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MOLECULAR MECHANISMS OF FIBROBLAST GROWTH FACTOR IN HEPATO-CELLULAR CARCINOMA

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ABSTRACT: Hepatocellular carcinoma (HCC) is a widespread and lethal cancer type that affects people worldwide. Growth factor signalling pathways are critical in non-alcoholic fatty acid liver disease (NAFLD) and HCC as they activate a cascade of events that disrupt normal liver function. Therefore, these pathways offer a promising therapeutic strategy for NAFLD associated HCC. Several studies have found that fibroblast growth factor (FGF) levels are increased in patients with HCC. The FGF family comprises 22 proteins that can be classified as paracrine, intracrine, or endocrine factors. Most FGFs transmit signals through transmembrane tyrosine kinase FGF receptors. The main FGF in HCC progression includes: FGF8, FGF19 and FGF21, holds potential for HCC treatment. The FGF inhibitors: Lenvatinib, H3B-6527, BLU9931, CXF-009 and FGF401 have shown promising effects, yet our knowledge against HCC is limited. This review summarizes recent research in types of FGF, FGF signalling and FGF inhibitors as therapeutic targets in HCC.

INTRODUCTION: Liver cancer is fourth leading cause of cancer-related deaths worldwide, attributing to significant global health concern. East Asia and Africa have the highest incidence and mortality rates for hepatocellular carcinoma (HCC) [1]. Europe and the United States have also seen an increase in HCC rates. In the US, HCC is the fastest-growing cause of cancer-related death and is projected to become the third leading cause by 2030 if current trends continue. Men have been found to be at greater risk of developing liver cancer than women [2]. The global male-to-female HCC incidence ratio is 8:1 [3].

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Traditionally HCC is link with chronic hepatitis viral infection however, it has been observed that obesity, sedentary lifestyle, and metabolic syndrome is equally contributing to causing a condition like HCC. NAFLD has emerged as a major cause of liver disease, progressing from hepatic steatosis to non-alcoholic steatohepatitis (NASH) characterized by liver cell damage and inflammation. The increasing incidence of NAFLD has led to a significant rise in NASH [4].

Studies indicate that NASH can lead to advanced fibrosis and cirrhosis, increasing the risk of HCC. Liver disease is the third leading cause of death among NAFLD/NASH patients, with HCC being the primary cause of death. Growth factors are essential molecules that regulate cell growth, differentiation, and survival. Dysregulation of growth factors and their receptors have been implicated in the development and progression of

HCC [5]. For instance, hepatocyte growth factor (HGF) and its receptor, MET, have been shown to promote HCC growth and invasion [6]. Similarly, vascular endothelial growth factor (VEGF) and its receptor, VEGFR, have been linked to tumour angiogenesis, a process that provides tumours with the nutrients and oxygen necessary for their growth and survival. Other growth factors such as insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF), and transforming growth factor-beta (TGF-β) have also been implicated in the development and progression of HCC. Through research and clinical trials, it has been found that fibroblast growth factor (FGF) plays an important role in the pathology of HCC also the FGF is over expressed in HCC [7]. This article aims to provide an overview of the role of FGF in the development of HCC, as well as explore the potential clinical applications of targeting FGF as a novel therapeutic option.

Hepatocellular Carcinoma Risk Factors and Pathogenesis: Hepatocellular carcinoma (HCC) is commonly associated with chronic infections of the hepatitis B virus and hepatitis C virus, with the prevalence of HCC reflecting the occurrence of these infections. Additional notable risk factors for HCC include alcoholic cirrhosis, non-alcoholic steatohepatitis (NASH) [8], consumption of aflatoxin-contaminated food and exposure to various chemical carcinogens. Alcohol abuse plays a significant role in the development of HCC and has been found to have a synergistic effect when combined with other risk factors like obesity and viral hepatitis [9].

