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Molecular Pathways and Oncogenic Signalling Mechanisms Underlying HBV- and HCV-Associated Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death globally. Despite the vast amount of information available on HCC, it remains difficult to manage because of its intricate molecular characteristics and aggressive nature. Hepatitis B virus (HBV) and hepatitis C virus (HCV) together account for an estimated 80% of hepatocellular carcinoma (HCC) cases worldwide. A detailed understanding of the molecular events and signalling pathways involved in HCC is imperative for understanding the possible therapeutic options. Given the strong epidemiological link between hepatitis viruses and HCC associated with oncogenic progression, many years of research have aimed to understand these complex processes. Viral oncoproteins from both HCV and HBV are key targets in the anticancer paradigm. Unchecked proliferation, aberrant cycling and recurrence of hepatic carcinoma cells occur when canonical signalling networks are subverted. This review provides a synthesis of the last few years of findings on the multiple molecular pathways involved in modulating HCC in the context of HBV and HCV infection.

Keywords:
Hepatitis C virus, hepatitis B virus, hepatocellular carcinoma, molecular pathway, human disease, liver cancer, molecular oncology, oncogenic signalling pathways

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Introduction

Hepatocellular carcinoma (HCC) is among the top three most common malignancies worldwide and the third leading cause of cancer death, but its clinical outcome is dismal because of the limited availability of effective therapeutic modalities. High incidences of HCC have historically been reported in Asian and African jurisdictions; however, in recent years, a clear increase in the incidence of this disease has been noted in countries such as the United States (El-Serag HB et al., 2024). Specifically, the viral proteins encoded by hepatitis B virus (HBV) and hepatitis C virus (HCV), immunologically mediated killing of infected hepatocytes, and simultaneous hepatic regeneration in patients who are chronically infected with both HCV and HBV and who are highly susceptible to HCC, strongly impact hepatocytic transformation. Approximately 257 million individuals worldwide live with chronic hepatitis B (CHB), with 48–60 million individuals also having HDV and an estimated 2.6 million individuals additionally infected with HCV (Miao et al., 2020).
With respect to viral hepatitis infections, coinfection with HBV and HDV results in the most severe form of liver disease, with the highest mortality rate (20%) due to acute liver failure, cirrhosis, and HCC. HCC is more likely to develop in individuals coinfected with HBV and HCV than in those infected with only one of these viruses. It is well known that infectious agents cause approximately 80% of hepatocellular carcinoma (HCC) cases. Moreover, the incidence of HCC and associated mortality increased to 24 and 1%, respectively, in patients with HBV/HCV coinfection compared with those with HBV monoinfection, further confirming the contributory role of these viruses in oncogenesis and tumor biology (Dimri M & Satyanarayana A, 2020). Owing to more severe liver damage and a quicker progression to cirrhosis than with a single virus, coinfection with HBV-HCV or HCV-HIV dramatically increases the likelihood of developing hepatocellular carcinoma (HCC), also known as liver cancer. HIV-induced immune suppression exacerbates HCV-induced liver damage, accelerating the development of cirrhosis and end-stage liver disease. Several signalling pathways are disrupted in hepatocellular carcinoma (HCC), contributing to uncontrolled cell growth and dissemination to the metastatic site. The inhibition of signalling pathways that mediate the HCC phenotype, such as dysregulation of proliferation, motility and metastatic potential, has the potential to slow disease progression (Wang et al., 2024). The exact molecular mechanisms and intercellular interactions that lead to hepatocarcinogenesis are not fully characterized, especially with respect to genomic aberrations; recurrent genetic alterations are present in more than 20–30% of tumors and are not easy to identify.

Chronic viral hepatitis infection and HCC

Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) and a combination of demographic factors such as age and sex, genetic predisposition and aflatoxin exposure are the key

factors that regulate the course of hepatic disease. While hepatocellular carcinoma (HCC) is known to sometimes develop in the context of chronic HBV infection without the presence of changes in cirrhosis, having cirrhosis is the most significant risk factor for the pathogenesis of HCC (Chao et al., 2020). Long-term HCV infection may induce steatohepatitis, which leads to increased fibrogenesis and promotes the development of cirrhosis. In HBV-associated HCC, the p53 and pRB pathways are often dysregulated; p53 DNA binding and transcription factor activities are inhibited by the viral HBV-X protein (HBx). The expression of neurogenic locus Notch homologue protein 1 (NOTCH1), which promotes the growth of HCC cells and may thus contribute to the carcinogenic process of HBV-associated HCC, is stimulated by the HBV HBx protein. As hepatic pathology progresses to HCC, an array of driver mutations, such as those of CTNNB1, AXIN1, the NFE2L2/KEAP1/RPS6KA3 axis, ARID1A/ARID2, KAK1, TP53, and telomerase reverse transcriptase, might occur, thus promoting oncogenic progression (Fig. 1).

