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Targeting the p53-angiogenesis axis in hepatocellular carcinoma: from mechanisms to therapeutics

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Abstract

Hepatocellular carcinoma (HCC) is driven by a complex combination of genetic, epigenetic, and microenvironmental factors. It is characterized by p53 failure and uncontrolled tumorigenic angiogenesis, which contribute to tumor development, metastasis, and therapeutic resistance. This article is mainly focused on the p53–angiogenesis axis and explains how p53 mutations increase angiogenesis, boosting vascular endothelial growth factor (VEGF) levels and altering the von Hippel–Lindau (VHL) and hypoxia-inducible factor 1 alpha (HIF-1α) pathways. The role of mutations in the genes involved in HCC is extensively reviewed with emphasis on p53 mutational impact. Investigation of HCC with respect to p53 functions, along with the impact of β-catenin hyperactivation on vascular remodeling and immune evasion in p53-deficient conditions. Furthermore, therapeutic interventions targeting VEGF, basic fibroblast growth factor (bFGF), thrombospondin 1 (TSP1), and endostatin are comprehensively reviewed, exploring novel dual- or multi-targeted anti-angiogenic strategies.

1. Introduction

Hepatocellular carcinoma (HCC), the most frequent histological form of primary liver cancer, is one of the top five malignancies globally and the fourth leading cause of cancer deaths [1]]. It accounts for 75–85% of liver cancer cases globally, notably in East and Southeast Asia and sub-Saharan Africa, where rates are almost 100 times higher than in North America and Western Europe [2]]. According to recent data from the Indian Council of Medical Research (ICMR), the etiology of this condition has shifted from viral hepatitis to non-viral causes such as alcohol abuse and non-alcoholic fatty liver disease (NAFLD), with a death rate of 6.8 per 100,000 males in India [3]. The state of Kerala conducted an observational study (2018–2020) that surprisingly revealed that HBV was the cause of only 7% of cases of HCC, compared to the national average of 60–80%. Synchronously, the Institute of Liver and Biliary Sciences (ILBS) (2017–2022), New Delhi, conducted a national-level multi-institutional hospital-based study at eleven locations in India. The data obtained clearly demonstrated that 35.5% of HCC cases were attributable to NAFLD, while HBV accounted for 21.2%, alcohol for 13.9%, and HCV for 18% [4]. The ILBS study validated the results of the Kerala investigation, highlighting their significance on a national level, which indicated a wider epidemiological shift from viral to metabolic and lifestyle-related factors contributing to HCC [5]. Given its high prevalence and multifactorial etiology, especially in India and across the globe, it is critical to elucidate the molecular pathogenesis of HCC. Clinically, HCC is characterized by the heterogeneity of molecular profiles, the high incidence of recurrence and metastasis, and limited therapeutic efficacy. In most HCC cases, P53, an important protector that regulates cell death, repair of DNA, and development of blood vessels, gets mutated. Deeper understanding of advanced HCC treatment and outcome necessitates investigation of the interaction with p53 dysfunction and simultaneously a better understanding of angiogenic targeted therapies. Therefore, this review provides a detailed and structured analysis that correlates the functions of p53 and angiogenesis with therapeutic implications that drive the pathogenesis and development of HCC.

2. Role of mutations in HCC

Studying the progression of HCC requires an in-depth analysis of the genes that contribute to its pathogenesis and disease progression. Among all the functional genes that play a role in tumor development, the *TP53* gene stands out as the guardian of the genome, protecting the DNA from damage and potential carcinogenesis. The *TP53* gene is considered an important regulator of cellular stress, DNA repair, and the suppression of tumors [6]. HCC is a disease that results not because of a single gene mutation but because of a culmination of several mutations put together, such as in essential fundamental processes like DNA repair, immune system and apoptosis failure, and angiogenesis.

For a better understanding, a comprehensive examination of the mutations involved in HCC is required (Table 1). According to the mutational data obtained from The Cancer Genome Atlas of the National Cancer Institute's Genomic Data Portal (GDC), specifically in the liver hepatocellular carcinoma cohort, the *TP53* gene shows the highest mutation rate of ~ 27% among a mixture of genes relating to HCC [7]. This suggests that *TP53* is the most affected gene in HCC, establishing its anti-carcinogenic role in the body. Following *TP53*, other genes, such as the *CTNNB1* gene, which produces β-catenin, has a mutation rate of ~ 23%. The *CTNNB1* gene plays a major role in the Wnt/β-catenin signaling pathway [8]. This pathway is involved in the transcription of other essential genes that are involved in cell growth metabolism, differentiation, and survival [8]. The *MUC16* gene, also called CA125, shows a mutation rate of ~ 20%. Although *MUC16* has been linked with ovarian cancer, its role in solid tumors such as HCC is well recognized [9]. The HCC-specific research on *MUC16* suggests that *MUC16* mutations may play a role in immune modulation and enhance tumor phenotype/cell survival, which results in a disruption in cell-cell and immune checkpoint interactions [10]. In HCC, these genes play an important role in influencing the HCC TME. Figure 1 illustrates the percentage of top mutated genes in HCC.

Table 1
Mutational roles of genes involved in HCC

Gene	Gene Type	Mutation Type	Cytoband	Functional role in HCC	References
TP53	Tumor suppressor	Missense, nonsense, frameshift (loss-of-function)	17p13.1	Regulator of cellular stress, DNA repair, tumor angiogenesis suppressor	[6], [7], [8], [15]
CTNNB1	Oncogene (β-catenin)	Missense (activating)	3p22.1	Wnt / β-catenin signaling pathway	[7], [8], [15]
MUC16	Oncogene (mucin family)	Missense, frameshift	19p13.2	Immune modulation and tumor cell survival	[7], [10]
CSMD3	Tumor suppressor (putative)	Missense, truncating	8q23.3	Regulation of immune responses	[7], [11]
LRP1B	Tumor suppressor	Missense, truncating	2q22.1 2q22.2	Affect hepatic cell proliferation and lipid metabolism	[7], [12]
ARID1A	Chromatin remodeler/tumor suppressor	Frameshift, nonsense (loss-of-function)	1p36.11	Component of SWI/SNF chromatin remodeling complex	[7], [13], [15]
BAP1	Tumor suppressor (chromatin modifier)	Missense, truncating	3p21.1	DNA damage repair and chromatin dynamics	[7], [14]
FAT3	Tumor suppressor (cadherin family)	Missense, truncating	11q14.3	Regulation of cell-to-cell interactions	[7], [15]
AXIN1	Tumor suppressor (Wnt pathway)	Frameshift, nonsense (loss-of-function)	16p13.3	Acts as scaffold protein in β-catenin degradation complex	[7], [8], [15]

