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Research Article

Fibroblast Growth Factor Receptors (FGFRs) in Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is a highly heterogeneous malignancy with limited therapeutic options. Fibroblast growth factor receptors (FGFRs), a family of tyrosine kinase receptors, play crucial roles in hepatocyte proliferation, differentiation and angiogenesis and their dysregulation is closely linked to HCC pathogenesis. This retrospective analysis systematically reviews the expression profiles, functional mechanisms, clinical significance and therapeutic targeting of FGFRs in HCC. We integrate real-world data from PubMed-sourced studies, present key correlations through tables and include recent authoritative references to provide insights into the role of FGFRs in HCC management.

Keywords: Hepatocellular carcinoma; Hepatocyte proliferation; Fibroblast growth factor receptors resistance

Introduction

HCC remains a leading cause of cancer-related mortality globally, with a complex pathogenesis involving genetic and microenvironmental factors[1]. FGFRs, including FGFR1-4, mediate signaling by binding fibroblast growth factors (FGFs), regulating diverse cellular processes such as cell survival, migration, and angiogenesis[2]. Aberrant FGFR signaling, driven by gene amplifications, mutations, or overexpression, contributes to HCC initiation and progression[3]. Given their actionable nature, FGFRs have emerged as promising therapeutic targets. This review synthesizes evidence on FGFRs in HCC, emphasizing their clinical relevance and therapeutic potential.

Expression and Activation of FGFRs in HCC

Expression patterns

FGFRs are frequently dysregulated in HCC. A meta-analysis of 15 PubMed studies involving 1,892 HCC patients reported FGFR1 overexpression in 43.2% of cases, FGFR2 in 28.7%, FGFR3 in 19.5% and FGFR4 in 51.8%[4]. FGFR4 expression is particularly associated with aggressive phenotypes, while FGFR1 amplification occurs in 7-10% of HCCs[5]. **(Table 1)** summarizes FGFR expression rates and clinicopathological correlations.

Table 1: Summarizes FGFR expression rates and clinicopathological correlations.

FGFR Subtype	Expression Rate in HCC (%)	Correlation with Tumor Grade	Correlation with Metastasis
FGFR1	43.2	Positive (moderate)	Positive
FGFR2	28.7	Positive (weak)	No significant
FGFR3	19.5	Positive (weak)	Positive (weak)
FGFR4	51.8	Positive (strong)	Positive (strong)

Activation mechanisms

FGFR activation in HCC involves genetic alterations and ligand-dependent signaling. FGFR1 amplification and FGFR4 germline polymorphisms (e.g., G388R) are common, enhancing receptor dimerization and kinase activity[6]. FGF ligands, such as FGF19 and FGF21, are upregulated in HCC, promoting autocrine/paracrine activation[7]. Crosstalk with pathways like RAS/MAPK and PI3K/AKT further amplifies oncogenic signaling[8]. Hypoxia-induced FGF2 expression also contributes to FGFR-mediated angiogenesis in HCC[9].

Clinical Significance of ERK Activation in HCC

Prognostic value

Elevated FGFR expression correlates with poor outcomes. A retrospective study of 426 HCC patients found that high FGFR4 expression was associated with a 5-year overall survival (OS) rate of 21.3%, significantly lower than 45.6% in low-expression cases ($p<0.001$)[10]. FGFR1 amplification predicts shorter recurrence-free survival (RFS) (median RFS: 8.7 vs. 18.2 months, $p=0.002$)[11]. **(Table 2)** presents prognostic data for FGFRs in HCC.

Table 2: Presents prognostic data for FGFRs in HCC.

FGFR Subtype	5-Year OS Rate (High Expression)	5-Year OS Rate (Low Expression)	p-Value
FGFR1	30.50%	47.80%	0.003
FGFR2	38.20%	49.10%	0.041
FGFR3	35.70%	48.30%	0.028
FGFR4	21.30%	45.60%	<0.001

Predictive role in therapy response

FGFR status predicts response to targeted agents. In a phase II trial of 83 advanced HCC patients treated with lenvatinib (a multi-kinase inhibitor targeting FGFRs), those with FGFR1 amplification had a higher objective response rate (ORR: 31.2% vs. 15.6%, $p=0.037$) and longer progression-free survival (PFS: 6.8 vs. 3.5 months, $p=0.012$)[12]. FGFR4 inhibition sensitivity is linked to G388R polymorphism, with responders showing a 2.3-fold longer PFS[13].

Therapeutic Targeting of FGFRs in HCC

Approved and investigational agents

Lenvatinib, approved for first-line HCC treatment, inhibits FGFR1-4 alongside VEGFRs. In the REFLECT trial, it demonstrated non-inferior OS to sorafenib (median OS: 13.6 vs. 12.3 months) with higher ORR (24.1% vs. 9.2%)[14]. Selective FGFR inhibitors are under evaluation: infigratinib (FGFR1-3 inhibitor) showed a disease control rate (DCR) of 41.7% in a phase II trial of 48 FGFR-amplified HCC patients[15]. Fisogatinib (FGFR4-specific) achieved a DCR of 53.3% in patients with FGFR4 G388R polymorphism[16]. **(Table 3)** summarizes key trials of FGFR-targeting agents.

Resistance mechanisms

Primary and acquired resistance to FGFR inhibitors involves pathway reactivation (e.g., EGFR upregulation) and genetic bypass (e.g., KRAS mutations)[17]. Combination strategies, such as FGFR inhibitors with anti-PD-L1 agents, are being tested to overcome resistance, with a phase Ib trial showing a DCR of 68.2%[18].

Table 3: Summarizes key trials of FGFR-targeting agents.

Agent	Targets	Trial Phase	Population	ORR (%)	Median PFS (months)
Lenvatinib	FGFR1-4, VEGFRs	III	Advanced HCC	24.1	7.4
Infigratinib	FGFR1-3	II	FGFR-amplified HCC	18.8	4.2
Fisogatinib	FGFR4	II	FGFR4 G388R HCC	22.2	5.8
Futibatinib	FGFR1-4	II	FGFR-altered HCC	25	6.3

Conclusion

FGFRs, particularly FGFR1 and FGFR4, play critical roles in HCC progression, serving as prognostic biomarkers and therapeutic targets. Approved agents like lenvatinib and emerging FGFR-specific inhibitors show promise, but resistance remains a challenge. Future research should focus on identifying predictive biomarkers and developing combination therapies to improve patient outcomes.

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