worldwide. Recent research suggests that the insulin-like growth factor (IGF) system, including insulin-like growth factor-1, insulin-like growth factor-2, and their receptors, may play a critical role in the pathogenesis and progression of

HCC. However, the precise mechanisms through which IGFs contribute to HCC development remain unclear. The objective of this review is to explore the association between IGF signaling and HCC, with a focus on understanding the molecular pathways through which the IGF axis influences the pathophysiology of HCC. The review also examines the potential of utilizing the IGF pathway as a therapeutic target for HCC. IGF-1R overexpression, elevated IGF-2 levels, and decreased IGF-1 levels are seen in HCC and are linked to a poor prognosis. The IGF-1R signaling pathway leads to activation of PI3K/AKT/mTOR and RAS/RAF/MEK/ERK, which increases cell growth and proliferation and inhibits apoptosis, resulting in HCC. Also, in diabetic conditions, low levels of IGF-1 contribute to a higher risk of HCC due to hyperinsulinemia, chronic inflammation, and diseases like non-alcoholic fatty liver disease (NAFLD) and its severe form, non-alcoholic steatohepatitis (NASH).
**Keywords:** Hepatocellular carcinoma; insulin-like growth factor-1; insulin-like growth factor-2; insulin-like growth factor-1 receptor; non-alcoholic fatty liver disease.



## Introduction

Liver cancer ranks as the sixth most prevalent form of cancer, yet due to its aggressive characteristics and poor prognosis, it escalates to the third leading cause of cancer-related fatalities.[1] Primary liver cancer comprises hepatocellular carcinoma (HCC), which accounts for approximately 75%–80% of total cases, followed by intrahepatic cholangiocarcinoma, along with a few additional minor forms.[2,3]

The primary risk factors for the occurrence of HCC are chronic liver disease and cirrhosis.[4] A vital phase in the HCC viral carcinogenesis process is cirrhosis. In addition, a significant risk factor for liver cancer is chronic hepatitis, which is brought on by infections with the hepatitis B virus (HBV) and hepatitis C virus (HCV). Most of the newly diagnosed cases of liver cancer happen in underdeveloped nations where HBV is prevalent.[5,6] Meanwhile, the primary cause of HCC in developed nations is non-alcoholic fatty liver disease (NAFLD).[7] Cigarettes, alcohol, and aflatoxin B1 are also linked to HCC.[8,9]

The liver function stage of the individual and the disease's current state influences the management of HCC. Surgical resection, liver transplantation, or local ablative therapy like microwave or radiofrequency ablation can all be used to treat early-stage HCC. In cases of advanced HCC, systemic medicines such as immunotherapy, chemotherapy, and targeted therapy are advised.[10,11] The Barcelona Clinic Liver Cancer (BCLC) 2022 update and recent international guidelines recommend atezolizumab plus bevacizumab or durvalumab plus tremelimumab as preferred first-line regimens in patients with preserved liver function and good performance status. When these are unsuitable, sorafenib, lenvatinib, or single-agent durvalumab may be used. Second-line options include cabozantinib, regorafenib, ramucirumab, or immune checkpoint inhibitors such as nivolumab plus ipilimumab.[11,12] Current consensus positions atezolizumab plus bevacizumab as the standard first-line therapy, while adjuvant use after resection or ablation is not recommended following recent American Association for the Study of Liver Diseases (AASLD) updates.[13]

The liver is responsible for various physiological processes, including macronutrient metabolism, blood volume regulation, immune system support, lipid and cholesterol homeostasis, and the breakdown of xenobiotic compounds, including many drugs.[14] One of the key roles of the liver is to synthesize various growth factors, one of which is insulin-like growth factors (IGFs). Liver functions such as differentiation, proliferation, and apoptosis are influenced by growth factors produced within the liver. Production of hepatic IGFs is stimulated by growth hormone (GH).[15]

The IGF family encompasses six high-affinity binding proteins (IGFBP-1 to IGFBP-6), two ligands (IGF-1 and IGF-2), and cell-surface receptors (IGF-1R and IGF-2R). Research based on animal models and in vitro studies indicates that components of the IGF system play a role in various cellular processes involved in hepatocarcinogenesis, including cell cycle progression, uncontrolled cell growth, survival, migration, apoptosis inhibition, protein synthesis, and overall cell growth.[16]

This review focuses on the most recent research on the association between IGF signaling and HCC, with a special focus on understanding the molecular mechanisms by which the IGF axis influences the pathophysiology of HCC. It also investigates the potential use of the IGF pathway as an HCC treatment target.

## Etiology of HCC

A multiphase process resulting from the combination of environmental and genetic factors gives rise to HCC, a particular kind of cancer. In HCC, the cells are autonomous, as they produce their own growth signals (autocrine stimulation), remain insensitive to growth-inhibitory signals, are resistant to apoptotic signals, and can perform angiogenesis.[17]

In the majority of patients, normal cells convert to dysplastic cells due to the favourable condition provided by the regenerating nodule produced during cirrhosis, making cirrhosis one of the main causes of HCC. The conversion of cirrhosis to HCC is eased by various genetic and epigenetic reasons. Various factors that lead to