3. Exploring HCC cells in the context of mutant p53 function

Exploring the role of p53 in HCC necessitates studying its contextual function in determining the onset of the disease and its progression. In this aspect, HCC in vitro cell lines offer themselves as stable and reproducible models that stand to mimic tumor phenotype and conduct molecular and diagnostic studies in a controlled environment. The

major cell lines that are used in liver cancer research are the HepG2, Hep3B, and Huh7 models. A peculiarity in the working of Huh7 was reported by Ghufran et al. (2022), who showed that when HepG2 cells (WTp53) were silenced using the siRNA-mediated gene silencing mechanism, they showed increased VEGF production; in comparison, Huh7 cells (mutant p53) did not show elevated VEGF levels nor show enhanced angiogenic responses altogether [16]. This can only imply that the correlation between p53 dysfunction and angiogenesis is not always linear but is context-dependent and can change based on the kind of environment and mutation it may possess.

Another significant factor worth considering with regard to mutant p53 is studying the detrimental effects of p53 amyloid formation in HCC. Evidence shows that p53 dysfunction in cancer is not only due to mutation or deletion but also due to amyloid/aggregate formation of the p53 protein [17]. Amyloidization converts p53 into a form that is unable to bind DNA and execute common canonical programs such as apoptosis, cell-cycle arrest, and DNA repair. Subsequently, it showed an increased seeding capacity and prion-like behavior (cell-to-cell transmission). This transmissibility, as a result, can propagate loss of p53 function in neighboring cells and may contribute to tumor heterogeneity [17].

3.1 CRISPR-based p53 gene correction

Novel research highly advocates for advanced genetic engineering of HCC cells with respect to p53 functions. This allows the creation of customized HCC cell line models. The CRISPR-Cas9 technology shows great promise for the correction of certain TP53 gene mutations, particularly missense mutations, which account for the bulk of TP53 mutations in various types of cancer. This method is able to potentially revert these mutations to a wild-type sequence by precisely editing the genome and thereby restoring normal p53 function [18].

The CRISPR technology has been used to drastically alter gene expression, introducing LOF or GOF mutations in both oncogenes and tumor suppressor genes [19]. Advanced gene-editing methods using Cas9-specific aptamers have been known to improve p53 mutant repair efficiency; specifically, in bladder cancer cell lines [20]. Studies using CRISPR/Cas9 to create full Trp53 knockout (KO) in mouse embryonic fibroblasts have shown that p53 disruption can rescue proliferation in cells lacking the G1/S checkpoint by restoring origin firing and reducing DNA breakage. As demonstrated in human cells with G1/S phase checkpoint defects, this p53 inactivation was able to reduce the accumulation of DNA double-strand breaks [21]. Furthermore, CRISPR-Cas9-mediated somatic gene disruption has been used to confirm the causative role of p53 and Pten somatic mutations in HCC development [22].

CRISPR-Cas9-based restoration of p53 comes with its own challenges. Most importantly, this can be the DNA damage induced by CRISPR-Cas9 inadvertently affecting cells with inactive or mutated p53. Issues pertaining to off-site mutations and the delivery of CRISPR-Cas9 to target HCC cells also need to be considered. This process could involve the use of viral vectors such as adeno-associated virus (AAV), which often leads to the usage of high doses and subsequently may complicate clinical applications. Additionally, the human immune system may also recognize the Cas9 protein, which can evoke adverse immune responses in vivo. Nevertheless, CRISPR-Cas9 gene correction for p53 restoration holds significant promise as a revolutionary approach to cancer therapy.

4. β-catenin-VEGF signaling in p53-null context

The Wnt/β-catenin signaling pathway is frequently unregulated in HCC and plays a key role in its inception and development, including regulating angiogenic growth factors like VEGF [23]. The Wnt/β-catenin signaling pathway is known to regulate the expression of various angiogenic growth factors, including VEGF-A, VEGF-C, MMP-2, MMP-9, and bFGF, in HCC cells [23]. Research shows that β-catenin, the primary effector of the Wnt pathway, is significantly and selectively overexpressed in Hep3B cells compared to HepG2 and Huh7 cells [24]. In p53-null Hep3B cells, β-

catenin accumulates in the nucleus and exhibits hyperactivation, indicating a compensatory adaptation that sustains or enhances critical tumorigenic processes in the absence of p53-mediated regulation [27]. As discussed earlier, the hyperactivation of β-catenin in Hep3B cells mostly leads to the production and release of pro-angiogenic factors like VEGF-A, which in turn leads to malignant phenotypes. These cells produce VEGF-A through a non-canonical pathway, independent of HIF-1α, which promotes endothelial cell recruitment, migration, and tumor neovascularization independent of hypoxia-dependent signaling [25].

In a p53-null scenario, β-catenin signaling invokes changes in the tumor immune microenvironment by actively stopping the recruitment of conventional type 1 dendritic cells (cDC1s) [26, 27]. The absence of the said dendritic cells leads to an impaired activation of cytotoxic T cells and a reduction in antitumor immunity, thereby potentially creating an immune-evasive, “cold” tumor microenvironment that shows resistance to immune checkpoint inhibitors [28, 29]. The induction of EMT (epithelial-mesenchymal transition) is another malignant hallmark that is facilitated by β-catenin [30]. In this case, β-catenin was shown to inhibit E-cadherin, which led to epithelial loss in the tumor. Consequently, it also elevated the expression of transcriptional repressors such as Snail and ZEB1, hence augmenting cancer cell motility and invasiveness. This mechanism facilitated the dissociation of tumor cells from the main tumor, infiltration into adjacent tissues, and later metastatic spread to other secondary organs [30, 31]. Figure 2 explains the mechanisms of tumor immune evasion and metastasis due to hyperactivation of β-catenin in a p53 null scenario.

