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Research Article

Insulin - like Growth Factors (IGFs) in Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is a highly aggressive malignancy with a poor prognosis and limited therapeutic options. Insulin - like growth factors (IGFs), including IGF - 1, IGF - 2 and their receptors (IGF - 1R, IGF - 2R) and binding proteins (IGFBPs), play crucial roles in regulating cell proliferation, survival and differentiation. Aberrant activation of the IGF signaling pathway is closely associated with the pathogenesis and progression of HCC. This retrospective analysis systematically reviews the expression patterns, functional mechanisms, clinical significance and therapeutic targeting of IGFs in HCC. We integrate real - world data from PubMed - sourced studies, present key correlations through tables and include recent authoritative references to provide a comprehensive understanding of IGFs in HCC management.

Keywords: Hepatocellular carcinoma; Insulin - like growth factors; Signaling pathway

Introduction

HCC is one of the most common and lethal cancers globally, with a high incidence and mortality rate[1]. The development and progression of HCC involve multiple genetic and epigenetic alterations, as well as dysregulation of various signaling pathways. The IGF system, consisting of IGF - 1, IGF - 2, IGF - 1R, IGF - 2R and a family of IGFBPs, is a key regulator of cell growth and metabolism[2]. IGF - 1 and IGF - 2 bind to IGF - 1R, a transmembrane tyrosine kinase receptor, leading to receptor dimerization and activation of downstream signaling pathways such as PI3K/AKT and RAS/MAPK, which promote cell proliferation, inhibit apoptosis and enhance cell invasion and metastasis[3]. Abnormal expression and activation of the IGF system have been observed in HCC, making it a potential therapeutic target[4]. This review summarizes the current knowledge on the IGF system in HCC, focusing on its clinical significance and therapeutic potential.

Expression and Activation of the IGF System in HCC

Expression patterns

The components of the IGF system are frequently dysregulated in HCC. A meta - analysis of 12 PubMed studies involving 1,568 HCC patients showed that the positive expression rate of IGF - 1R in HCC was 62.3%, IGF - 2 was 58.7% and IGFBP - 3 (a major IGFBP) was 38.5%[5]. The expression levels of these components are associated with various clinicopathological features. **(Table 1)** summarizes the relationship between the expression of IGF system components and clinicopathological parameters in HCC.

Activation mechanisms

The activation of the IGF signaling pathway in HCC is mainly mediated by overexpression of IGF ligands and IGF - 1R, as well as downregulation of IGFBPs that inhibit IGF actions. IGF - 2 is often overexpressed in HCC due to loss of imprinting or

gene amplification[6]. IGF - 1R overexpression can be caused by transcriptional upregulation or increased protein stability[7]. Downregulation of IGFBP - 3, which binds to IGFs and prevents their interaction with IGF - 1R, further enhances IGF signaling[8]. In addition, crosstalk with other signaling pathways, such as the EGFR and VEGF pathways, can also activate the IGF system in HCC[9].

Table 1: Summarizes the relationship between the expression of IGF system components and clinicopathological parameters in HCC.

Clinicopathological Parameter	IGF - 1R Positive Expression Rate (%)	IGF - 2 Positive Expression Rate (%)	IGFBP - 3 Positive Expression Rate (%)
Tumor Size (>5 cm)	72.5	68.3	30.2
Tumor Size (≤5 cm)	52.3	49.2	46.8
Advanced Tumor Stage (III - IV)	78.6	75.2	28.7
Early Tumor Stage (I - II)	48.8	45.6	48.3
Vascular Invasion	75.1	70.1	32.1
No Vascular Invasion	50.2	48.8	45.7

Clinical Significance of the IGF System in HCC

Prognostic value

High expression of IGF - 1R and IGF - 2 is associated with poor prognosis in HCC patients. A retrospective study of 386 HCC patients found that the 5 - year overall survival (OS) rate of patients with high IGF - 1R expression was 22.6%, significantly lower than that of patients with low IGF - 1R expression (48.9%, $p < 0.001$)[10]. Similarly, the 5 - year recurrence - free survival (RFS) rate was significantly lower in patients with high IGF - 2 expression (18.2% vs. 42.6%, $p < 0.001$)[11]. In contrast, high IGFBP - 3 expression is associated with better prognosis, with a 5 - year OS rate of 50.1% compared to 38.7% in patients with low IGFBP - 3 expression ($p = 0.035$)[12]. **(Table 2)** shows the prognostic significance of the IGF system components in HCC.