cirrhosis include alcohol consumption and other viral pathogens such as HBV and HCV.[17,18]
In cases with chronic alcohol exposure, liver cells show increased sensitivity to the cytotoxic effects of tumour necrosis factor-α (TNFα), which leads to chronic hepatocyte destruction–regeneration, stellate cell activation, cirrhosis, and finally HCC.[19] Chronic alcohol exposure may also cause oxidative stress, which might influence HCC-relevant signaling pathways, such as the documented depletion in tyrosine phosphorylation of STAT1 (signal transducer and activator of transcription 1), decreased STAT1-directed activation of interferon-α signaling, and the loss of the protective effects of interferon-α with consequent hepatocyte damage. Oxidative stress might also cause the accumulation of oncogenic mutations.[20,21]
A vaccination effort against the virus has reduced the incidence rates of HCC over time; however, HBV still accounts for 54% of cases of HCC. Despite the efforts to promote vaccination against HBV, some indigenous areas still have a notably elevated risk. Approximately 31% of chronic HCV cases result in liver cirrhosis, which leads to HCC. HCV, not being inherited since birth, unlike HBV, is acquired later in life, usually through contaminated syringes or needles in drug abuse or through infected blood products.[22,23] Both host- and viral-related factors are identified as causes of HCC development. The interactions between hosts and viruses appear to play a role in the development of liver cancer in various ways. While a strong T-cell immune response is triggered to fight off the viral infection, this response also leads to the death of liver cells, inflammation, and subsequently, tissue regeneration, ultimately contributing to the onset of cancer.[3]
Another serious cause for the development of HCC is aflatoxin. It is a fungal toxin distinguished as B1, B2, G1, and G2. Out of all, aflatoxin B1 is considered a mutagen, being the most severe one.[22] Incidence of HBV infection increases the risk of HCC, as aflatoxins are known to suppress the immune system, further leading to cirrhosis.[23]
Another important cause of cirrhosis and HCC is non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH).[24] Abdominal obesity, elevated triglycerides, reduced high-density lipoprotein, hypertension, and impaired fasting glucose, collectively known as metabolic syndrome, are some of the risk factors leading to NAFLD/NASH and further developing into liver fibrosis, cirrhosis, and HCC.[25]
Type 2 diabetes mellitus (T2DM) is also considered a risk factor for HCC. Although the clear mechanism of the relationship between these two is not clearly understood, it is postulated that insulin resistance and activation of the insulin receptor and IGF-1 signaling pathways are among the main factors in the initiation and further development of HCC.[26,27] The insulin receptor has a variety of metabolic and molecular effects that lead to inflammation, oxidative stress with resultant DNA damage, and stimulation of cellular pathways that result in cellular growth and proliferation, all potentiating HCC development. The insulin receptor also leads to changes in visceral adipose tissue, including increased fatty acid oxidation and liberation, along with changes in the inflammatory and adipokine secretory profile, resulting in increased levels of tumour necrosis factor-alpha (TNF-α), interleukin-6, and leptin, which further result in states of hepatic inflammation and fibrosis, perpetuate insulin resistance, and result in carcinogenesis.[28]

**Type 2 Diabetes Mellitus (T2DM), IGF, and HCC**
A complex network of cellular and metabolic pathways connects IGF, HCC, and T2DM.[29] T2DM is a prevalent metabolic disorder characterized by chronic hyperglycemia due to insulin resistance and relative insulin deficiency. This condition has widespread effects on various metabolic and physiological processes in the body, including the IGF system. IGF, particularly IGF-1, plays a critical role in regulating cell growth, differentiation, and survival. In individuals with T2DM, IGF-1 levels are often found to be lower than in non-diabetic individuals.[30] This reduction in IGF-1 can be attributed to several factors, including increased insulin resistance, hyperglycemia, and alterations in the growth hormone (GH) axis, which in turn impacts IGF-1 synthesis in the liver.[30,31]

The reduction in IGF-1 has far-reaching consequences for liver physiology. IGF-1 is known to promote liver regeneration, inhibit apoptosis, and exert anti-inflammatory and anti-fibrotic effects. In T2DM, low IGF-1 levels compromise these protective mechanisms, contributing to the establishment of a pro-inflammatory and pro-fibrotic hepatic microenvironment. Over time, this environment facilitates the progression from non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and ultimately HCC.[32] Moreover, the metabolic disturbances in diabetes, including hyperinsulinemia, dyslipidemia, and oxidative stress, enhance the activation of mitogenic and anti-apoptotic pathways downstream of the IGF-1 receptor (IGF-1R), such as PI3K/AKT and MAPK, which play key roles in hepatocarcinogenesis.[33]

Patients with type 2 diabetes had a 2–4 times greater chance of HCC recurrence, irrespective of the reason for their current liver condition or the existence of cirrhosis.[34] Dyslipidaemia and hyperinsulinemia, two metabolic disorders associated with type 2 diabetes, have been related to cancer.[35]

Anomalous lipid and carbohydrate metabolism is a hallmark of diabetes. As the condition worsens, persistent hyperglycaemia and peripheral tissue's inadequate response to circulating insulin cause IR to develop.[36] In a 2013 study, regardless of age, sex, body mass index, waist-to-height ratio, education level, smoking, or alcohol consumption, T2DM was associated with an increased incidence of both HCC and bile tract cancer over an 8-year follow-up. The study included 8,588 T2DM patients who had no cancer or metastases at baseline and 363,426 non-diabetic individuals.

The pathophysiological processes that connect HCC with T2DM are intricate and multifaceted. The main causes include inflammation, hyperinsulinemia, and chronic hyperglycemia. Furthermore, a possible contributing factor to the higher risk of HCC in diabetic patients is low levels of IGF-1.[26,37]. Mechanistically, IGF-1 deficiency alters the expression of key apoptotic and cell cycle regulators (e.g., Bcl-2, Bax, cyclins), disrupts mitochondrial function, and impairs immune surveillance—making the liver more vulnerable to transformation under diabetic conditions.[38]

At the cellular level, oxidative stress and elevated pro-inflammatory cytokines—hallmarks of chronic inflammation in T2DM—drive genetic and epigenetic changes conducive to malignant transformation. Hyperglycemia can enhance the generation of reactive oxygen species (ROS), while low IGF-1 levels fail to counteract this oxidative stress, leading to DNA damage, impaired repair mechanisms, and hepatocyte senescence. These factors create a tumor-promoting niche in the liver, advancing fibrosis and carcinogenesis.[39]