HCC aggressiveness can be attributed to the fact that it is driven by uncontrolled β-catenin signaling in p53-deficient contexts, demonstrating the tumor cells' capacity to remodel signaling networks leading to survival and growth even in the absence of significant tumor suppressors [32, 33]. This interaction makes it clear why β-catenin signaling, rather than just p53 reactivation or VEGF/angiogenesis suppression, could be a potential therapeutic target for HCC. Currently, studies targeting the β-catenin protein are employing different kinds of small molecule inhibitors and ASOs that are efficiently able to overcome resistance in genetically sensitive HCC subgroups [34, 35]. Consequently, investigating the β-catenin molecular pathway in p53-independent contexts advocates for its therapeutic targeting in advanced HCC.

5. Targeting the p53–VHL–HIF-1α Axis: A Key Regulator of Angiogenesis in HCC

Angiogenesis is a tightly controlled process that requires a balanced interaction between pro- and anti-angiogenic factors [36]. HCC is distinguished by its hypoxic conditions seen in the tumor microenvironment. Therefore, to counteract the “angiogenic switch” caused by hypoxia and oncogenic stress, WTp53 plays a crucial role as an anti-angiogenic regulator under given physiological circumstances. In HCC, p53 has been shown to enhance the expression of the von Hippel–Lindau (VHL) protein, a crucial regulator of cellular adaptation to oxygen levels. Conversely, VHL also positively regulates the tumor suppressor p53 by inhibiting Mdm2-mediated ubiquitination and recruiting p53-modifying enzymes [37].

VHL functions as part of an E3 ubiquitin ligase complex, specifically targeting HIF-1α for proteasomal degradation in HCC cells under normoxic conditions. VHL binding and hydroxylation result in the proteasomal breakdown and ubiquitination of HIF-1α. Usually, in hypoxic HCC cells, VHL levels typically decrease, impairing its ability to target HIF-1α for proteasomal degradation [38]. HIF-1α is well known for undertaking the activation of genes responsible for angiogenesis, glucose metabolism, proliferation, invasion, and metastasis in HCC [39]. In HCC tissues, the HIF-1α expression was found to be a staggering 71.11%, which was significantly higher than in adjacent tissues (36.8%) [40]. In the hepatic microenvironment, p53 and VHL together suppress VEGF pathways to maintain the normal liver

vasculature and promote vascular quiescence. Maintaining low levels of HIF-1α and VEGF essentially helps in the regulation of tissue homeostasis, prevention of tumor formation and intravasation [41].

Therapeutically, to induce the downregulation of HIF-1α at the mRNA level, ASOs or siRNAs are being extensively used in preclinical trials and have shown great prospects in reducing the conventional HIF-1α levels [42, 43]. However, Vanderborght et al. (2020) note that these isoform-specific ASOs that were used to primarily target HIF-1α or HIF-2α failed to reduce tumor burden in murine HCC models. Instead, it was shown to have led to worsened liver inflammation and fibrosis, raising safety and viability concerns [42]. Additionally, lentiviral siRNA knockdown of HIF-1α, made cells more sensitive to chemotherapy and less resistant to multiple drugs in vitro and in xenograft models, especially when used with standard chemotherapy drugs [43]. Small molecules like sitagliptin, a DPP-4 inhibitor, have shown anti-HCC activity by reducing HIF-1α directly or by inhibiting pathways that regulate its stability and expression. This molecule in question was shown to inhibit the AKT-AMPKα-mTOR pathway and was able to effectively decrease angiogenesis while simultaneously enhancing apoptosis, and sitagliptin was also able to demonstrate anti-proliferative, anti-inflammatory, and anti-fibrotic properties in HCC models [44]. Despite the bright prospects, targeting the p53-VHL-HIF-1α axis still continues to prove a challenging feat, particularly in the case of HCC. One major concern is the dynamic behavior of p53 in hypoxic conditions. Another issue is that only a small percentage of HCC patients have "actionable" oncogenic drivers on the axis for therapeutic targeting, which limits patient-specific and biomarker-driven therapy (e.g., wild-type p53; intact VHL function) [45].

6. Investigating therapeutic interventions of angiogenic factors in HCC

HCC is known to be one of the most vascularized tumors. It depends almost entirely on a dense and aberrant network of blood vessels to sustain its rapid growth and metastatic spread. Most importantly, as the tumor progresses, it remodels liver vasculature towards an increased arterial supply which makes angiogenesis not just a hallmark of HCC progression but also a critical therapeutic target. Therefore, investigating angiogenic factors that play a critical role in aiding this process is of utmost importance. In this aspect, novel therapeutic interventions targeting angiogenic factors such as VEGF, bFGF, TSP1, and endostatin not only deepen our understanding of HCC pathophysiology but also pave the way for multi-targeted, precision-based interventions that may transform outcomes in the disease.

6.1 Vascular Endothelial Growth Factor (VEGF)

VEGF is considered an important facilitator of angiogenesis, the process by which new blood vessels are made [46, 47]. It binds to receptors, VEGFR1, VEGFR2 (KDR), and VEGFR3, on endothelial cells and is responsible for the activation of the downstream signaling cascades of the PI3K/Akt, MAPK, and HIF-1 pathways [48, 49]. VEGF expression in HCC is generally stimulated by hypoxic conditions that are usually observed in the tumor microenvironment, typically mediated by HIF-1α [50]. Therefore, it emphasizes the all-round examination of VEGF in the therapeutic targeting and prognostic capacities in HCC development.