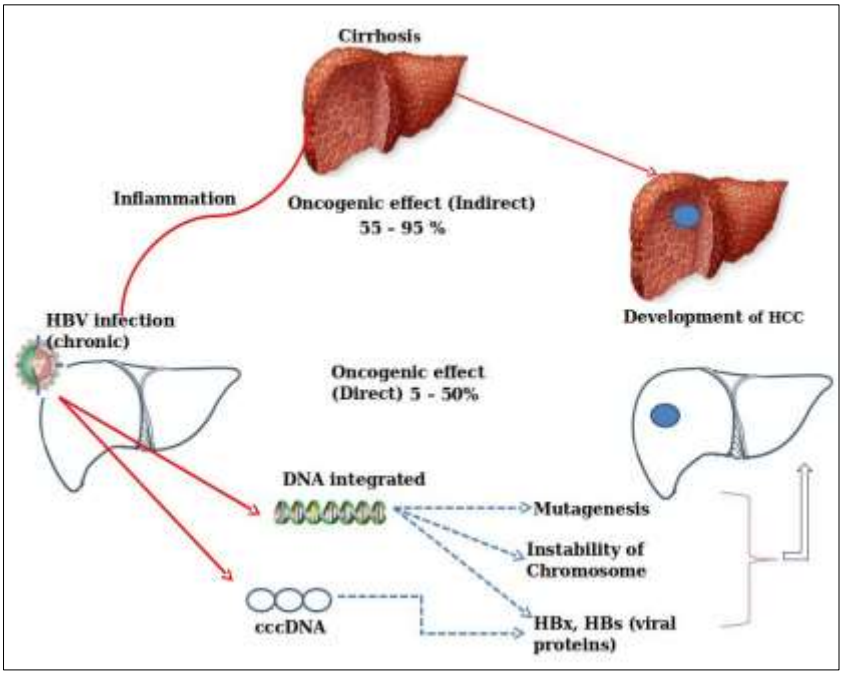

Fig. 1. Chronic viral hepatitis infection and HCC

Development of HCC with HBV and HCV Infection

Globally, virus-induced HCC is more prevalent; however, there is a clear distinction between HCC caused by HBV or HDV and that resulting from HCV. In countries with low to moderate human development, human papillomavirus and hepatitis B virus are more frequently associated with head and neck cancer, whereas HCV-induced HCC is more common in nations with a low human development index (Hong et al., 2020). The development of HCC, HBV, and HCV involves various mechanisms, with the most common mechanisms associated with these viruses being

I) Immune-mediated oxidative stress damage and persistent liver inflammation from chronic viral infection

II) The viral proteins Hbx, HCV core, NS3, and NS5A/B are involved in the deregulation of cell signalling pathways.

III) Viral proteins cause oxidative stress in cells.

Integration of HBV DNA

In the life cycle of HBV, integration is not a crucial phase, although reverse transcriptase is utilized for replication. Typically, the reverse transcription of pgRNA results in the formation of rcDNA with an incomplete double strand. In rare cases, when rcDNA is not produced, double-stranded linear DNA is generated instead. rcDNA acts as a DNA source to replenish the cellular chloroplast complementary DNA (cccDNA) pool, playing a role in the production of viable virions that generally infect new hepatocytes. In individuals with acute HBV infection and very young children, integration of dsDNA is observed in infected hepatocytes. Genomic instability is a hallmark of cancer. Through viral integration, HBV can trigger genomic instability, leading to cellular transformation. In non-HCC

patients, HBV integration sites were not evenly distributed, and there were no enriched sequence mutations. In most chronic HBV-associated HCC cases, gene copy number variations and chromosomal rearrangements contribute to chromosomal instability (Sigafoos AN et al., 2021).

Viral proteins and oxidative stress

Individuals with chronic hepatitis C virus (HCV) infection, similar to those with hepatitis B virus (HBV) infection, show a reduction in antioxidant enzyme activity in line with an increase in oxidative stress both in the blood circulation and in liver tissue. Persistently increased oxidative stress is usually linked to the generation of protein and DNA crosslinks, lipid peroxidation, and an increase in reactive oxygen species, especially free oxygen radicals. The HCV core protein, the nonstructural proteins NS4B and NS5A and the envelope glycoproteins E1 and E2 are involved in the induction of oxidative stress. NS4B, in association with the viral glycoproteins E1 and E2, precipitates the unfolded protein response inside the endoplasmic reticulum and, in this manner, stimulates the production of hydrogen peroxide and the release of calcium (Zhang et al., 2020).

HCC characterization

Hepatocytes and liver cells are involved in hepatocellular carcinoma (HCC), and hepatocytes and liver cells are known to be involved. The tumor microenvironment can inappropriately activate certain signalling pathways because of disruptions in extracellular signals or intracellular regulators. This leads to increased gene expression levels and abnormal epigenetic changes in cancerous hepatocytes, resulting in the loss of differentiated or mature hepatocytes. Under these conditions, E-cadherin expression is downregulated, and the cytoskeleton undergoes reorganization, whereas the upregulation of key transcription factors such as ZEB, Snail, and Twist induces a mesenchymal cellular phenotype and triggers epithelial-to-mesenchymal transition (EMT). The expression of matrix metalloproteinases (MMPs) is increased for angiogenesis and cell migration (Farzaneh et al., 2021). In hepatocellular carcinoma (HCC), telomerase activity is elevated by 90%, apoptotic mechanisms are suppressed, and cell cycle control is disturbed, which results in metastasis, increased cell survival and uncontrolled proliferation.

Signalling Pathways of HCC

n hepatocellular carcinoma (HCC), dysregulation of several signalling pathways, including the Hedgehog (Hh), EGF, Notch, TGF-β, HGF, Wnt/β-catenin, JAK/STAT, HIF, Hippo, and VEGF signalling pathways, leads to uncontrolled cell proliferation.