In summary, the interplay between T2DM, low IGF-1 levels, and HCC is rooted in a shared pathophysiological framework involving chronic inflammation, metabolic dysregulation, and aberrant cell signaling. These insights underscore the importance of metabolic control in diabetes management, not only to prevent cardiovascular complications but also to reduce the risk of liver malignancy. Therapeutic strategies aimed at restoring IGF-1 homeostasis, mitigating insulin resistance, and controlling oxidative stress may offer promising avenues for HCC prevention in diabetic patients.[40]

**IGF Ligands, Receptors, and Signaling Pathways**

The IGF family comprises two ligands, IGF-1 (somatomedin C) and IGF-2 (somatomedin A), six high-affinity binding proteins, IGFBP-1 through IGFBP-6, and cell-surface receptors, IGF-1R and IGF-2R, as mentioned in Table 1 and shown in Figure 1. IGFs have a molecular weight of approximately 7.5 kDa, therefore being tiny ligands.[41,42] IGFs belong to a similar family of ligands as insulin, a dipeptide having a third disulfide bond inside the A chain and two disulfide links connecting the A and B chains. The C-terminal D-domain extension and the bridging C-domain set the two IGF ligands, IGF-1 and IGF-2, apart. Furthermore, their sequence homology with the insulin A and B chains is quite high (~45–52%). Like insulin, IGFs' three interior disulfides enable appropriate folding and allow for classical activities. The receptors that mediate the effects of IGF-1, IGF-2, and insulin include cell surface tyrosine kinases, type 1 IGFR, and insulin receptor.[43]

Peptide hormones IGF-1 and IGF-2, which resemble insulin structurally, are essential for growth and development. IGF-1 is a protein of 70 amino acids and a molecular weight of roughly 7649 Da. Its domains are like those of proinsulin. With a molecular weight of about 7500 Da, IGF-2 is significantly smaller and consists of 67 amino acids with similarly organized domains.[44] IGF-1 binds to the receptor tyrosine kinase IGF-1R, which is the main mechanism by which it affects postnatal growth and metabolic control. IGF-2 is a key player in fetal development. It primarily interacts with the mannose-6-phosphate receptor, or IGF-2R, and to a lesser extent with the IGF-1R.[45]

Yet another important regulator of IGF-1 and IGF-2 activity are IGFBPs, responsible for the bioavailability and distribution of the IGF ligands. N-terminal, central, and C-terminal regions that promote IGF binding are shared by the six high-affinity IGFBPs (IGFBP-1 to IGFBP-6). By enclosing IGFs, these proteins control the way IGFs interact with IGF receptors, either by increasing or decreasing their contact. To lengthen the half-life of IGF and control systemic IGF activity, IGFBP-3, the most prevalent IGFBP in circulation, combines with IGF and the acid-labile subunit to form a ternary complex.[46] Proteases can cleave IGFBPs, releasing free IGFs that bind to their receptors and affect cell development, metabolism, and communication. Furthermore, IGFBPs interact with cell surface receptors and the extracellular matrix to influence cell signaling, apoptosis, and migration in ways that are not dependent on IGF.[47] Changes in IGFBP levels are important in both physiological and pathological situations, since they are linked to diseases such as diabetes, cancer, and growth problems. Their

regulatory functions are being investigated for possible therapeutic applications in circumstances when IGF activity regulation is advantageous.[44]

Growth, development, and cellular metabolism are all significantly impacted by IGF-1R, a transmembrane receptor tyrosine kinase that is essential to the mediation of IGF-1 and IGF-2 signaling.[48] The structural makeup of IGF-1R consists of two alpha subunits and two beta subunits that combine to create a heterotetramer. The alpha subunits are found outside of cells and are important in binding to ligands, while the beta subunits are found across the membrane and include intracellular tyrosine kinase domains.[49] When an IGF-1 or IGF-2 receptor binds, certain tyrosine residues within its intracellular domains cause the receptor to undergo autophosphorylation, which creates docking sites for adaptor proteins like IRS-1 and Shc.[50] The MAPK/ERK and PI3K/AKT signaling pathways are triggered by this activation. By phosphorylating and activating important proteins like mTOR and preventing apoptosis through the transcription factors BAD and forkhead box transcription factors (FOXO), the PI3K/AKT pathway enhances cell survival, growth, and metabolism. Simultaneously, the MAPK/ERK pathway entails a kinase cascade comprising Raf, MEK, and ERK, which ultimately leads to the control of gene expression that oversees cell division, proliferation, and survival. IGF-1R signaling is intimately controlled by feedback mechanisms to preserve cellular homeostasis. Dysregulation of this signaling has been linked to several illnesses, including cancer, making it a prime candidate for therapeutic interventions.[48,51]

Comparably, IGF-2R is a multipurpose transmembrane protein that plays important roles in controlling cell division and has a unique structure. IGF-2R is a single-chain polypeptide with a single transmembrane region, a short cytoplasmic tail, and a sizable extracellular domain with fifteen repeating motifs. Instead of having intrinsic tyrosine kinase activity like IGF-1R does, IGF-2R mainly acts by binding IGF-2, which sequesters it from IGF-1R and decreases IGF-2-mediated signaling.[52] This binding helps regulate cellular growth and development by modulating the availability of IGF-2. Additionally, IGF-2R is involved in the trafficking of lysosomal enzymes by binding mannose-6-phosphate (M6P)-tagged proteins and directing them to lysosomes. The receptor's role in IGF-2 regulation and lysosomal enzyme trafficking is crucial for maintaining cellular homeostasis and proper metabolic functioning. IGF-2R's ability to clear IGF-2 from the extracellular environment helps prevent excessive cell proliferation, which is particularly important in preventing tumor growth and progression. Dysregulation of IGF-2R expression or function can lead to pathological conditions, including cancer and developmental disorders, underscoring its significance in both normal physiology and disease states.[53]

**IGF Signaling in HCC**

**IGF-1**

The anterior pituitary cells secrete GH, which regulates the secretion of IGF-1 and IGF-2. Studies have demonstrated that GH directly stimulates IGF transcription in hepatocytes, which are the main sources of IGF-1 and IGF-2 in mice and rats.[54,55]
Hepatocytes produce the precursor of IGF-1 first after receiving the GH signal, and then cleave it to produce the mature IGF-1 peptide.[16]