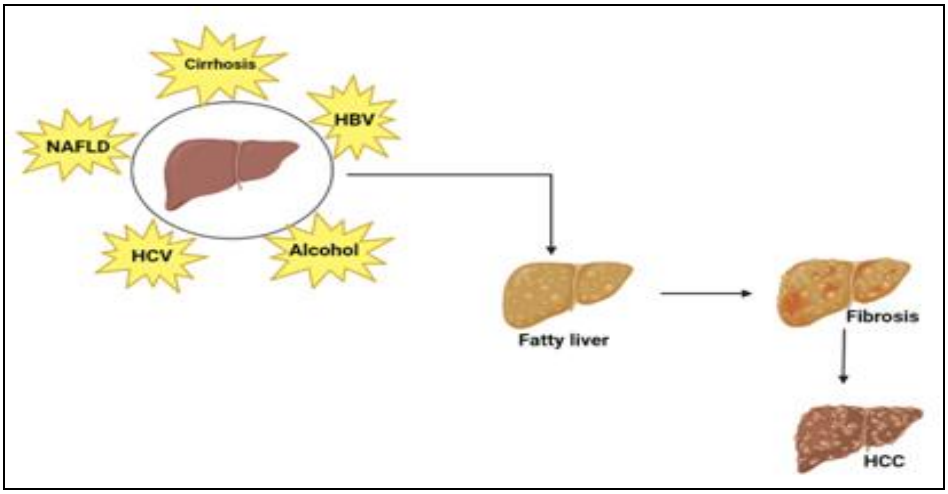

FIG. 1: MAJOR FACTORS RESPONSIBLE FOR HCC. Major factors responsible for contribution in the progression of HCC includes cirrhosis, HBV, HCV, alcohol and NAFLD. The first stage is fatty liver, over the time period of having continue exposure of above factors it will leads to fibrosis, then ultimate stage of HCC has been achieved.

As shown in **Fig. 1.** cirrhosis, HBV, HCV, alcohol, NAFLD is the major factor that contribute to the pathology of HCC, the broader description of these factors are discussed as:

Chronic Hepatitis and Liver Cirrhosis: Liver cirrhosis affects more than 80% of HCC patients. Chronic hepatitis and liver cirrhosis leads to the development of HCC. Hepatitis or any injury to the liver activates the regeneration ability of the liver. Prolongation of normal wound healing or regeneration of the liver leads to liver fibrosis. Cirrhosis is a severe form of liver fibrosis [10]. Cirrhosis causes the shunting of blood supply to hepatic central veins. It leads to a continuous cycle of necrosis and regeneration, which may cause genomic alteration and thus loss of control over cell growth. This monoclonal expansion leads to HCC [11].

Non-alcoholic Fatty Liver Disease: Insulin resistance is the primary cause of non-alcoholic fatty liver disease (NAFLD). It results in elevated insulin and insulin-like growth factor-1 (IGF-1) levels. Insulin binds to its receptor, activating the PI3K/AKT pathway [12]. Another factor is increased in oxidative stress, which is often observed in NAFLD, can cause DNA damage in liver cells. This DNA damage may contribute to the development of cancerous cells over time [13].

Alcohol: The liver metabolizes alcohol through enzymes like alcohol dehydrogenase (ADH) and mitochondrial aldehyde dehydrogenase (ALDH). ADH breaks down ethanol into acetaldehyde, which is then converted into acetate by ALDH [14]. Acetaldehyde is reactive and can cause DNA damage, lipid peroxidation, and mitochondrial impairment [15]. Another enzyme called CYP2E1, along with NADPH, metabolizes alcohol and generates reactive oxygen species (ROS), which can damage DNA and proteins. Chronic alcohol abuse induces CYP2E1, leading to increased acetaldehyde levels in the liver. These effects collectively contribute to the initiation and development of HCC [16].

Hepatitis B Virus: Hepatitis B virus (HBV) is the most common cause of HCC worldwide. HBV DNA is highly integrated into chromosomes 11 and 17[17]. Viral DNA insertion can cause chromosomal rearrangements such as deletions and translocations. The integrated HBV DNA encodes the X gene and its transcript (HBx). HBx activates many cellular and viral genes, including those that control cell growth and apoptosis [18]. HBx causes late G1 cell cycle arrest, which leads to the induction of apoptosis. Mutations in the HBx gene have been found in HCC patients. It induces growth-suppressive and apoptotic effects. These effects contribute to the progression of HCC.

Hepatitis C Virus: Chronic hepatitis C (CHC) infection induces an inflammatory response, which is a protective physiological process of the liver. Chronic HCV infection elevated the levels of pro-inflammatory cytokines, chemokines, liver residential macrophages, and different immune cells in the liver [19].

Exposure to macrophages promoted inflammasome formation. Inflammasome has NOD-like receptors (NLRs) that sense viral pathogen-associated molecular patterns (PAMPs). NLRs activation leads to the formation of IL-1β and IL-18. This may lead to the activation of quiescent hepatic stellate cells (HSCs) and the formation of myofibroblasts [20]. Myofibroblasts promote the formation of extracellular matrix (ECM) in the liver. Increased ECM levels result in the development of fibrosis and cirrhosis progressing towards to HCC [21].