Hedgehog (h) signalling

Following liver injury, Kupffer cells and hepatocytes release Sonic Hedgehog (SHH) ligands. The SHH pathway is also activated by the presence of HBV. SHH activates smooth receptors and interacts with the Ptch receptor, initiating nuclear translocation factors, glioma proteins, and signalling cascades. In hepatocellular carcinoma (HCC), SHH induces the expression of genes specific to cancer stem cells, as well as those related to invasion and the cell cycle, such as c-Myc and cyclin D. Gli enhances tumor angiogenesis and VEGF expression (Wang et al., 2020). SHH also promotes metastasis and epithelial–mesenchymal transition (EMT) through interactions with the Notch and TGF-β pathways. The expression of the HCC cell lines HepG2, Sk-Hep1, Huh7, Hep3B, Gli, and Smo was notably increased. Cyclopamine inhibits GANT61 and SMO.

ermal growth factor (EGF) signalling

Abnormal activation of the EGF pathway results in the secretion of paracrine and autocrine factors, which subsequently stimulate cell proliferation and migration. Upon binding to its receptors, EGF initiates downstream signalling that activates the MAPK/ERK, P38/MAPK, and PI3K/Akt pathways. EGFR is frequently overactivated in hepatocellular carcinoma (HCC). Additionally, the epidermal growth factor (EGF) signalling pathway promotes the influx of inflammatory cells to secrete interleukin (IL). SHBM1009 and BEZ-235 are competitive inhibitors of PI3K, whereas U0126 is an ERK antagonist. EGCG generally inhibits the PI3K/Akt, MAPK/ERK and epidermal growth factor receptor (EGFR) signalling pathways (Jung Y-S & Park J-I, 2020).

Notch signalling

In hepatocytes, the Notch signalling pathway is regulated by the stimulation of two receptors located on neighboring cells, one of which is a Notch receptor and the other acts as a ligand. Cleavage of the Notch receptor by gamma-secretase is then followed by the translocation of the Notch receptor to the nucleus, where it binds transcription factors. The expression of markers that are linked to cancer cell proliferation, apoptosis, and invasion is regulated by genes in the Notch pathway, such as cyclin-D, p53, c-Myc, and Hes1. Moreover, the invasive characteristics of separate HCC cell lines are related to the level of Notch pathway activity. The inhibition of gamma secretase activity is usually performed with PF-03084014 or other gamma secretase inhibitors (GSIs). The inhibition of Notch3 and the modulation of tyrosine kinases increase apoptosis in HCC cells and promote the accumulation of p53 protein (Liu et al., 2020).

Transforming growth factor-β signalling

In liver tumors, cancer-associated fibroblasts (CAFs), which are derived from hepatocytes or stromal cells, are the major source of secreted transforming growth factor-beta (TGF-beta). Usually, the binding of TGF-beta to its cognate receptors leads to the phosphorylation of TbetaR1 and TbetaR2 and, in turn, activates the Smad2/3 complex. These phosphorylated proteins, together with Smad4, move to the nucleus. TGF-beta induces epithelial–mesenchymal transition (EMT) in polarized hepatocytes through upregulation of Snail expression and downregulation of E-cadherin expression. The TGF-beta signalling axis is involved primarily in the proliferation of hepatocellular carcinoma (HCC) cells and in the maintenance of the cancer stem cell (CSC) subpopulation. This cascade also causes endothelial cells to accumulate at the tumor site and promotes the expression of growth factor, FGF, or vascular endothelial growth factor (VEGF). In HCC, TGF-beta, which acts together with the Wnt, SHH and EGF pathways, enhances the mesenchymal nature of cell lines. TGF-v reprograms tumor-associated macrophages into M2-like phenotypes and thus increases neo-angiogenesis, proliferation and metastasis in HCC (Wang W et al., 2019).

Hepatocyte growth factor (HGF) signalling

HGF plays a vital role in the metastasis, development, and survival of HCC cells. The interaction between the c-Met receptor and HGF triggers the activation of the PI3K, Jnk/Stat3, and ERK pathways. Clinical trials targeting liver tumors have evaluated the effectiveness of c-Met inhibitors such as tepotinib and capmatinib. In HCCLM3 and MHCC97 cells, c-Met is notably overexpressed. The entire process of hepatocarcinogenesis is thought to involve the cooperation of multiple cellular mechanisms, including alterations in the tumor microenvironment, necroinflammation, oxidative stress, and hypoxia, as well as additional molecular mechanisms, such as transcription and activation of growth factors, chemokines, and cytokines; DNA damage; and DNA methylation. Numerous clinical and epidemiological investigations have shown a clear link between the development of cancer and inflammation. The use of c-MET inhibitors such as PHA665752, AMG 337, and 3-(1H-benzimidazole-2 methylene)-5-(2-methylphenylaminosulfo)-2-indolone (Indo5) has been shown to decrease tumor growth, HCC proliferation, and migration (Koni et al., 2020).

Wnt/B-catenin signalling

In liver tumors, macrophages and HCC cells have emerged as novel sources of Wnt ligands. Mutations in various components, often caused by environmental risk factors, can lead to overactivation of Wnt signalling. When lipoprotein receptor-related protein (LRP) receptors and Frizzled (Fzd) bind to the Wnt ligand, Disheveled is phosphorylated. This process, along with receptor activation, prevents the degradation of the axis inhibition protein (Axin) and complex proteins such as GSK3β and adenomatous polyposis coli (APC), thereby releasing β-catenin (Kim et al., 2023). The binding of activated β-catenin to the histone acetyltransferase CREB-binding protein (CBP)/p300 or T-cell factor (TCF) proteins and lymphoid enhancer factor (LEF) initiates the transcription of numerous target genes. LGR5 plays a significant role in HCC metastasis and the Wnt/β-catenin pathway. High levels of LGR5 expression have been observed in HepG2 and PLC cell lines. Wnt/β-catenin also contributes to the regulation of angiogenesis in liver tumors. Additionally, β-catenin activation can be induced by hypoxic conditions, HGF, and TGF-β. Targeting this pathway at the receptor–ligand level can activate HCC (Han Z et al., 2020). Inhibitors of the CBP-β-catenin interaction can induce CSC differentiation (Fig. 2).