Liver cell regeneration and function can be negatively impacted by IGF-1 deficiency, as it plays a crucial role in regulating cell division, growth, and survival. Low levels of IGF-1 are associated with fibrosis and chronic inflammation, two conditions that are major causes of liver carcinogenesis.[40,56,57]. A pro-carcinogenic milieu is fostered by chronic inflammation, and cirrhosis—a key risk factor for HCC—can arise from fibrosis.[58,59] Furthermore, insulin resistance and hyperinsulinemia, which are prevalent in type 2 diabetes, are frequently associated with low IGF-1 levels, aggravating metabolic dysregulation and creating an environment conducive to the development of HCC.[34]

The growth and proliferation of healthy liver cells depend on IGF-1. Its absence inhibits these functions, lowering the activation of pathways including Ras/Raf/MAPK and PI3K/Akt, which are critical for survival and progression of the cell cycle. This deficiency promotes apoptosis and causes injured cells to proliferate in response, creating an environment favorable to cancer development.[60] Because low IGF-1 levels are correlated with higher levels of inflammatory cytokines, including TNF-□, IL-6, and IL-1□, they are also associated with chronic inflammation. In addition to promoting oxidative stress, cellular damage, and genetic abnormalities, chronic inflammation creates a microenvironment that aids in the development of cancer.[61,62]

**IGF-2**

The GH/IGF-1 axis is the main regulator of postnatal growth, even though IGF-2 appears to be important during fetal development.[63] Genetic changes such as gene amplification or loss of imprinting (LOI) frequently cause IGF-2 to become overexpressed in HCC, leading to biallelic expression. It is also possible to raise IGF-2 levels by hypomethylating the IGF-2 gene promoter.[64] Like IGF-1, IGF-2 interacts with IGF-1R and the IR isoform A to activate important signaling pathways necessary for increasing cell proliferation and preventing apoptosis, such as PI3K/AKT/mTOR and RAS/RAF/MEK/ERK.[65]

HCC cancer cells can create IGF-2, which acts in a paracrine way to affect the tumor microenvironment and in an autocrine loop to continuously promote the cancer cells' growth and survival. To further encourage tumor growth and metastasis, IGF-2 also interacts with other oncogenic pathways, including Wnt/β-catenin and HGF/c-Met.[66] IGF-2 supplies the blood supply required for tumor sustenance by promoting angiogenesis. These mechanisms highlight the possibility of employing gene silencing methods, small molecule inhibitors, or monoclonal antibodies to block the oncogenic signals by targeting the IGF-2/IGF-1R axis as a treatment approach in HCC.[67]

**IGF-1R Expression**

In HCC, IGF-1R is frequently found to be overexpressed. This overexpression enhances the cancer's aggressiveness by making tumor cells hypersensitive to growth-promoting signals. IGF-1R is a transmembrane tyrosine kinase receptor that plays a critical role in regulating cell growth, survival, and proliferation.[68] When its natural ligands—insulin-like growth factors IGF-1 or IGF-2—bind to the extracellular domain of IGF-1R, the receptor undergoes autophosphorylation on specific tyrosine residues within its intracellular domain. This autophosphorylation is a key step that activates the receptor’s intrinsic kinase activity and initiates a cascade of downstream signaling events.[69]

One of the major signaling pathways activated by IGF-1R is the PI3K/AKT pathway. Upon activation, IGF-1R recruits and phosphorylates insulin receptor substrates (IRS-1 and IRS-2).[70] These phosphorylated substrates then serve as docking platforms for phosphoinositide 3-kinase (PI3K), which becomes activated and converts PIP2 into PIP3. PIP3, in turn, recruits AKT to the cell membrane, where it becomes activated through phosphorylation. Activated AKT promotes tumor cell survival and proliferation by phosphorylating and inactivating several pro-apoptotic proteins, including BAD and caspase-9.[71]

Additionally, AKT activates mTOR, a central regulator of protein synthesis and cell growth, further supporting cancer cell expansion and metabolic adaptation.[72]

Simultaneously, IGF-1R activation attracts SOS and growth factor receptor-bound protein 2 (Grb2), which in turn activates MEK, ERK, Ras, and Raf, initiating the MAPK pathway. After translocating into the nucleus, ERK regulates the expression of genes involved in cell cycle progression and division, as shown in Figure 2.[71,73]

These proliferative and anti-apoptotic pathways are continuously stimulated by IGF-1R overexpression in HCC, leading to oncogenic processes such as enhanced cell survival, proliferation, angiogenesis, and resistance to apoptosis. This aberrant signaling has been associated in HCC patients with a reduced overall survival rate and larger tumors.[74]

The persistent stimulation of these oncogenic pathways contributes to several hallmarks of cancer in HCC, including unchecked cell division, resistance to apoptosis, angiogenesis, and metastatic potential.[75] Clinically, this aberrant signaling is associated with larger tumor sizes, more aggressive disease progression, and reduced overall survival in patients. These findings highlight the central role of IGF-1R signaling in liver cancer biology and underscore its potential as a therapeutic target.[67]

To address the pathological role of IGF-1R in HCC, multiple therapeutic strategies are under investigation. Tyrosine kinase inhibitors (TKIs) have been developed to block the receptor’s autophosphorylation and thereby prevent the activation of downstream signaling.[76] Additionally, monoclonal antibodies targeting the extracellular domain of IGF-1R can block ligand binding, effectively silencing the receptor’s activity. Another approach involves antisense oligonucleotides or small interfering RNA (siRNA) designed to reduce IGF-1R

expression by degrading its mRNA or inhibiting its translation. These therapeutic strategies aim to restore normal cell signaling dynamics, reduce tumor growth, and improve patient outcomes.[77]