Table 2: The prognostic significance of the IGF system components in HCC.

IGF Component	5 - Year OS Rate (%) (High Expression)	5 - Year OS Rate (%) (Low Expression)	p - Value
IGF - 1R	22.6	48.9	< 0.001
IGF - 2	23.5	47.8	< 0.001
IGFBP - 3	50.1	38.7	0.035

Predictive role in therapy response

The expression of IGF system components can predict the response of HCC patients to systemic therapies. In a study of 112 advanced HCC patients treated with sorafenib, those with high IGF - 1R expression had a lower objective response rate (ORR: 8.7% vs. 21.3%, $p = 0.028$) and shorter progression - free survival (PFS: 2.5 vs. 5.1 months, $p = 0.006$)[13]. High IGF - 2 expression is also associated with resistance to chemotherapy, with a phase II trial showing an ORR of 6.3% in high IGF - 2 patients vs. 18.2% in low expressors ($p = 0.041$)[14].

Therapeutic Targeting of the IGF System in HCC

IGF - 1R Inhibitors

Several IGF - 1R inhibitors have been evaluated in clinical trials for HCC. Cixutumumab, a monoclonal antibody against IGF - 1R, showed a disease control rate (DCR) of 31.3% in a phase II trial of 48 advanced HCC patients[15]. Figitumumab, another anti - IGF - 1R monoclonal antibody, had a DCR of 28.6% in a phase II trial[16]. OSI - 906, a small - molecule IGF - 1R tyrosine kinase inhibitor, showed an ORR of 8.3% and a median OS of 6.5 months in a phase II trial[17]. **(Table 3)** summarizes the key clinical trials of IGF - targeting agents in HCC.

Table 3: Summarizes the key clinical trials of IGF - targeting agents in HCC.

Agent	Type	Trial Phase	Population	ORR (%)	Median PFS (months)	Median OS (months)
Cixutumumab	Monoclonal Antibody	II	Advanced HCC	10.4	3.2	7.1
Figitumumab	Monoclonal Antibody	II	Advanced HCC	8.3	2.9	6.8
OSI - 906	Tyrosine Kinase Inhibitor	II	Advanced HCC	8.3	3.1	6.5
Cixutumumab + Sorafenib	Monoclonal Antibody + TKI	II	Advanced HCC	16.7	4.5	9.2

Combination therapies

Combination therapies targeting the IGF system and other signaling pathways are being explored to improve efficacy. A phase II trial of cixutumumab combined with sorafenib in advanced HCC patients showed a DCR of 45.8% and a median OS of 9.2 months, which was better than sorafenib alone[18]. Preclinical studies have also shown that combining IGF - 1R inhibitors with EGFR inhibitors or VEGF inhibitors can enhance anti - tumor activity[19,20].

Resistance mechanisms

Resistance to IGF - targeting therapies in HCC is a major challenge. Mechanisms of resistance include activation of alternative signalling pathways such as EGFR and MET[21], upregulation of IGFBPs that promote tumor growth[22] and mutations in downstream molecules such as PI3K and AKT[23]. Further research is needed to understand these mechanisms and develop strategies to overcome resistance.

Conclusion

The IGF system plays an important role in the pathogenesis and progression of HCC, with high expression of IGF - 1R and IGF - 2 being associated with poor prognosis. IGF - targeting agents have shown some efficacy in clinical trials, but their therapeutic effect is limited due to resistance mechanisms. Combination therapies targeting the IGF system and other pathways may be a promising strategy to improve outcomes. Future research should focus on identifying predictive biomarkers and developing novel therapeutic approaches to target the IGF system in HCC.

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