Role of Growth Factors in HCC Pathogenesis: Growth factor receptors are involved in tumorigenic activity by activating signalling pathways. The human liver produces various growth factors during foetal development, but their production decreases in the normal adult liver. After liver injury, certain growth factors are upregulated to aid in liver regeneration [22]. However, in chronically injured livers, dysregulated growth factor receptor signalling in adult hepatocytes contributes to hepato-carcinogenesis [23].

Platelet Derived Growth Factor: The platelet-derived growth factor (PDGF) family consists of four polypeptides that form dimers, including PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD. Mesenchymal cells produce PDGF, and two receptors, PDGFR-alpha and PDGFR-beta, form different dimersand activate various adapter proteins upon binding. This leads to effects like cell growth, movement, apoptosis, angiogenesis, and chemotaxis. Elevated PDGF/PDGFR expression is observed in 64% of HCC cases, particularly PDGFAA and PDGF-CC [24].

Insulin-like Growth Factors: Insulin-like growth factors (IGF) include IGF-1 and IGF-2, share 76% homology. There are seven binding proteins and 75% of the circulating IGF is bound. IGF receptors 1 and 2 exist as dimers that may also include the insulin receptor [25]. IGF-2 mRNA was discovered in all humans HCC tissue and was found to be elevated in 22% of human HCC samples. In HCC cell lines exposed to aflatoxin B1, showed elevated IGF-2 and IGF-1R expression [26]. It has been discovered a decrease in IGF-BP3, the primary IGF-binding protein, in HCC compared to surrounding tissue (27). It has been discovered IGF pathway activation in 21% of cases, which was related with elevated IGF-2 expression, downregulation of IGFBP3, and allelic loss of IGFR2. Many of the effects of IGF pathway activation were inhibited by an IGFR-1 antibody (A12) [27].

Epidermal Growth Factor Receptor: It is discovered epidermal growth factor receptor (EGFR) in tumour-associated endothelial cells. The EGFR family consists of four closely related members and expressed in hepatocytes [28], biliary

epithelial cells, and hepatic stellate cells, not in Kupffer cells or normal endothelial cells. Ligands such as EGF, TGF-alpha, and others interact with the EGFR family and play important roles in liver signalling [29]. Cytokines like IL8, IL1-beta, IFN-gamma, and TNF-alpha activate EGFR, which in turn activates proteins involved in cell migration and cytoskeletal rearrangement, including FAK, caveolin, E-cadherin, and beta-catenin. It is estimated that EGFR expression occurs in up to 80% of HCC, with ErbB1 present in 75% of nodules, ErbB2 in 89%, and ErbB4 in 62% of tumours [30]. EGF expression is also enhanced in HCC samples compared to the normal liver. This disparity in studies suggests that EGFR must be studied more before being labelled as a cause of HCC.

Vascular Endothelial Growth Factors: Vascular endothelial growth factors (VEGF) are platelet-derived growth factor subfamily members with cysteine knots, generated by mesenchymal and endothelial cells and can be increased in hypoxic and non-hypoxic situations by IGFI and Sp1 [31]. Activation of the VEGF/VEGFR axis may occur early in HCC, with higher expression in well-differentiated HCC and decreasing as tumour size grows [32]. Accessory molecules such as neuropilin-1, EphA1, aldosterone blockade, and HBxAg have been linked to VEGF/VEGFR activity in HCC. It is discovered a higher prevalence of VEGFR-3 short-form splice variant expression in HBxAg-positive HCC. This shows that VEGF may be a risk factor for HCC, although more research is needed to validate this.

Role of Fibroblast Growth Factors and its Receptors in HCC: In 1939, the first FGF having mitogenic activity was discovered and was isolated in the 1970s. The FGF family is divided into seven subfamilies, based on their mechanism of action as shown in **Fig. 2**; **Table 1** [33]. Fibroblast growth factors (FGFs), specifically paracrine and endocrine, transmit cellular signals by attaching to and activating tyrosine kinase receptors located on the surface of target cells. Structurally, the FGF protein has FGFR-binding domains and HS (heparin sulfate)-binding domains, which are required for FGFR dimerization and activation [34]. There are four members in the family of FGFR gene family, FGFR1-4, that have been identified to function as RTKs (receptor tyrosine kinases). Interaction of FGFs with FGFRs in presence of cofactors, activating intracellular pathways Ras/MAPK, PI3K/Akt, and PLCγ/PKC to regulate gene transcription in the target cells [35]. The potential to regulate cell proliferation, differentiation, and survival through FGF/FGFR signalling indicates this pathway could be a target for treating multiple tumours. Abnormal FGF/FGFR signalling has been linked to the pathogenesis of several types of cancer. The FGF/FGFRs also serve as valuable biomarkers for patient identification, which is crucial for detecting interpatient heterogeneity in HCC.