Recent studies have also highlighted the intricate crosstalk between IGF-1R signaling and other key oncogenic pathways in HCC, further deepening our understanding of its tumor-promoting effects. One important interaction is with the Wnt/β-catenin pathway. IGF-1R signaling can enhance the stability and nuclear accumulation of β-catenin by inhibiting glycogen synthase kinase-3β (GSK-3β) through AKT activation. This inhibition prevents the degradation of β-catenin, allowing it to translocate into the nucleus and activate genes involved in proliferation, stemness, and dedifferentiation. The Wnt/β-catenin pathway is frequently dysregulated in HCC and plays a major role in early tumor initiation, contributing to cancer cell survival and drug resistance.[78]

Additionally, IGF-1R cooperates with the transforming growth factor-beta (TGF-β) signaling pathway, which has a dual role in liver cancer. While TGF-β initially suppresses tumor formation, it shifts toward a pro-tumorigenic role during later stages of HCC, promoting epithelial-mesenchymal transition (EMT), fibrosis, and metastasis. IGF-1R can amplify these effects by activating the PI3K/AKT and ERK pathways, which facilitate SMAD2/3 phosphorylation and further enhance TGF-β-mediated transcriptional activity that supports invasion and immune evasion.[79]

Furthermore, IGF-1R signaling intersects with the JAK/STAT pathway, particularly STAT3, which is known to drive inflammation-associated hepatocarcinogenesis. Although IGF-1R does not directly phosphorylate STAT3, it induces upstream signaling via PI3K/AKT and MAPK that results in sustained STAT3 activation. This activation promotes transcription of genes involved in survival (e.g., Bcl-2, Bcl-xL), angiogenesis (e.g., VEGF), and cell proliferation (e.g., Cyclin D1). In the context of chronic liver inflammation or cirrhosis, this synergy between IGF-1R and STAT3 signaling creates a favorable environment for tumor growth and progression.[49]

Together, these inter-pathway interactions position IGF-1R as a critical hub within a broader oncogenic network in HCC. Targeting IGF-1R alone may not be sufficient; therefore, current research is also exploring combination therapies that simultaneously inhibit IGF-1R and its interacting pathways—such as Wnt/β-catenin or STAT3—to overcome resistance and improve clinical outcomes.[77]

**IGFBPs**

The bioavailability and activity of IGFs, especially IGF-1 and IGF-2, which are essential for cellular growth and survival, are significantly regulated by IGFBPs.[79] IGFBPs play a major role in regulating the impact of IGFs on the formation and progression of HCC tumors. IGFBP-1 through IGFBP-6 are the six primary IGFBPs, and they all play different functions in HCC. High-affinity binding of IGFs by these proteins regulates their interaction with IGF-1R and, therefore, their biological activity.[80]

The most widely distributed IGFBP, IGFBP-3, can impede IGF-mediated signaling by isolating IGFs from IGF-1R.[49] This prevents the activation of downstream proliferative and anti-apoptotic pathways, including the MAPK and PI3K/AKT pathways. In contrast, IGFBP-3 and other IGFBPs can act without the help of IGF. IGFBP-3, for example, can internalize and translocate to the nucleus, where it affects the transcription of genes related to apoptosis and cell cycle regulation. Through the regulation of p53 and other cell death mechanisms, it can cause apoptosis.[42]

Changes in IGFBP expression levels are frequently observed in the setting of HCC and have the potential to impact tumor behavior. For instance, decreased IGFBP-3 expression is frequently seen in HCC, which is associated with elevated IGF-1R signaling and tumor expansion. However, depending on how they interact with other cellular components and IGFs, IGFBP-1, IGFBP-2, and IGFBP-5 can have a variety of effects—sometimes limiting tumor formation and other times increasing it.[85] Depending on the tumor microenvironment and post-translational modifications, these IGFBPs can either inhibit or promote tumorigenesis. For instance, IGFBP-2 has been implicated in promoting epithelial-to-mesenchymal transition (EMT), migration, and metastasis in various cancers, including HCC, potentially through integrin signaling and interaction with the extracellular matrix.[81]

This dual nature of IGFBPs—both IGF-dependent and IGF-independent—makes them versatile regulators of tumor biology. By binding IGFs, they control proliferative and anti-apoptotic signaling through IGF-1R. Simultaneously, they engage in IGF-independent mechanisms to regulate apoptosis, differentiation, migration, and even angiogenesis through pathways involving TGF-, integrins, nuclear hormone receptors, and epigenetic modulation. These non-canonical roles are particularly important in the context of metastasis and therapy resistance, making IGFBPs both biomarkers and potential therapeutic targets.[65]

Understanding the distinct molecular mechanisms and context-dependent behavior of individual IGFBPs in HCC could provide valuable insights into novel therapeutic strategies. Targeting their IGF-independent pathways may offer a promising approach for controlling tumor progression and overcoming resistance to conventional IGF-targeted therapies.

**IGF-related biomarkers for patient stratification and prognosis**

Recent studies have shed light on the prognostic and predictive significance of insulin-like growth factor (IGF)-related biomarkers in hepatocellular carcinoma (HCC), opening new avenues for personalized treatment strategies.[82] Components of the IGF axis—including IGF-1, IGF-2, IGF-1R, and IGF-binding proteins (IGFBPs)—play not only a pathophysiological role in HCC but also hold promise as clinical indicators for patient stratification and outcome prediction.[83] Among them, serum IGF-1 levels have received particular attention. Several large cohort studies have demonstrated that reduced circulating IGF-1 levels are strongly associated with poor liver function, advanced tumor stage, and decreased overall survival in HCC patients.