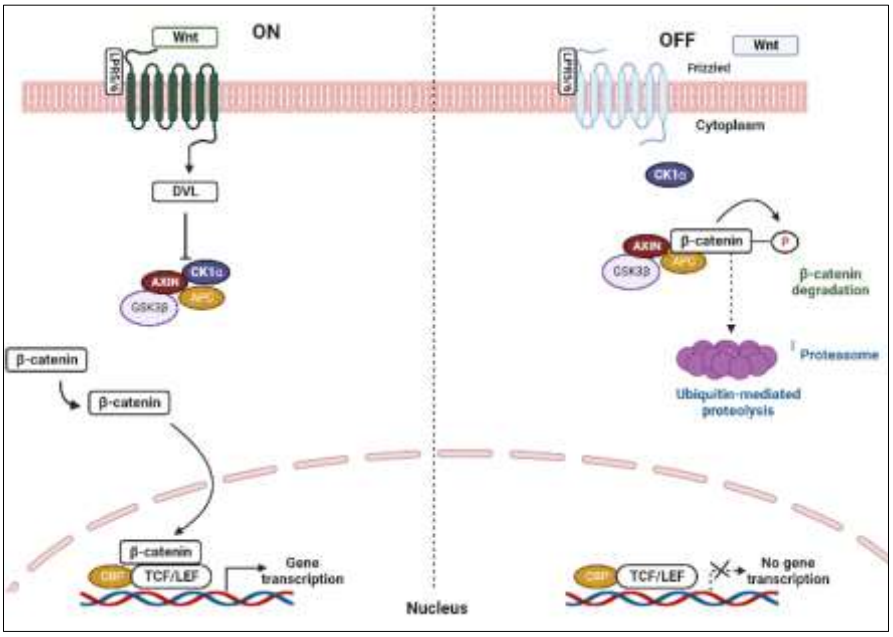

Fig. 2. Wnt-β-catenin pathway in cancer.

Janus kinase (Jak)/Stat3 signalling

Inflammatory cytokines such as HGF, EGF, TGF-β, tumor necrosis factor (TNF), and interleukins activate the Jak/Stat3 pathway. Stat3, which functions as a transcription factor, facilitates angiogenesis, tumor survival, metastasis, and proliferation in HCC (Hou et al., 2020). HIF-1a enhances vascular endothelial growth factor (VEGF) expression and promotes angiogenesis, which plays a significant role in signal transduction pathways in HCC. In addition, HIF-1a mediates the interaction between TGF-v and its receptors, which promotes cell proliferation and HCC survival. Hypoxia promotes downstream Notch target gene activation along with HIF-1a recruitment in HCC metastasis and simultaneously modulates the hedgehog (Hh) pathway. In addition, the Wnt signalling pathway also induces the upregulation of HIF-1a in HCC. Yes-associated protein (YAP) is known to interact with HIF-1a and stabilize it. Pharmacologic inhibition with PT2385 downregulates HIF-activated proteins such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), extracellular signal kinase (ERK), and signal transduction and activation of transcription 3 (STAT3) (Park H et al., 2023).

Hippo signalling

The YAP signalling pathway is activated by several growth factors, such as epithelial growth factor (EGF), Notch, Wnt, and SHH. Following activation, YAP moves into the nucleus, where it interacts with the transcriptional coactivator TEAD and PDZ-binding motif, ultimately resulting in increased metastasis, cell proliferation, and inhibition of apoptosis in hepatocellular carcinoma. Increased levels of TAZ and YAP have been reported in hepatocellular carcinoma cell lines and in a range of hepatic tumor cells. Activation of the Hippo pathway leads to the phosphorylation of several kinases. In the field of anticancer strategies, inhibition of the transcriptional activities of TAZ, TEAD and YAP is often sought (Mu H et al., 2020). Verteporfin disrupts the interaction between TEAD and YAP in the complex.

VEGF signalling

Growth factors released by hepatic neoplasms trigger angiogenesis, hence ensuring a sufficient supply of oxygen and nutrients. Several families of signalling cascades, such as those involving VEGF, PDGF, HGF and FGF, trigger this angiogenic process. VEGF interacts with RTK in an autocrine manner, leading to the activation of PI3K and Akt in HCC. Sorafenib inhibits the FGF, PDGF, and VEGF pathways, thereby reducing neovasculogenesis in HCC. Tyrosine kinase inhibitors (TKIs) are examples of targeted medicines that target signalling pathways in HBV/HCV-induced HCC. These strategies, which are frequently combined, involve blocking the Ras/Raf/MAPK and VEGF/VEGFR pathways, which promote angiogenesis, metastasis, and cancer progression. To lower the risk of developing HCC, direct-acting antivirals (for HCV) and nucleos(t)ide analogues (for HBV) are utilized

for viral clearance. Additionally, the use of a TGF-β inhibitor in HCC results in decreased neovascularization and VEGF secretion (Ramalingam et al., 2025).