A new development in treating HCC is using a combination of VEGF and immune checkpoint inhibitors (ICIs). This new approach considers the ability of VEGF in modifying the immune system [51]. Ongoing clinical investigations are using combinations of multi-targeted TKIs (tyrosine kinase inhibitors) (e.g., lenvatinib, regorafenib, and cabozantinib) with ICIs; this approach is supported by preclinical evidences indicating synergistic immunomodulatory effects and sustained responses [52, 53]. These rigorous yet innovative regimens are designed to not only fight against resistance linked to monotherapies but also to suppress several angiogenic and neoplastic processes. Apart from sorafenib and lenvatinib, other multikinase inhibitors are regorafenib and cabozantinib, which are usually prescribed for patients who have progressed on sorafenib.

Cabozantinib targets MET and AXL; these are RTKs (receptor tyrosine kinases) that play a well-defined role in cancer development [54, 55]. Ramucirumab is an antibody that is designed to specifically target VEGFR-2 and demonstrates efficacy, especially in patients with elevated alpha-fetoprotein levels [56]. Cediranib, a pan-VEGFR tyrosine kinase inhibitor, was also the subject of phase II studies. At three months, its progression-free survival (PFS) rate was 77%, and the median overall survival (OS) rate was 11.7 months. However, it has side effects, which include high blood pressure and low sodium levels, diarrhea, and fatigue [57]. Humanized antibodies, such as suvemcitug (BD0801), which are designed to show low immunogenicity in the human body, have shown promising preclinical effectiveness in suppressing HCC cell proliferation and promoting apoptosis [58]. Table 2 lists and compares the anti-VEGF drugs used in HCC therapies.

Table 2
Comparison of anti-VEGF drugs in HCC therapies: structure, molecular weight, targets, clinical role, side effects and approvals

Drug	Structure type	MW (kDa)	Main binding targets	Clinical role	Common side effects	Approvals	References
Sorafenib	Small molecule TKI	~ 0.46	VEGFR1-3, PDGFR, RAF, KIT	1st-line, advanced HCC	Hand-foot skin syndrome, diarrhea, hypertension	FDA, EMA, Japan (2007)	[59] [60] [61],[62], [63]
Lenvatinib	Small molecule TKI	~ 0.43	VEGFR1-3, FGFR1-4, PDGFRα, RET, KIT	1st-line, non-inferior to sorafenib	Hypertension, diarrhea, appetite loss, weight loss	FDA, EMA, Japan, China (2018)	[60], [64], [65], [66]
Regorafenib	Small molecule TKI	~ 0.48	VEGFR1-3, TIE2, PDGFRβ, FGFR, KIT, RET, RAF, BRAF	2nd-line after sorafenib	Hypertension, fatigue, hand-foot skin syndrome	FDA, EMA, Japan (2017)	[60], [61], [67], [68]
Cabozantinib	Small molecule TKI	~ 0.63	VEGFR1-3, MET, AXL, RET, KIT, TIE2	2nd-line after sorafenib	Diarrhea, fatigue, hand-foot skin syndrome	FDA, EMA (2019)	[60], [54]
Ramucirumab	Monoclonal antibody	~ 0.15	VEGFR2	2nd-line, AFP ≥ 400 ng/mL	Hypertension, proteinuria, bleeding	FDA, EMA (2019)	[60], [56]
Cediranib	Small molecule TKI	~ 0.45	VEGFR1-3, PDGFR, c-KIT	Investigational	Hypertension, fatigue, diarrhea	Not approved for HCC	[58], [60]
Suvemcitug	Monoclonal antibody	~ 0.15	VEGF-A	Investigational	Not fully characterized	Not approved	[60], [58]

Furthermore, unconventional approaches like molecular docking studies have led to the discovery of several interesting novel inhibitors that target VEGFR-1, which showed robust binding affinities and selectivity in silico, positioning them as ideal candidates for drug development. In 2024, several potential VEGFR-1 candidate compounds

were developed and assessed by using cheminformatics techniques like RD-Kit; the designing of these compounds utilized unorthodox techniques like deep learning algorithms and virtual libraries [69]. The use of such novel techniques for VEGFR-specific drug development saw an uptrend in recent years, mainly due to increased efficiency and cost-effectiveness. Also, the use of such methods has played a major role in the biochemical understanding of VEGF-binding, which enabled the precise identification of small molecular inhibitors with optimal activity and selectivity profiles [70]. Most of the earlier research was focused on VEGFR-2 because of its strong kinase activity and established role in angiogenesis. However, in recent years, research focus has seen a major shift in favor of VEGFR-1 inhibitors that are being used to target several pathways in the process of creating novel anticancer drugs. The use of these VEGF inhibitors has shown an increase in survival and response rates in patients with advanced and incurable HCC when used either in the form of monotherapy or in combination regimens with immunotherapies or multi-target kinase inhibitors.

6.2 Basic Fibroblast Growth Factor (b-FGF)

bFGF, also called FGF-2, is a potent polypeptide that plays a crucial role in cell proliferation, differentiation, survival, and angiogenesis [71]. The bFGF protein is primarily known to exert its effects by binding and activating fibroblast growth factor receptors (FGFRs), mainly FGFR1 and FGFR4 receptors in liver tissue [71].

Xie et al. (2021) and Wang et al. (2021) established the role of small molecule inhibitors used in targeting FGF receptors as an important strategy in mitigating the pro-tumorigenic effects of bFGF [72, 73]. These kinds of special FGFR4 inhibitors are crucial because FGF19/FGFR4 abnormal signaling is considered a common occurrence and can lead to the development of HCC [74]. Interestingly, a phase I clinical study of fisogatinib (BLU-554), a highly specific FGFR4 inhibitor, was able to demonstrate an overall response rate of 17% in FGF19-positive advanced HCC patients, with mild stomach side effects like diarrhea, nausea, and vomiting [75]. Other FGFR inhibitors, such as Infigratinib (BGJ398) and NVP-FGF401, that work against a wider group of FGFRs, are currently being tested in humans. These FGFR inhibitors have shown promise in the laboratory setup in effectively suppressing tumor growth, proliferation, and angiogenesis [72, 73].