TABLE 1: THE TABLE ILLUSTRATES THE LEVELS OF FGFS ARRANGED ACCORDING TO THEIR SUBFAMILIES AND THEIR AFFINITY TOWARDS SPECIFIC RECEPTOR [36]

FGF Subfamily	FGF Family Members	Affinity Towards FGFR	Type of FGF
FGF1	FGF1	1b, 1c, 2b, 2c, 3b, 3c, 4	Paracrine FGF
	FGF2	1c, 3c, 2,c 1b, 4	
FGF4	FGF4	1c, 2c, 3c, 4	Paracrine FGF
	FGF5		
	FGF6		
FGF7	FGF3	1b, 2b	Paracrine FGF
	FGF7		
	FGF10		
	FGF22		
FGF8	FGF8	3c, 4, 2c, 1c, 3b	Paracrine FGF
	FGF17		
	FGF18		
FGF9	FGF9	3c, 2c, 1c, 3b, 4	Paracrine FGF
	FGF16		
	FGF20		
FGF11	FGF11	Unknown	Intracellular FGF
	FGF12		

FGF19	FGF13 FGF14 FGF19 FGF21 FGF23	1c, 2c, 3c, 4	Endocrine FGF

Fibroblast Growth Factor Associated Endocrine Signalling Pathways in HCC: FGF signalling is initiated when FGFs bind to specific transmembrane receptors known as FGF receptors (FGFRs). There are four FGFR isoforms (FGFR1-4), and each isoform has a unique expression pattern and ligand-binding specificity [37]. Upon ligand binding, FGFR undergoes dimerization and autophosphorylation, leading to the activation of downstream signalling pathways [38]. The primary downstream signalling pathways activated by FGF signalling are the Ras/MAPK pathway and the PI3K/Akt pathway. In the Ras/MAPK pathway, the activated FGFR recruits and activates the adaptor protein Grb2, which in turn activates the Ras protein. Activated Ras stimulates a cascade of protein kinases, ultimately leading to the activation of extracellular signal-regulated kinases (ERKs) and the induction of gene expression [34]. In the PI3K/Akt pathway, activated FGFR recruits and activates PI3K, which generates phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 then recruits and activates Akt, which regulates various downstream processes, including cell proliferation and survival as shown in **Fig. 2** [32]. FGF signalling is tightly regulated by various mechanisms, including the action of extracellular inhibitors such as Sprouty and Sef, which prevent FGFR activation, and the action of intracellular negative regulators such as the protein tyrosine phosphatase SHP2, which dephosphorylates activated FGFRs [40].

Paracrine Signalling Pathways: FGFs are a family of signalling proteins that bind to specific receptors on the surface of target cells to activate downstream signalling pathways. The FGF family consists of 22 members, which are divided into seven subfamilies based on their structural and functional similarities [40]. In the paracrine signalling pathway, FGFs are secreted by a signalling cell and then diffuse through the extracellular matrix to bind to FGF receptors (FGFRs) on neighbouring target cells. FGFRs are transmembrane receptors with an extracellular ligand-binding domain and an intracellular tyrosine kinase domain [39].

Upon FGF binding, the receptor dimerizes, and the intracellular domains become phosphorylated, which initiates downstream signalling. The downstream signalling pathways activated by FGFs are diverse and include the mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol 3-kinase (PI3K) pathway, and the protein kinase C (PKC) pathway as shown in **Fig. 2** [41].