HBV and HCV Metabolic Signalling Pathways in Hepatocarcinogenesis

Wnt/β-catenin signalling in HBV

Mutations in the CTNNB1 gene, which encodes β-catenin, are linked to more than 40% of HBV-HCC cases. Like activated Wnt/β-catenin, the tumor suppressor gene APC becomes inactive because of hypermethylation. This was demonstrated by the altered expression of proteins in the Wnt/β-catenin metabolic pathway in HBV-related HCC. In tumor tissues, compared with those in nontumoral mucosa, the expression of Wnt/β-catenin regulators such as Frizzled 2, Frizzled 7, segment polarity protein disheveled homologue DVL-3, secreted frizzled-associated protein 4, Wnt-1 inducible signalling pathway protein 1, transducin-like enhancer protein, naked cuticle 1 (NKD1), and NKD is increased. Hbx protein promotes the Wnt metabolic pathway by repressing SFRP1 and SFRP5, which subsequently inhibits E-cadherin through various mechanisms, including promoter hypermethylation, changes in SNAIL gene expression, and Src signalling activation. Conversely, the interaction of HBx with APC disrupts β-catenin degradation. The Wnt signalling pathway is further unnaturally activated by inhibiting the activity of the GSK3b-reducing complex and increasing the expression of URG7, leading to the upregulation of genes such as c-myc, CTFG, and WISP2. The differential expression of HBsAg between normal and cancerous tissues (cytoplasmic versus nuclear) suggests its involvement in the Wnt pathway during carcinogenesis (Pobbati AV & Hong W. 2020).

Wnt/ß in HCV

Mutations in CTNNB1 are strongly enriched in hepatocellular carcinoma (HCC) associated with hepatitis C virus (HCV), with an incidence of approximately 26% compared with 12% in hepatocellular carcinoma (HCC) caused by hepatitis B virus (HBV) and 21% in nonviral hepatocellular carcinoma. This trend is supported by empirical studies that have shown that changes in CTNNB1 expression occur after an HCV infection. They are mutations that are involved in the effects of impairments in DNA repair processes triggered by the HCV NS3 protein, which may trigger oncogenic transformation. Notably, these observations are quite surprising, especially considering that the virus does not incorporate its genetic content into the host DNA; hence, additional studies are needed to obtain conclusive evidence to determine causality. Even though CTNNB1 mutation is a key factor in the pathogenesis of HCV-induced oncogenesis, other HCV proteins affect the establishment of Wnt/catenin metabolism signalling pathways. One such protein is the core protein, which can activate this pathway by affecting nuclear hepatocyte transcription factors (Lugano et al., 2020).

NF-κB pathway in HBV

NF-B comprises five proteins: NF-B1 (p105/p50), NF-B2 (p100/p52), Rel A (p65), cRel, and RelB. Each of these proteins features a Rel homology region for nuclear localization, and three of them (p65, cRel, and RelB) also have a transactivation region. Shokri et al.'s recent study explored this component further, emphasizing the role of viruses in the NF-B pathway. The abnormal expression of genes in these pathways is crucial for carcinogenesis and tumor progression, highlighting their importance in vital biological processes. Given the success of NF-B inhibitors in treating other cancers, they may also be effective against HCC. Studies have shown that HBx activates NF-kB by affecting both related and unrelated proteins. HBx induces a sustained NF-B response by enhancing IKB phosphorylation and degradation and releasing Rel-A, which is achieved by reducing the cytoplasmic levels of p105 and p50. Additionally, by substituting p50, HBx can initiate the NF-κB pathway (Hamdy et al., 2020).

NF-κB pathway in HCV

In HCV-HCC, NF-κB is involved in liver inflammation, fibrosis, cancer development, and tumor formation. HCV's impact on this pathway can be both suppressive and stimulatory. Previous studies have shown that NF-B is overexpressed in individuals infected with HCV. Activation of this pathway necessitates the triggering of the TNF receptor (TNFR), whose core proteins can achieve this activity either directly or by mimicking proinflammatory cytokines such as TNF. Viral proteins facilitate the phosphorylation of extracellular signal-regulated kinases (ERKs), p38 mitogen-activated protein kinases (MAPKs), and c-Jun N-terminal kinases (JNKs), all of which support NF-κB activation. Once active, NF-B enters the nucleus and activates numerous genes, including cyclooxygenase-2 (COX-2)

and interleukin-8 (IL-8) (Tang W et al., 2020). In contrast, COX-2 suppresses NF-B activity by inhibiting the production of prostaglandins J2, A2, and A1 (Fig. 3).

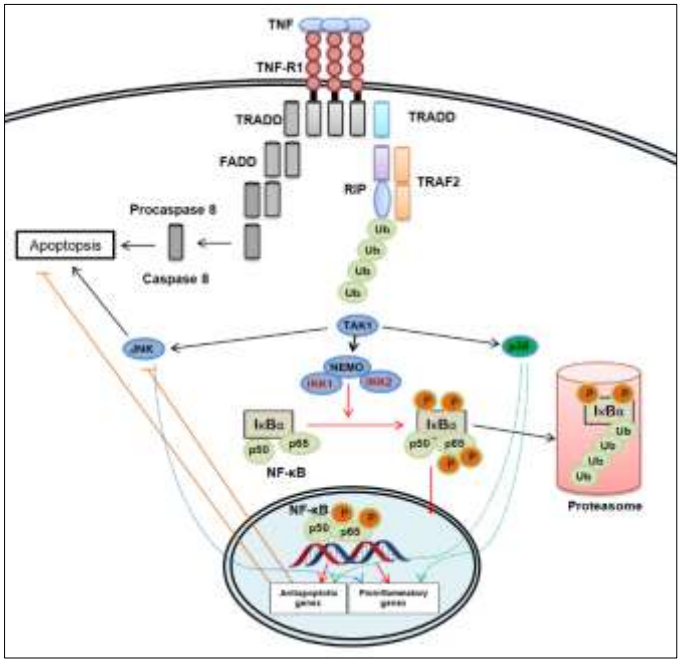

Fig. 3. NF-κB in the liver.