A very promising approach in the targeting of the bFGF molecule is the development of specific monoclonal antibodies (mAbs). Hu et al. (2016) reported the use of a ^{125}I-labeled mAb against bFGF that was able to effectively inhibit tumor growth in a mouse HCC xenograft model [76]. The study found that combining targeted radiotherapy with angiogenic suppression of bFGF neutralization effectively reduced tumor growth, resulting in a 47.9% reduction in volume. This approach proved effective in murine models by impairing angiogenic signaling pathways through the reduction of bFGF, FGFR, and PDGF mRNA levels. However, unexpectedly high VEGF mRNA levels were obtained subsequently, which may indicate a compensatory overexpression of VEGF levels in response to bFGF inhibition and, thus, a possible vascular renormalization [76].

Despite showing promising preclinical and early-phase clinical results supporting bFGF-targeted treatment in HCC, significant hurdles still remain. Therapy effectiveness is usually hampered mainly due to factors such as tumor heterogeneity, compensatory angiogenic mechanisms, and acquired resistance. Also, a better understanding of biomarker-based patient selection is of utmost importance for improving clinical outcomes. Anti-bFGF therapies, when combined with ICIs and cytotoxic chemotherapy, show great prospects in increasing therapeutic effectiveness and survival in advanced HCC patients. Therefore, clinically, bFGF presents itself as a challenging yet promising competitor in the therapeutic intervention strategies in HCC.

6.3 Thrombospondin-1 (TSP1)

TSP1 is a large, multifunctional glycoprotein that is produced by a variety of cells, such as endothelial cells, fibroblasts, and different types of tumor cells within the tumor microenvironment [77]. The role of TSP1 in the context of HCC is considered complex and has been a subject of significant discussions in recent years, as clinical evidence exists for both its tumor-promoting and tumor-suppressing functions. Furthermore, TSP1 has proved to be a critical regulator of the TGF-β pathway, capable of activating latent TGF-β. In turn, this action is associated with liver fibrogenesis, immune modulation, and, indirectly, the development of the TME in HCC [78]. The TSP1 protein, via its receptor CD47, promotes immunosuppressive signaling in the TME by suppressing phagocytosis and facilitating immune escape [79]. Directly targeting the TSP1-CD47 interaction using antibodies or peptides has been demonstrated to increase antitumor responses, especially when combined with ICIs. In preclinical HCC models, these combinations demonstrated promising results in reducing tumor-initiating stem cell populations and enhancing immunotherapies by promoting anticancer immunity [80].

Interestingly, Luo et al. (2025) discovered that hypoxia in HCC TME can reduce TGFβ1's anti-angiogenic effect [81]. Under normoxic conditions, in chick CAM (chorioallantoic membrane) and zebrafish models, TGFβ1 protein inhibits angiogenesis by increasing endothelial cell TSP1 production and upregulation. However, hypoxic TME within mouse hepatoma xenografts did not reflect this pattern. They noticed that the increased levels of HIF1α reverse the angiogenesis-suppressive impact of TGFβ1 by reducing SMAD2 and SMAD3 synthesis. HIF1α also upregulated miR-145 expression. Evidently, miR-145 directly targeted the 3'-UTRs of SMAD2 and SMAD3, reducing their mRNA and protein levels. The primary endothelial cells that were derived from the HCC tissues have shown decreased levels of SMAD3 and TSP1 and increased levels of miR-145. Although TSP1 was not specifically the subject of this study, its contextual function in the TGF-β1-SMAD2/3-TSP1 axis explains the context-dependent nature of TSP1 production and its anti-angiogenic effects in HCC [81].

Gwag et al. (2021) discovered TSP1 as a significant factor in liver inflammation and fibrosis in the progression of non-alcoholic steatohepatitis (NASH), a primary precursor to HCC [82]. The research revealed a marked increase in TSP1 expression in NASH that primarily originated from liver-resident macrophages, cholangiocytes, and hepatic stellate cells. They showed that the usage of a macrophage-specific TSP1 knockout mouse model (TSP-1^ΔmΦ) resulted in a significant reduction of liver inflammation and fibrogenesis, despite no changes in hepatic fat accumulation. TSP1 was shown to inhibit SMPDL3B, a negative regulator of TLR4 signaling, hence enhancing pro-inflammatory and fibrotic responses via the TLR4–NFκB pathway [82]. Both these studies showcase the multiple regulatory functions of TSP1 in hepatocarcinogenesis, thereby establishing TSP1 as a crucial molecular node integrating angiogenesis, inflammation, and fibrogenesis in the development of HCC and establishing its potential as a dual-context therapeutic target.

Apart from conventional therapeutics, novel RNA-based techniques, including siRNAs, ASOs and miRNAs, that aim at selectively silencing TSP1 or modifying its downstream signaling pathways have emerged due to advances in RNA biological studies [83]. Remarkably, these RNA therapies are able to specifically target the "undruggable" components of TSP1.

Our understanding of the genetic, epigenetic, and post-translational control of TSP1, particularly in liver cancer, is significantly deficient, despite extensive study over several decades. The net effect of TSP1 often becomes difficult to predict because of its dynamic interactions with various mixtures of components in the TME. Due to the large number of proteins that TSP1 binds to, our knowledge of the signaling pathways that it activates is limited. Better knowledge and proper understanding of the TSP1 signaling networks, effective drug design (with better delivery systems), and the rational application of TSP1-targeted strategies within selected patient populations are necessary to overcome these complicated biological and translational hurdles.

6.4 Endostatin

Endostatin is a 20-kDa C-terminal fragment of collagen XVIII that is primarily synthesized through proteolytic cleavage by matrix metalloproteinases, including MMP-2 and MMP-9 [84]. The endostatin protein is able to attract substantial interest in the field of cancer research, particularly due to its function of selectively suppressing tumor neovascularization without compromising the normal vasculature; which makes it a potent endogenous angiogenesis inhibitor.