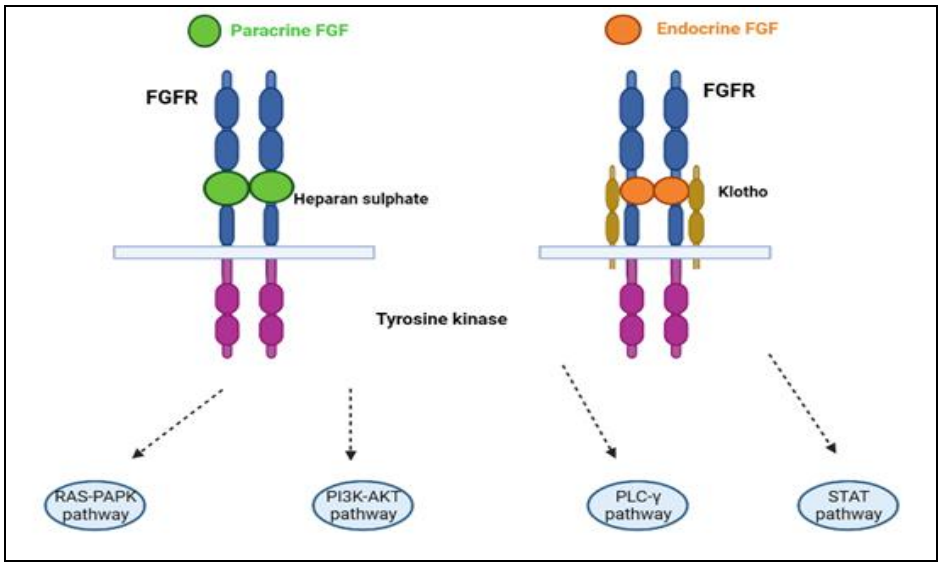

FIG. 2: TWO MAJOR SIGNALLING PATHWAYS OF FGF THAT LEADS TO ACTIVATION OF FURTHER CASCADES IN HCC

These pathways regulate various cellular processes such as cell proliferation, differentiation, survival, and migration. In addition to activating downstream signalling pathways, FGF signalling also regulates the expression of other signalling molecules. For example, FGFs can induce the expression of heparansulfate proteoglycans (HSPGs), which can bind to and potentiate the activity of FGFs, thereby enhancing the paracrine signalling. FGF signalling is involved in many biological processes, including embryonic development, tissue repair, and angiogenesis. Dysregulation of FGF signalling has been implicated in various diseases, such as cancer, skeletal disorders, and cardiovascular disease.

Receptor Tyrosine Kinase Pathways: FGF regulates various cellular processes, including angiogenesis, cell proliferation, and differentiation, through binding to FGF receptors (FGFRs), a type of RTK. FGFRs consist of four members: FGFR1, FGFR2, FGFR3, and FGFR4 **Table 1** [13]. Activation of FGFRs leads to the activation of downstream signalling pathways, such as the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt pathways, which are involved in cell proliferation, survival, and migration. Dysregulation of these pathways contributes to the development and progression of HCC [10]. In HCC, the dysregulation of FGF signalling is a common feature, with upregulation of FGF ligands and/or overexpression of FGFRs being observed in a significant proportion of cases [13].

RAF/ERK/MAPK Pathways: Hepatocellular carcinoma (HCC) is characterized by activation of the RAF/MEK/ERK pathway, which is driven by mutations in the RAS gene, overexpression of growth factors and their receptors, and HBV infection [10]. The RAF/ERK/MAPK pathway regulates cell proliferation, differentiation, and survival, and its dysregulation is common in HCC. Fibroblast growth factor (FGF) and its receptors (FGFRs) are involved in activating this pathway. This pathway is often dysregulated in cancer, including hepatocellular carcinoma (HCC). Fibroblast growth factor (FGF) is one of the ligands that activate this pathway by binding to FGF receptors (FGFRs) [42]. Genetic alterations in genes encoding pathway components and amplification of FGFRs contribute to HCC tumour growth, invasion, and metastasis. Hepatocellular carcinoma is characterized by activation of the RAF/MEK/ERK pathway through two mechanisms: oncogenic mutation in the RAS gene and overexpression of growth factors and their receptors. HBV infection can also activate this pathway in HCC [43].

PI3K/Akt/mTOR Signalling Pathways: The PI3K/Akt/mTOR signalling pathway is a critical intracellular pathway that plays a vital role in several cellular processes, including cell growth, proliferation, differentiation, and survival [44]. This pathway is frequently dysregulated in many cancers, including hepatocellular carcinoma (HCC), a primary liver cancer with high morbidity and mortality rates. Studies have shown that the PI3K/Akt/mTOR signalling pathway is a central regulator of HCC pathogenesis, and its activation contributes to the growth, progression, and metastasis of HCC cells [45]. One study demonstrated that activation of the PI3K/Akt/mTOR pathway is associated with HCC tumour progression, and inhibition of this pathway can suppress HCC growth and invasion. The PI3K/AKT/mTOR signalling pathway is activated when growth factors bind to receptors, leading to the production of PIP3b and activation of AKT. Activated AKT regulates transcription factors and phosphorylates various cytoplasmic proteins including mTOR, which regulates phosphorylation of several proteins involved in promoting cell cycle progression. The mTORC1 is activated by AKT and regulates protein synthesis, leading to cell cycle progression from G1 phase to S phase [46].

FGF and FGF Receptors Involved in the Development and Progression of HCC:

FGF19-FGFR4: Preclinical research has shown that signalling through FGFR receptors may contribute to the development of HCC. FGFR3 and FGFR4 are the main FGFRs expressed in liver tissue and have been implicated in the mechanisms underlying HCC tumorigenesis [47]. FGF19 binds to FGFR4 and forms a complex with FRS2 and GRB2, activating signalling pathways that promote cell proliferation, survival, and anti-apoptotic effects as shown in **Fig. 3** [48]. FGF19/FGFR4 signalling plays a significant role in hepatocellular carcinoma (HCC) development and progression, leading to poor prognosis.