Hippo-YAP/TAZ pathway in HBV

Deactivation of the Hippo–YAP/TAZ pathway in the liver is associated with fibrosis, liver cancer development, and tumor characteristics. In a recent study, Moon et al. explored the role of viruses in the Hippo–YAP/TAZ pathway. The Hippo pathway, which is primarily composed of a protein complex, is widely acknowledged as a vital tumor suppressor. In the absence or inhibition of this pathway, YAP and TAZ in the nucleus regulate the activation of transcription factors that are crucial for processes such as cell division, survival, miRNA processing, metastasis formation, and stem cell maintenance. Evidence indicates that miR levels and nuclear YAP expression can predict HBx expression in HCC tissues. By increasing the expression of FOX-1A and male-specific lethal 2 (MSL2), a ubiquitin E3 ligase, HBx influences p53 and the ubiquitination of histone H2B, which plays a role in transcriptional regulation (Ayele A, et al., 2020).

Hippo-YAP/TAZ in HCV

Like studies on HBV-related head and neck cancer, studies on hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) have predominantly concentrated on the Hippo–YAP-1 signalling pathway. The NS5B protein of HCV seems to promote epithelial–mesenchymal transition (EMT) by inhibiting Hippo signalling, which in turn enhances Snail activity and facilitates PI3K/AKT activation. Some studies suggest that the HCV E2 protein imitates the function of CD81, the main receptor for glypican 3, which significantly reduces proliferation by decreasing Hippo activity and YAP expression. Because CD81 acts as an entry receptor for HCV, its removal during the early stages of carcinogenesis allows tumor cells to incorporate HCV during the initial development of HCC, thereby contributing to the unchecked proliferation of tumor cell clones, unlike nontumorigenic cells (Kamali et al., 2021).

Angiogenesis pathways in HBV

In hepatocellular carcinoma (HCC), standard chemotherapy regimens are often not effective, largely because of the high degree of cellular heterogeneity in tumors, which is supported by the underlying angiogenic signalling pathways. As such, a faster transformation toward the creation of targeted interventions that are selective for disrupting the vasculature, which is an aspect that would remain relatively stable during the therapeutic course, has been observed in the field. RTK signalling pathways and other routes constitute the two primary types of cellular signalling pathways in HCC cells. These two types of pathways play crucial roles in activities such as cell migration, proliferation, and survival when examined in preclinical and clinical settings. Developing targeted treatments and improving

cancer treatment approaches could benefit from an understanding of these pathways. The current therapeutic paradigm for HCC focuses on antiangiogenic agents; in particular, the upregulation of vascular endothelial growth factor (VEGF) has been shown to occur in HBV-induced models of HCC in mice, which is empirically supportive of the strategic target of this process. In HBV-HCC tumor tissues, both COX-2 and VEGF levels were elevated, and VEGF expression was linked to the density of microvessels, an indicator of angiogenesis. HBx is a major inducer of VEGF expression in HBV-HCC cells. This protein enhances VEGF production in transfected cells and other cell cultures by stabilizing HIF or activating mTOR and IKK. In addition to VEGF, it triggers mitogen-activated protein kinase (MAPK) in liver tissue, leading to increased production and secretion of angiopoietin-2 (Ang-2) (Karaşahin EF et al., 2021).

Angiogenesis pathways in HCV

Although the core protein of HCV is most notably linked to angiogenic processes, it is only one of several HCV components that influence hepatocarcinogenesis. Activation of growth factor signalling pathways leads to elevated levels of angiogenic factors, including VEGF and angiopoietin-2 (Ang-2). It has been suggested that the core protein stimulates STAT3, thereby enhancing VEGF production via transcription mediated by the androgen receptor. However, some studies have not reported an increase in STAT3 expression despite the established connection between androgen and VEGF expression. These discrepancies may be attributed to variations in the experimental setups that also include core protein genotypes. Similarly, the involvement of core proteins in the PIK3 and MAPK pathways during VEGF stimulation has yielded inconsistent results. Recent research suggests that the proangiogenic effect of the HCV core protein is dose dependent and involves an increase in vascular endothelial growth factor. Additionally, the core protein initiates angiogenesis, resulting in increased expression of endoglin (CD105), which is crucial for TGF-β signalling (Kazmi et al., 2022).

Liver Inflammation by HBV and HCC

Damage to the liver, resulting from the immune system's attack on HBV-infected liver cells and subsequent liver regeneration, is the most common cause of the development of HBV-related HCC. The infiltration of immune cells and elimination of HBV-infected hepatocytes are associated with liver injury. In chimpanzees, the initial wave of immune cells can take up to three months after experimental HBV infection. Before the arrival of immune cells, HBV can infect most liver hepatocytes, and innate immune responses can effectively clear the virus without causing cellular damage. Studies in chimpanzees have elucidated the processes leading to chronic HBV infection and its clearance, although the number and scope of these studies are limited by cost and ethical considerations. Furthermore, cirrhosis and HCC are not typically observed in chimpanzees with persistent HBV infections. HBV-transgenic mice serve as a crucial, experimentally manageable model system; numerous research groups have produced and studied these mice (Wanlapakorn et al., 2025). Continuous attempts are being made by the host immune system to destroy HBV-infected hepatocytes. Insufficient HBV infection leads to continuous hepatocyte proliferation and liver regeneration. High levels of reactive oxygen species (ROS) can cause mutagenesis directly by causing injury to DNA at specific loci, especially in a chronic inflammatory background.