Because IGF-1 is primarily synthesized in the liver, its levels also serve as a surrogate marker for hepatic reserve and are currently being evaluated for use in pre-treatment risk scoring models, including modified Child-Pugh and HCC staging systems.[84]

In contrast, elevated IGF-2 levels, often caused by loss of imprinting or promoter hypomethylation, are commonly found in early HCC and have been implicated in tumor initiation. IGF-2 overexpression may therefore serve as an early detection biomarker, especially in patients with cirrhosis or non-alcoholic steatohepatitis (NASH), where surveillance is crucial.[85] Similarly, IGF-1R overexpression has been correlated with tumor aggressiveness, poor differentiation, vascular invasion, and resistance to targeted therapies like sorafenib, making it a candidate predictive biomarker for treatment response. Moreover, IGFBPs, particularly IGFBP-3 and IGFBP-7, have shown dual roles depending on the context—either inhibiting IGF signaling by sequestering ligands or exerting IGF-independent tumor-suppressive functions, such as promoting apoptosis and modulating the tumor microenvironment. Decreased expression of IGFBP-3 has been linked with enhanced proliferation and poorer prognosis in HCC patients.[16]

Collectively, these findings underscore the potential utility of IGF-axis biomarkers in improving clinical decision-making. By integrating these biomarkers into diagnostic and therapeutic workflows, clinicians may be better equipped to identify high-risk patients, predict treatment efficacy, and personalize therapeutic strategies for improved outcomes in HCC management.

**IGF signaling as a potential target for the treatment of HCC**

Since the IGF signaling system is essential for tumor growth, survival, and resistance to apoptosis, targeting it as a therapeutic approach appears to be a promising approach for treating HCC. IGF-1, IGF-2, and IGF-1R interact with one another through the IGF/IGFR axis. IGF-1R undergoes autophosphorylation on tyrosine residues upon binding of IGF-1 or IGF-2, activating multiple downstream signaling pathways, including the PI3K/AKT and MAPK pathways.[16,86]

The PI3K/AKT pathway is initiated by IGF-1R activation, which then attracts and activates PI3K, which phosphorylates PIP3. AKT is brought to the plasma membrane by PIP3, which functions as a second messenger and phosphorylates it there. By phosphorylating and blocking pro-apoptotic proteins like BAD and caspase-9 and activating mTOR, a crucial regulator of cell growth and protein synthesis, activated AKT promotes cell survival and proliferation.[71,87].

Son of Sevenless (SOS) and growth factor receptor-bound protein 2 (Grb2) are recruited by IGF-1R activation in the MAPK pathway, and this helps to activate Ras. Following Ras's activation of the Raf-MEK-ERK kinase cascade, ERK is phosphorylated and activated. Once in the nucleus, ERK translocates and controls the expression of genes related to cell cycle progression and division.[71,87]

In HCC, IGF-1R is usually overexpressed and hyperactivated, contributing to the aggressiveness of the malignancy and its poor prognosis. Tumor growth, survival, angiogenesis, and metastasis are all facilitated by this overactivation, which causes proliferative and anti-apoptotic signaling pathways to be continuously stimulated.[67]

Several tactics are used to target the IGF signaling pathway in HCC to interfere with these carcinogenic signals. Monoclonal antibodies against IGF-1R can be used, which stop receptor activation. TKIs can prevent IGF-1R from autophosphorylation, which stops downstream signaling. By encouraging the mRNA of IGF-1R to degrade, antisense oligonucleotides can reduce the production of the protein.[88-90]

These targeted treatments seek to impede the growth and progression of tumors by attenuating the abnormal signaling caused by the IGF axis.[90] These medicines have the potential to significantly improve clinical results by precisely targeting the mechanisms underlying the formation and progression of HCC, offering a more accurate and efficient means of treating this difficult-to-treat malignancy. There is still hope for better management and therapy of HCC thanks to continuous research and development of various therapeutic approaches, which may also increase patient quality of life and survival rates.[89]

Numerous medications aimed at this route vary in their clinical development stages. Monoclonal antibodies that are specially made to bind to the IGF-1R include figitumumab (CP-751,871), cixutumumab (IMC-A12), and dalotuzumab (MK-0646). These antibodies inhibit receptor activation and subsequent downstream signaling through pathways important for cell growth and survival, such as PI3K/AKT/mTOR and Ras/Raf/MEK/ERK.[91,92]

Linsitinib (OSI-906) and BMS-754807 are two TKIs that specifically target the intracellular kinase domain of IGF-1R. For example, linsitinib suppresses both the IR and IGF-1R's kinase activity, inhibiting their autophosphorylation and subsequent signaling pathway activation. In HCC, where compensatory mechanisms can activate IR in the absence of IGF-1R signaling, this dual inhibition is especially advantageous.[93]

A different approach is provided by small molecule inhibitors such as NVP-AEW541 and picropodophyllin (PPP), which bind to the IGF-1R's ATP-binding site to stop its activation. By attaching to another location on the receptor, PPP, a non-ATP-competitive inhibitor, inhibits the receptor's function without going up against ATP directly. These inhibitors diminish IGF-1R-mediated signaling, which in turn causes angiogenesis, apoptosis, and decreased tumor cell proliferation.[92,94]

These IGF/IGFR-related medications not only directly stop tumor growth but also negatively impact the tumor microenvironment by lowering angiogenesis and boosting the body's defenses against cancerous cells. Clinical trials have brought to light issues such as possible toxicities and medication resistance, which might result from compensatory processes or mutations.[101] As a result, current research is concentrated on improving existing medications, either by creating next-generation inhibitors with increased specificity and fewer side effects or by combining treatments with other targeted therapies.[95]

Emerging data suggest that resistance to IGF-targeted therapies is frequently mediated through compensatory activation of parallel signaling cascades, including the insulin receptor (IR), epidermal growth factor receptor (EGFR), and MET pathways. Even when IGF-1R is successfully inhibited, these alternative receptors can maintain activation of downstream effectors such as PI3K/AKT or MAPK, sustaining tumor proliferation and survival. Additionally, feedback loops within the mTOR pathway and upregulation of insulin receptor substrate (IRS) proteins may re-stimulate oncogenic signaling, further complicating treatment efficacy.[91]