It enhances tumour growth, invasion, and metastasis in HCC. Overexpression of FGF19 and FGFR4 is observed in human HCC tumour samples, and neutralizing FGF19 with an antibody prevents Xenograft HCC tumour formation in mice. Preclinical studies suggest that FGF19 and FGFR4 contribute to hepatocyte proliferation and HCC tumour development. Genomic studies have identified FGF19 as one of 18 overexpressed genes associated with HCC tumours [49]. FGF19 transgenic mice had elevated alpha fetoprotein (AFP) and accumulation of beta-catenin was found in the liver tumour cells. The cause of increased beta-catenin could be activation of Wingless/Wnt signalling pathway which caused hepatocellular proliferation. These finding suggest that FGF19 promotes HCC development. It has been reported that FGF19 has a vital role in the progression of HCC, so to examine this FGF19 antibody 1A6 is administered to transgenic mice. The FGF19 antibody 1A6 prevented phosphorylation of FGF receptor substrate 2 (FRS2) [50]. In summary, the evidence suggests that FGF19 plays a critical role in HCC development and progression by promoting tumour growth and regulating HCC stem cells. Therefore, FGF19 may serve as a potential therapeutic target for the treatment of HCC **Fig. 3**.

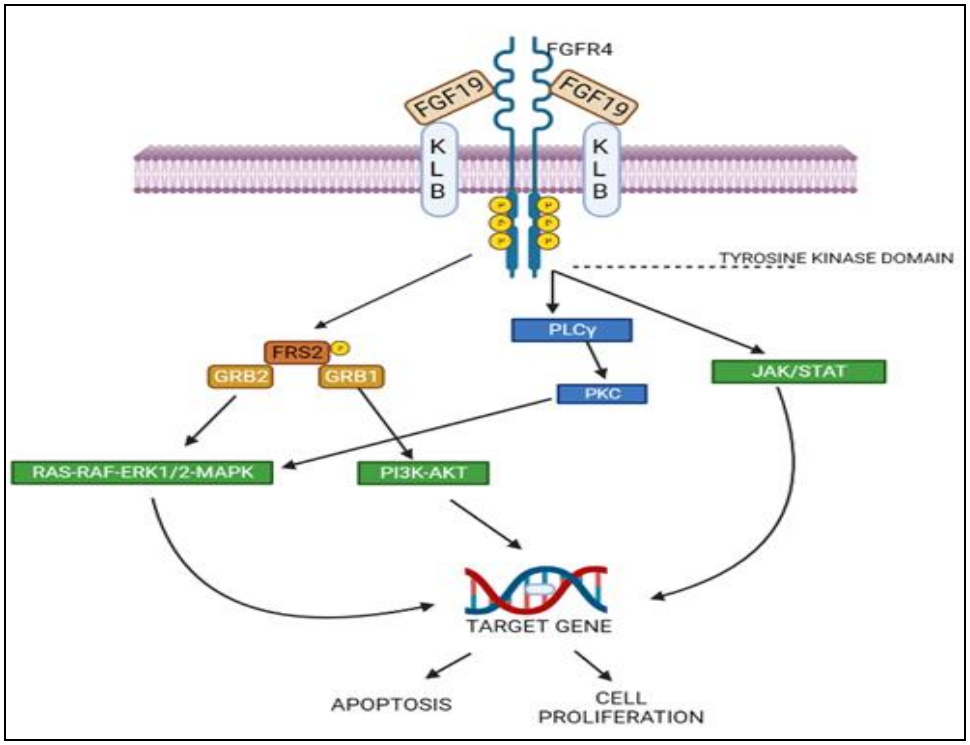

FIG. 3: SIGNAL TRANSDUCTION MECHANISM FOR FGF19-FGF4 PATHWAYS LEADING TO THE ACTIVATION OF FURTHER CASCADES AND REGULATING APOPTOTIC AND CELL PROLIFERATION LIKE ACTIVITY