Chronic inflammation caused by HCV-related HCC

A widely accepted explanation for HCV-induced liver cancer is continuous liver damage. This theory is supported by multiple lines of evidence: 1. HCV is an RNA virus whose life cycle is completed in the cell nucleus without integration into the host genome; 2. The progression of HCC in HCV-infected individuals is notably slow, taking 30–40 years, as shown by the natural course of infection and epidemiological studies, suggesting that the local environment may influence HCC development. Key pro-carcinogenic factors in chronic HCV infection include oxidative stress, steatosis, and insulin resistance (Rodriguez-Montano et al., 2025). Since HCV was identified in 1990, numerous research centers have endeavoured to understand the complex relationship between the host immune response and HCV infection in various experimental settings. Studies have indicated that HCV affects a wide range of signalling pathways, such as oxidative stress, endoplasmic reticulum stress, calcium signalling, transforming growth factor (TGF), p53, RB, Raf/MAPK, and Wnt/β-catenin. As these pathways are also regulated during HBV infection, they suggest common viral mechanisms for liver cancer development. Patients with chronic HCV infection frequently exhibit DNA methylation and iron accumulation. Transgenic mice expressing the HCV polyprotein are prone to developing HCC

when they are exposed to excess iron, which can damage the mitochondria. Some instances of chromosomal abnormalities and oncogene activation in HCV-related HCC can be attributed to insertional mutagenesis (Kowo et al., 2021).

HBV and HCV proteins in HCC Signal Transduction Pathways

H B X Protein

Hepatitis B has an open reading frame, with the X gene encoding the HBx protein, a 154-amino-acid entity whose role in HBV infection remains unclear. In woodchucks, the expression of this protein is crucial for HBV infection and replication in vitro (Mazhar et al., 2021). Although HBx does not directly bind to DNA, it influences gene transcription by activating various viral and cellular transcriptional components, including transcriptional regulators, such as promoters and enhancers, as well as transcription factors and proto-oncogenes (Odimayo et al., 2020). However, studies on HBx-transgenic mice have not demonstrated a predisposition to HCC. In certain mouse strains, the HBx protein was undetectable in the liver, whereas in others, it was only sporadically expressed. These findings indicate that cancer development may require prolonged HBV infection with sustained HBx production (Son et al., 2021). The "second-hit theory could also be relevant. Chronic HBV infection accompanied by ongoing inflammation may increase the risk of mutations leading to cancer in the presence of HBx. This notion is supported by evidence showing that chemical shock to the liver (using diethyl nitrosamine) results in increased tumor occurrence and size in HBx-transgenic mice. Similarly, the formation of liver tumors accelerated when c-Myc-transgenic mice were crossed with HBx-transgenic mice. Hbx-induced oncogenesis has been linked to various cell signalling pathways and transcription factors (Fig. 4).

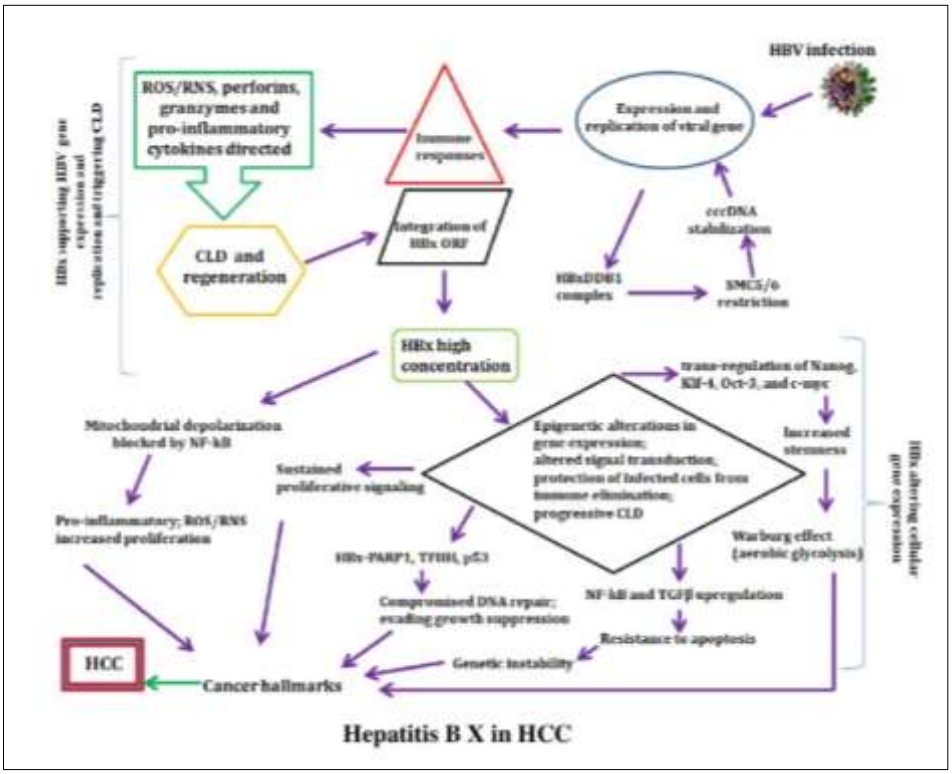

Fig. 4. Hepatitis B X in HCC 3

HCV Core Protein

The HCV core protein, comprising 191 amino acids, has a molecular mass of 23 kDa. Known as p23, this peptide is located near the start of the HCV polyprotein. It is cleaved from the polyprotein and processed into its mature form, p21, with a mass of 21 kDa, by a cellular signal peptidase (Sung H et al., 2021). The p21 core protein is believed to form a viral capsid, which likely plays a role in the assembly and packaging of the HCV RNA genome, although its exact function remains unclear. Immunohistochemistry revealed increased core protein expression in tumors compared with that in the surrounding tissue when tumors were induced in the livers of mice. Hepatic tumors were not observed in transgenic mice carrying E1 and E2 HCV envelope genes or those carrying the gene encoding all