To address these limitations, combination therapy is gaining attention as a rational strategy. Co-targeting IGF-1R along with other pathways—such as mTOR inhibitors (e.g., everolimus), EGFR inhibitors, or immune checkpoint inhibitors like anti-PD-1/PD-L1—can help circumvent resistance and provide synergistic anti-tumor effects.[96] These combinations not only suppress tumor-intrinsic signaling but also modulate the tumor microenvironment and immune evasion mechanisms, offering a more holistic therapeutic approach in HCC.[97]

Furthermore, personalized medicine strategies are being explored to identify biomarkers that predict response to IGF-targeted therapy. Stratifying patients based on IGF-1R expression, gene mutations, or activation of compensatory pathways could optimize treatment selection and improve outcomes. Continued preclinical and clinical efforts are essential to refine these strategies, develop fewer toxic agents, and ultimately translate IGF pathway inhibition into durable responses in HCC management.[98]

**Agents in Clinical Trials for HCC**

Only a few medications are available for the clinical treatment of HCC, even though it is one of the deadliest health problems in the world. However, rigorous basic research and multiple clinical trials in HCC have led to significant advances in the development of new medications in recent years. There are currently over a thousand active clinical trials pertaining to HCC, indicating a thriving environment in the field of HCC medication research.[99,100] Table 2 mentions the pharmacological interventions in clinical trials that target IGF-1R for the treatment of HCC.

**Conclusion**

This review includes evidence for dysregulated IGF/IGF-1R signaling in HCC. Many factors, such as hepatitis virus infection, diabetes, and imbalance of IGF-1R modulators, can start carcinogenesis in the pathophysiology of HCC. In conclusion, there is an increase in IGF-1R expression in HCC tissues, which is influenced by a few clinical variables, along with an increase in IGF-2 levels and a decrease in IGF-1 levels. When combined, IGF-1R has the potential to be a useful prognostic biomarker for HCC. While some IGF-1R-targeting drug trials have demonstrated limited efficacy or safety concerns, more research into this combination of anti-cancer medications and agents that block IGF/IGF-1R signaling is hoped to result in a successful treatment for HCC.

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**Table 1.** IGF Family- ligands (IGF-1 and IGF-2), receptors (IGF-1R and IGF-2R) and binding proteins (IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-3, IGFBP-4, IGFBP-5 and IGFBP-6)

| S. No. | Components | Role |
|---|---|---|
| 1. | Ligands – IGF-1, IGF-2 | IGF-1 promotes postnatal growth, bone development, and tissue repair, while IGF-2 is vital for prenatal development. Both ligands enhance glucose uptake, influence insulin sensitivity, and play roles in lipid metabolism. Additionally, IGF-1 supports neuroprotection and muscle regeneration. |
| 2. | Receptors – IGF-1R, IGF-2R | IGF-1R and IGF-2R, mediate the actions of IGF ligands. IGF-2R is less directly involved in signaling compared to IGF-1R |
| 3. | Binding Proteins – IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, IGFBP-6 | IGFBPs play essential roles in regulating the bioavailability and activity of IGF ligands. They bind to IGF-1 and IGF-2, extending their half-life, controlling their distribution in tissues, and modulating their interaction with cell surface receptors. |

**Table 2.** Pharmacological interventions in clinical trials that target IGF-1R for treatment of HCC

| Compound | Targets | Phase | ID | Reference |
|---|---|---|---|---|
| Ganitumab | Monoclonal anitibody targeting IGF-1R | Phase II | NCT01204177 | [101] |
| OSI-906 (Linsitinib) | Tyrosine kinase inhibitor targeting IGF-1R | Phase II | NCT01100931 | [102] |
| CP-751871 (Figitumumab) | Monoclonal antibody targeting IGF-1R | Phase II | NCT01013300 | [103] |

| | | | | |
|---|---|---|---|---|
| MK-0646 (Dalotuzumab) | IGF-1R inhibitor | Phase I/ II | NCT01051080 | [104] |
| XL288 | Multi-kinase inhibitor targeting IGF-1R | Phase I | NCT00788219 | [105] |
| Dalotuzumab (MK-0646) and MK-2206 | IGF-1R inhibitor and akt inhibitor | Phase II/III | NCT01483027 | [104] |
| R1507 | Monoclonal antibody targeting IGF-1R | Phase II | NCT00596830 | [106] |
| Ficlatuzumab (AV-299) | Anti-HGF antibody that may indirectly affect IGF signaling | Phase I | NCT01631717 | [107] |



**Legends**

**Figure 1**: IGF Family. The IGF family consists of ligands IGF-1 and IGF-2, IGFBPs, and receptors IGF-1R and IGF-2R. The IGFs are bound by binding proteins in the circulation and upon release binds to the receptor.

**Figure 2:** IGF-1 signaling. The ligand IGF-1 binds to the IGF-1R receptor which causes conformational changes in the receptor and autophosphorylation of the cytoplasmic part of the receptors. By a series of phosphorylation reactions, the signal is transduced into the nucleus. This involves the participation of many cytoplasmic proteins such as Grb2, Ras, Raf, MEK, and ERK and others such as IRS-1, PI3K, PDK1 and AKT.