FGF8: FGF8 is a member of the FGF family of growth factors, which are known to regulate a variety of cellular processes such as cell proliferation, differentiation, and migration. FGF8 has been shown to be overexpressed in HCC tissues compared to normal liver tissues, and this overexpression is associated with a poor prognosis for HCC patients [51]. Human FGF8 protein (26 kD) consists of 233 amino acids. The FGF8 subfamily contains ligand FGF8, FGF17, FGF18. These ligands have high affinity to FGFR4 and the IIIC isoforms of FGFR 2 and 3. FGF8, FGF17, and FGF18 promoted the growth of hepatic stellate cells found in the stroma of HCC patients [52]. FGF8, a growth factor, activates FGF tyrosine kinase receptors and regulates embryonic development, cell differentiation, proliferation, and migration. While rare in adult tissues, FGF8 is often overexpressed in various human tumors, including HCC. Overexpressing FGF8 or adding recombinant FGF8 increases HCC cell proliferation. AP1, a coactivator in the Hippo signaling pathway, and elevated YAP1 expression or activity stimulate cancer cell proliferation in HCC. FGF8 may

enhance cancer cell resistance to EGFR inhibitors and upregulate EGFR expression by activating YAP1 [53]. FGF8, FGF17, and FGF18 are all up-regulated in HCC, with the main receptors being FGFR3 and FGFR4. Several studies have investigated the role of FGF8 in HCC development and progression. For instance, a study has demonstrated that FGF8 promotes HCC cell proliferation and invasion through the activation of the PI3K/Akt pathway [54]. Another study showed that FGF8 enhances HCC cell migration and invasion through the upregulation of matrix metalloproteinase 7 (MMP7). FGF8 plays a crucial role in HCC development and progression by promoting cell proliferation, invasion, migration, and regulating HCC stem cells. It activates the Wnt/β-catenin signalling pathway to enhance self-renewal and tumorigenicity of liver cancer stem cells. Targeting FGF8 may hold promise as a potential therapeutic approach for HCC treatment [53].

FGF21: FGF21 is a member of the FGF family of proteins, which play important roles in regulating cellular processes such as cell growth, differentiation, and metabolism. FGF21 is predominantly expressed in the liver and has been shown to have beneficial effects on glucose and lipid metabolism. In addition, FGF21 has been shown to have anti-tumor effects in various cancer types, including HCC [55]. FGF21 is a type of hormone-like protein that plays a role in regulating glucose and lipid metabolism. It belongs to a subfamily of fibroblast growth factors (FGF), which includes FGF19 and FGF23, and is different from typical FGFs in that it does not have a conventional FGF heparin-binding domain. Instead, it can diffuse away from its tissue of origin and function as an endocrine regulator [56]. FGF21 binds to FGFRs through the presence of β-klotho co-receptor. β-klotho is found in metabolic tissues like the liver, pancreas, and adipose tissues, while FGFRs are expressed in various tissues including the liver, adipose tissues, skeletal muscle, and kidney. This receptor-ligand interaction is crucial for FGF21's effects in metabolic tissue. FGF21 expression in the liver is influenced by PPARα, activated by fatty acids from adipocytes, leading to decreased lipogenesis and increased fatty acid β-oxidation [57]. A study found that serum FGF21 levels were increased in NAFLD and positively correlated with intrahepatic TG, indicating that FGF21 could be a potential biomarker of NAFLD. FGF21 mRNA expression and protein levels in liver tissues were significantly higher in Grade 1 steatosis compared to Grade 0. The study suggests that FGF21 may be more sensitive than ultrasonography in detecting mild steatosis. FGF21 circulating concentrations were also found to correlate with its protein levels in the liver [58]. FGF21 levels are initially elevated during hepatic stress but reduced in advanced HCC due to factors like high hepatic lipid concentration, G9a-mediated epigenetic suppression, and hypoxia. High liver lipid levels contribute to HCC development, leading to decreased FGF21 levels. G9a suppresses FGF21 expression, and hypoxia further lowers FGF21 mRNA levels, which are common in solid tumours. The downregulation of FGF21 in developed HCC is attributed to G9a and liver hypoxia [59].

Therapeutic Interventions Targeting FGF in HCC:

Lenvatinib: Lenvatinib effectively inhibited the proliferation of HCC cell lines by targeting the activated FGF19-FGFR4 axis. It bound to VEGFR2 and FGFR1, similar to FGFR2, 3, and 4. Lenvatinib suppressed the FGF signalling pathway by reducing phosphorylation of FRS2 and Erk1/2. In Xenograft studies, Lenvatinib demonstrated anticancer efficacy against HCC with overexpressed FGF19, whereas sorafenib showed no significant inhibition. Lenvatinib's antiangiogenic activity was superior to sorafenib, especially in PDX models [60]. Lenvatinib effectively targeted FGFR4 in HCC cells, leading to the downregulation of PD-L1 protein expression and inhibition of GSK3 phosphorylation [61]. It also reduced Treg infiltration and enhanced the anti-PD-1 immune response. FGFR4 expression and Treg infiltration were identified as indicators for the efficacy of Lenvatinib with anti-PD-1 treatment in HCC patients. In animal studies, Lenvatinib combined with an anti-PD-1 antibody demonstrated superior tumour growth inhibition and improved survival compared to tumours with silenced FGFR4 [62].