Jia et al. (2012), using *the S. typhimurium* vector, explored a novel combination therapy with endostatin and Stat3-specific siRNA. This method considerably showed better anti-tumor effects compared to other monotherapies when tested in an orthotopic HCC model (C57BL/6 mice). This combination therapy significantly altered Stat3 and endostatin levels, decreased cell proliferation, downregulated VEGF, induced apoptosis, and inhibited angiogenesis, while also boosting immune system regulation [85]. Endostar, a recombinant form of human endostatin that includes a His-tag at its N-terminal (MGGSHH-HHH), works by downregulating pro-angiogenic factors, including VEGF, CD31, MMP-2, and MMP-9. In vitro studies showed that Endostar suppressed HUVEC migration, adhesion, proliferation, and tube formation in response to HCC-conditioned condition [86–87].

Gene therapy represents a significant pathway for endostatin delivery, mainly due to its sustained and high-level expression of therapeutic protein at the targeted site. In groundbreaking research, Chen et al. (2025) aimed at exploring a novel combination gene therapy strategy that sought to enhance the antitumor efficacy of the RFA (radiofrequency ablation) method in combination with endostatin [88]. The experiment aimed to overcome immune evasion and angiogenesis barriers by creating a co-expression plasmid containing endostatin and a PD-L1 siRNA. The main objective was to reduce tumor cell PD-L1 expression, restore immune surveillance, and inhibit neovascularization through endostatin production. The plasmid was administered using PEI (polyethyleneimine)-modified nanoparticles in an attenuated Salmonella strain which was injected into an H22 subcutaneous tumor mouse model that demonstrated a significant decrease in VEGF expression and microvessel density, indicating angiogenesis suppression. PD-L1 knockdown was able to restore T cell-mediated immune recognition, removing residual tumor cells. All while endostatin blocked endothelial proliferation and neovessel formation [88]. This study provides a compelling proof-of-concept for integrating gene therapy and combining anti-angiogenic agents like endostatin with minimally invasive non-surgical methods like thermal ablation in HCC. By the simultaneous addressing of the immune escape problem and angiogenesis, this approach was able to considerably boost the therapeutic potential of endostatin and the RFA technique. And more importantly, it highlights the utility of gene delivery platforms in precisely sensitizing tumors to physical interventions [88].

Endostatin-targeted therapies face several challenges for widespread clinical application in HCC. In recent years, there has been a noticeable lack of novel research specifically targeting endostatin in HCC. While the anti-angiogenic properties of endostatin are well-documented, its specific anticancer mechanisms and signal transduction routes remain ambiguous. In recent years, endostatin-based interventions in HCC have lost favor due to the rapid development and clinical success of other systemic therapies, particularly TKIs and ICIs. But its use in combination strategies such as gene therapies has cemented its role as a multimodal therapeutic and anti-angiogenic agent, particularly in HCC.

7. Conclusion and prospects

HCC poses as a clinically challenging and biologically complex malignancy, with angiogenic and p53 dysfunction emerging as central, interdependent mechanisms that drive tumor advancement. Mutations in the gene generally lead

to alternate angiogenic pathways and ultimately contribute to EMT and metastasis. Overall, the evidence supports a context-dependent relationship between p53 dysfunction and angiogenic signaling in HCC.

Novel anti-angiogenic therapies, including VEGF/VEGFR inhibitors and innovative therapeutic strategies targeting the FGF/FGFR, TGF-β1-SMAD2/3-TSP1 axis and endostatin-mediated pathways, show promising results but exhibit inconsistent efficiency among varied molecular subtypes. Investigating the impact of mutant p53 GOF on angiogenesis remains underexplored. Furthermore, lack of accurate biomarkers to measure biochemical pathway activity hinders the ability to make real-time strategic adjustments to therapy. Also, the therapeutic potential of ncRNAs, chromatin remodelers, and gene therapy interventions in modulating angiogenesis in a p53-dependent context, particularly insights into the restoration of mutant p53 by the CRISPR system, remains prospective. With changing dynamics, the inclusion of functional assay studies, integrative genomics, and single-cell transcriptomics poses as a trending novel strategy. Incorporating p53 status into the anti-angiogenic therapy paradigm can open several doors in improving clinical outcomes and addressing therapeutic resistance in advanced HCC patients.

Declarations

Compliance with Ethical Standards

Not applicable

Conflict of interest

The authors declare that they have no conflict of interest

Author Contribution

SAK and SB conceived the whole idea of manuscript. SAK wrote the manuscript and created figures and tables. PS, SG and SB revised the manuscript. All authors read and approved the final manuscript and consent for publication was obtained from all participants.