**Figure 1**

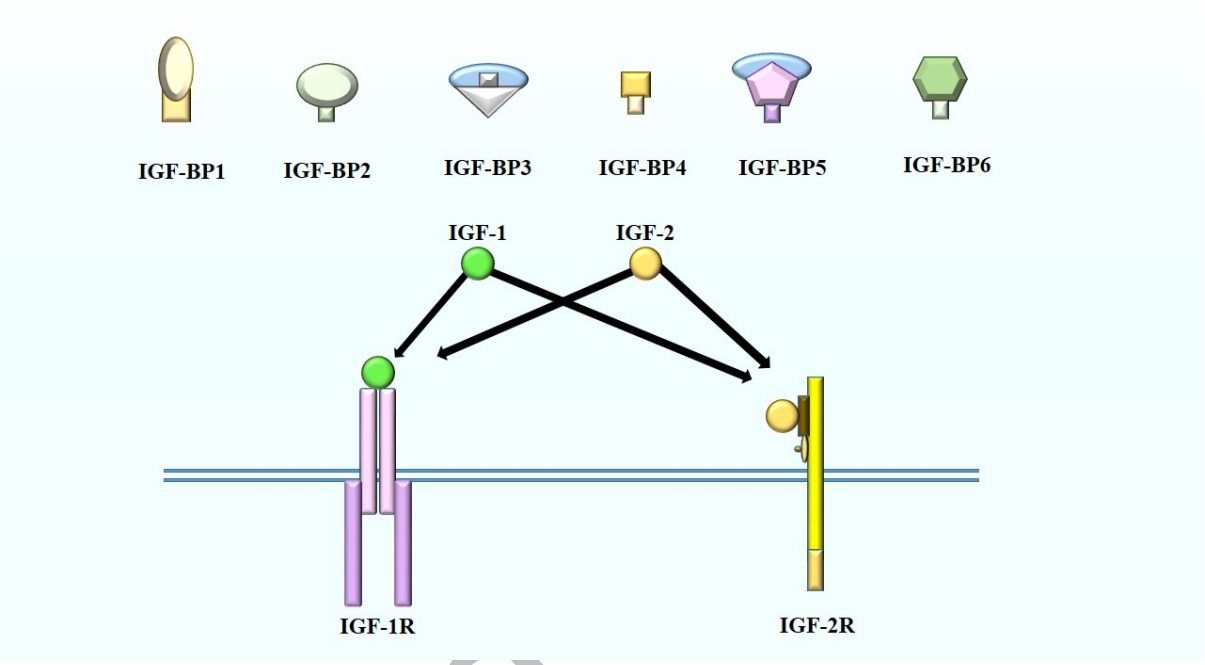
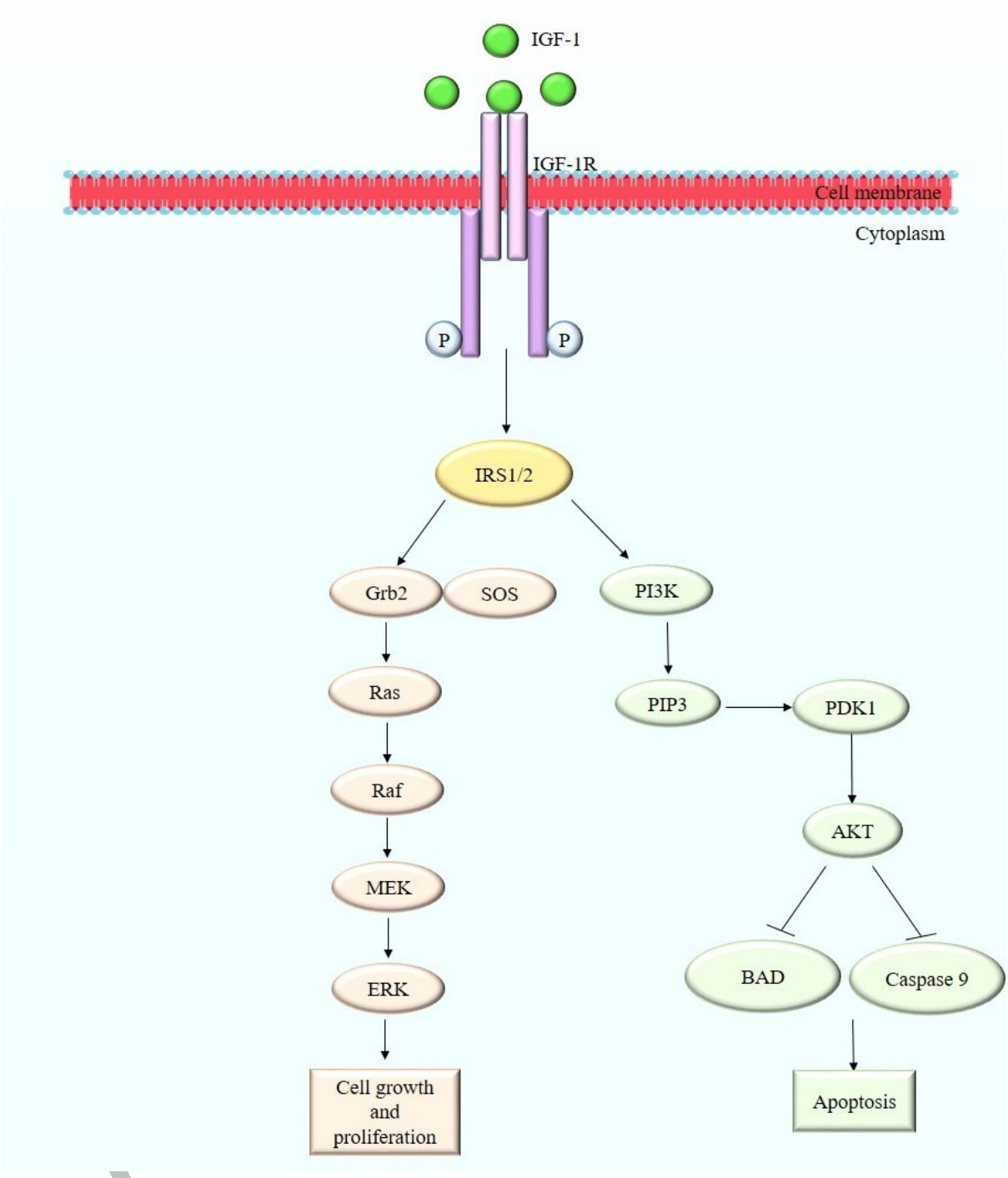





**Figure 2**


IGF-1
IGF-1R
Cell membrane
Cytoplasm
P
P
IRS1/2
Grb2
SOS
PI3K
Ras
PIP3
PDK1
Raf
AKT
MEK
BAD
Caspase 9
ERK
Cell growth and proliferation
Apoptosis