H3B-6527: In kinase testing, H3B-6527 showed potent inhibition against FGFR4 among 395 kinases. Treatment of Hep3B cells with H3B-6527

led to dose-dependent activation of caspase-3/7, indicating cell death in HCC cell lines [63]. Oral administration of H3B-6527 reduced tumour development **Table 2** and caused regression in subcutaneous xenograft models. In FGF19-overexpressing HCC PDX models, combining H3B-6527 with Lenvatinib resulted in significant tumour shrinkage and partial growth suppression. The combination treatment was well tolerated, reducing body weight loss compared to Lenvatinib monotherapy in Hep3B xenografts [48].

BLU9931: BLU9931 is a small-molecule inhibitor that is highly selective, covalent, and targets FGFR4. It was utilised to see if blocking FGFR4 could stop FGF19/FGFR4 signalling and cellular processes associated with NASH development[64]. Co-culture with Caco-2 cells dramatically elevated cyclin D1 levels, and Oil Red O staining suggested increased levels of lipid build-up in Hep3B cells, while BLU9931 therapy decreased the up-regulated levels. These findings showed that inhibiting FGFR4 signalling **Table 2** could reduce the negative cellular and molecular processes associated with NASH development and NASH-HCC progression [65].

CXF-009: CXF-009 is a dual-warhead covalent inhibitor of FGFR4 that binds to the FGFR4-specific Cys477 and Cys552 residues [65]. CXF-9001 shows good selectivity against FGFR4 according to mass spectrometry data and structural analysis, making it a viable lead chemical for future anticancer drug research [66].

FGF401: FGF401 is a highly specific and powerful FGFR4 inhibitor with outstanding drug-like qualities that exhibits substantial anticancer action in FGFR4-dependent tumour models such as HCC models with FGF19 overexpression [67]. FGF401 outperformed sorafenib in antitumor activity in HUH7 xenografts. FGF401 has entered clinical trials, and a Phase I/II investigation in HCC is presently underway [51].

TABLE 2: CLINICAL TRIAL STUDIES TARGETING FGF/FGFR IN HCC PATIENTS [51]

Drug	Drug Target	Condition	Phase
Regorafenib	VEGFR1-3, RAF kinase, FGFR1-2	HCC	Phase 2
BLU554	FGFR4	HCC	Active, not-recruiting
H3B-6527	FGFR4	HCC	Phase 1
Regorafenib + Nivolumab	VEGFR1-3, RAF kinase, FGFR1-2	HCC	Phase 1 Phase 2
Pembrolizumab+ Lenvatinib	VEGFR1-3, FGFR1-4,	LiverTransplant, Complications; HCC Recurrent	Not Applicable
Durvalumab + Lenvatinib	VEGFR1-3, FGFR1-4	Livercarcinoma, Complications; HCC Recurrent	Not Applicable
Camrelizumab+Lenvatinib	Multitarget kinase	HCC	Phase 1 Phase 2
Lenvatinib + Toripalimab	VEGFR1-3, FGFR1-4	HCC	Phase 2
Lenvatinib + TACE versus Sorafenib + TACE	VEGFR1-3, FGFR1-4	HCC	Phase 4

CONCLUSIONS: FGF is a promising target for the treatment of HCC due to its role in metabolic regulation and its anti-tumour effects. Several studies have demonstrated the anti-tumour effects of FGF and its subfamily in HCC, and clinical trials investigating the use of FGF21, FGF19, FGF8 as a therapeutic agent in HCC are ongoing. In conclusion, fibroblast growth factors (FGFs) have been shown to play an important role in hepatocellular carcinoma (HCC). Specifically, FGF19 has been found to be overexpressed in HCC and is involved in promoting tumour growth and regulating HCC stem cells. FGF19 achieves this by binding to the FGFR4 and β-Klotho receptors, which activate downstream signalling pathways such as AKT and ERK. Several studies have also demonstrated that targeting FGF19 through siRNA or neutralizing antibodies can inhibit the proliferation, migration, and invasion of HCC cells, making it a potential therapeutic target for the treatment of HCC. Therefore, a better understanding of the role of FGFs in HCC may lead to the development of novel therapeutic strategies for the treatment of this deadly disease.

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CONFLICT OF INTEREST: Authors declare no conflict of interest.

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