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Data availability

No/Not applicable

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Figures

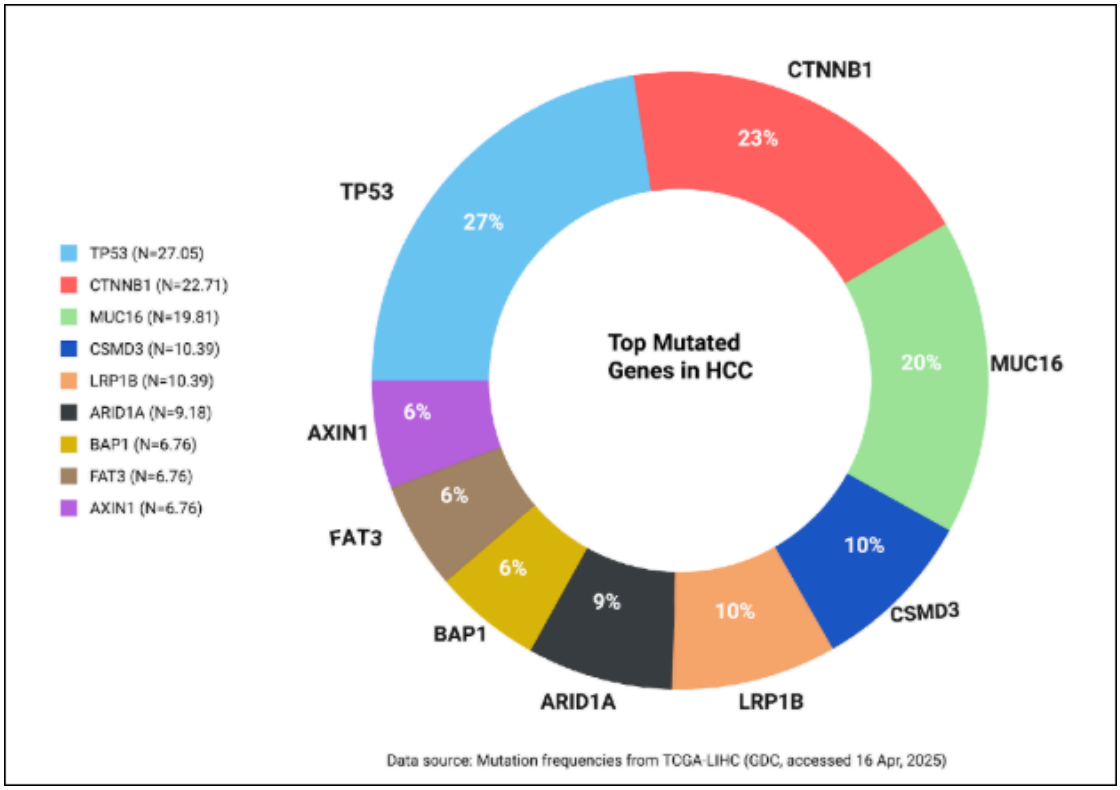

Figure 1

Mutation frequency distribution of major driver genes in HCC based on the TCGA-LIHC dataset. The chart illustrates the approximate percentage of mutations in key genes, including *TP53*, *CTNNB1*, *MUC16*, *CSMD3*, *LRP1B*, *ARID1A*, *BAP1*, *FAT3*, and *AXIN1*.

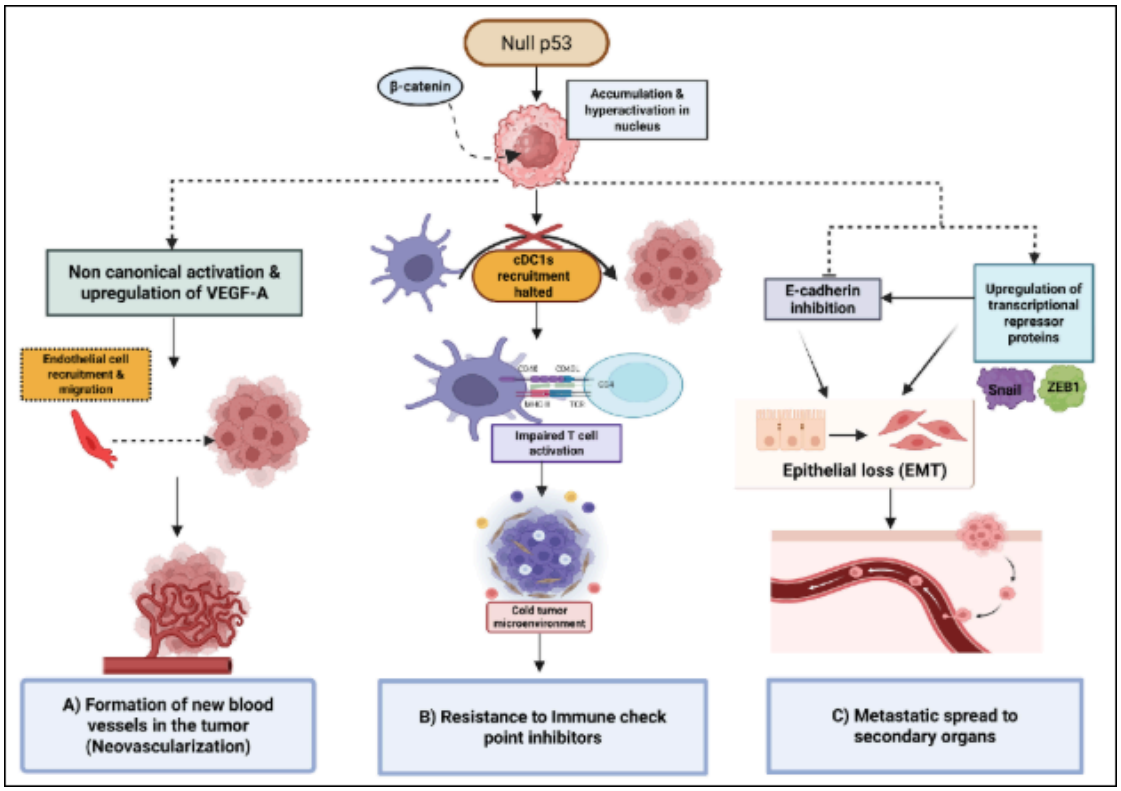

Figure 2

Mechanisms of tumor immune evasion and metastasis due to hyperactivation of β-catenin in a p53 null context. Scenario A describes neovascularization via non-canonical VEGF-A activation; Scenario B describes impaired T cell activation due to non-recruitment of cDC1s leading to a cold tumor microenvironment that shows resistance to immune checkpoint inhibitors; Scenario C describes Ecadherin inhibition and upregulation of SNAIL and ZEB1 leading to EMT and metastasis