nonstructural envelope components. Lerat et al. also created transgenic C57BL/6 lines expressing full-length HCV polyproteins or structural proteins (core, E1, and E2p7) (Agwa RH et al., 2022). By 13 months of age, several animals developed hepatocellular tumors (Fig. 5).

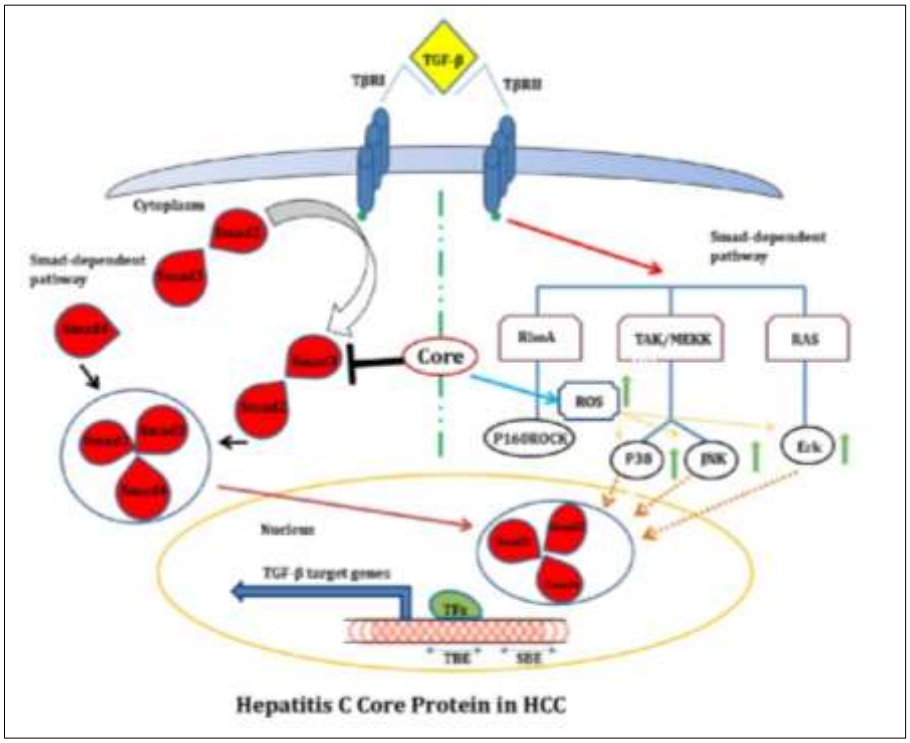

Fig. 5. Hepatitis C Core Protein in HCC

Extensive animal model research has indicated that chronic synthesis of the HCV core protein is linked to an increased risk of malignant transformation in hepatocytes. The mechanisms involved include ongoing inflammation, necrosis, regeneration/repair, and accumulated mutations that may act independently or in combination. Research involving transgenic mice has experimentally confirmed the role of the HCV core protein in cancer development, a conclusion supported by in vitro studies. Immunohistochemical analysis revealed that the core protein was located primarily in the nucleus (Sivalingam AM, 2025). An existing REF cell line was used for cotransfection, and an altered phenotype was observed, with the 19 kDa product exclusively produced by these cells. These findings support the hypothesis that the HCV core protein plays a role in oncogenic transformation, either independently or in conjunction with other factors (Balakrishnan et al., 2025).

In a previous study, Huh-7 cells were transfected with the HCV 1b core protein, resulting in increased transcription of Wnt-1 and WISP-2. This effect is the result of rapid increases in proliferation, increased DNA replication, and cell cycle progression in such cells. Downregulation of Wnt through siRNA has an inhibitory effect on cell growth. The presence of secreted Wnt-1 in the supernatant of these core-transfected cells suggests that these cells can stimulate proliferation. In addition, ectopic expression of Wnt-1 in Huh-7 cells can result in a significant increase in growth (Nagarjuna D & Karthikeyan E, 2025; Goyal K et al., 2025).

Conclusion

Different signalling pathways should be targeted strategically to manage hepatocellular carcinoma (HCC) malignancy. However, the dysregulation of many key pathways in HCC promotes antiapoptotic resistance mechanisms, metastasis, vasculogenesis, and cell cycle progression. Current treatment options for HCC include immunotherapeutic regimens, multikinase inhibitors, angiogenesis inhibitors and pathway-specific therapies. The epidemiologic relationships among hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatocellular carcinoma are strong, and it is important to elucidate the molecular mechanisms that contribute to prognosis and oncogenesis. An understanding of the mechanisms and pathways of HBV-associated and HCV-associated carcinogenesis can aid in the

identification of new therapeutic targets and thus sharpen the prognostic weaponry in the case of HCC.

Author Contributions
All the authors contributed equally.

Conflict of Interest
The authors declare that they have no conflicts of interest.

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