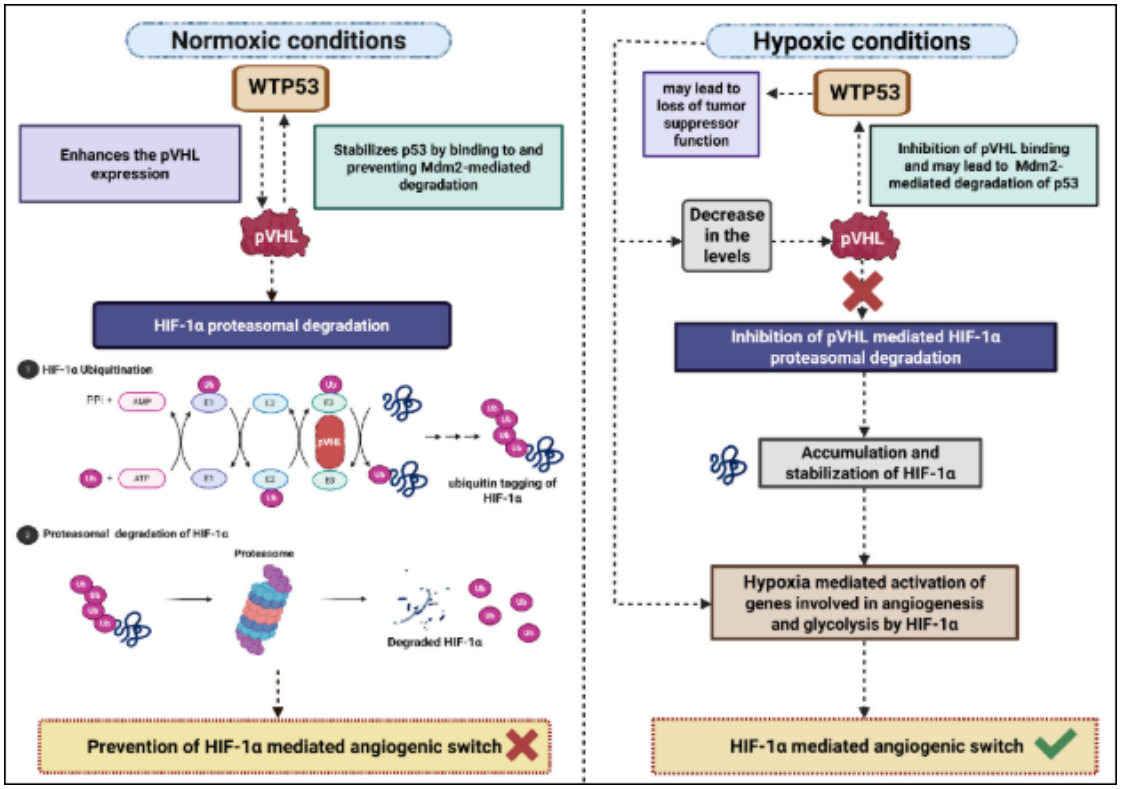

Figure 3

describes the p53 context-dependent effect of pVHL-mediated E3 ubiquitin ligase on HIF-1α under normoxic conditions and hypoxic conditions. Under normoxic conditions, pVHL causes ubiquitination and proteasomal degradation of HIF-1α, preventing the HIF-1α-mediated angiogenic switch. Under hypoxic conditions, inhibition of pVHL-mediated HIF-1α proteasomal degradation causes accumulation and stabilization of HIF-1α and activation of hypoxia-mediated genes by HIF-1α, leading to the angiogenic switch

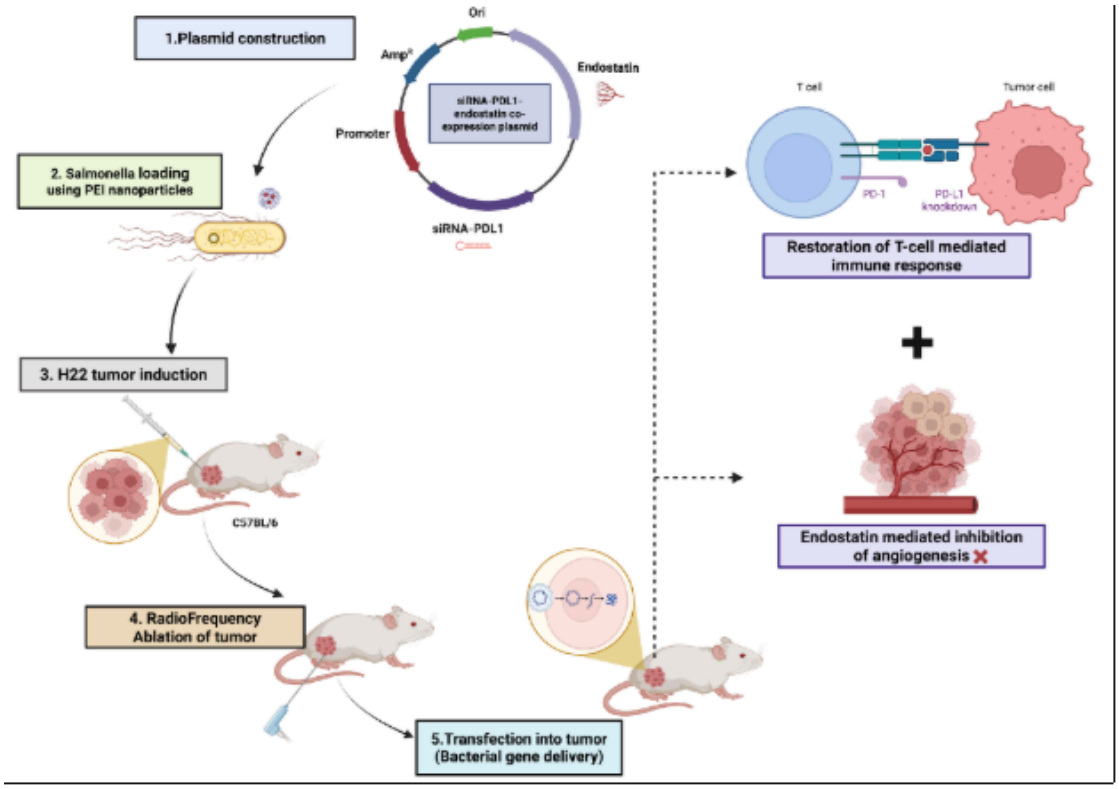

Figure 4

describes the enhanced therapeutic effect of radiofrequency ablation combined with siRNA-PDL1-endostatin co-expression plasmid delivery in H22 tumor-induced C57BL/6 mouse model. The figure describes 1. construction of the siRNA-PD-L1-endostatin co-expression plasmid, 2. Loading of the plasmid using PEI nanoparticles into attenuated Salmonella strain, 3. Subcutaneous H22 tumor induction in C57BL/6 mouse model, 4. Radiofrequency ablation of the induced tumor, followed by 5. Transfection of plasmid into tumor via salmonella-mediated gene delivery. Leading to PD-L1 knockdown and restoration of T cell-mediated immune response and endostatin-mediated inhibition of angiogenesis