Advanced Pharmaceutical Bulletin

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

Review Article

How to cite this article:
Bindra S, Kumar S, Nair AS, Bhaskar V, Sudan KM, Nath LR, Maliyakkal N, Parambi DG, Kumar A, Mathew B, Pappachen LK. Hepatocellular Carcinoma Therapy and Mechanism of Action: Current Perspectives. Advanced Pharmaceutical Bulletin, doi: 10.34172/apb.46537

Hepatocellular Carcinoma Therapy and Mechanism of Action: Current Perspectives

Sandeep Bindra[1], Sunil Kumar[1], Athira Sujathan Nair[2], Vaishnav Bhaskar[1], Krishnadas Madhu sudan[3], Lekshmi R Nath[4], Naseer Maliyakkal[5], Della Grace Thomas Parambi [6], Arun Kumar[7], Bijo Mathew[1*], Leena K Pappachen[1*]

[1]Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Amrita Health Science campus, Kochi 682041, India. [2]School of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, Selangor, Malaysia. [3]Department of Pharmacology, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Amrita Health Science campus, Kochi 682041, India. [4]Department of Pharmacognosy, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Amrita Health Science campus, Kochi 682041, India. [5]Department of Basic Medical Sciences, College of Applied Medical Sciences, Khamis Mushait, King Khalid University, 62569, Kingdom of Saudi Arabia. [6]Department of Pharmaceutical Chemistry, College of Pharmacy, Jouf University, Sakaka, Aljouf 72341, Saudi Arabia. [7] School of Pharmacy, Sharda University, knowledge Park III Greater Noida, India.

ARTICLE INFO

Keywords:
Hepatocellular carcinoma,
Liver cancer,
Lipid metabolism,
Stem cell,
Chemotherapy,
Targeted therapy

Article History:
Submitted: October 27, 2025
Revised: August 03, 2026
Accepted: August 14, 2026
ePublished: September 09, 2026

ABSTRACT

Purpose: Hepatocellular carcinoma (HCC) is the most common primary liver cancer, accounting for nearly 90% of cases and causing over 700,000 deaths annually. Increasing evidence indicates that dysregulated lipid metabolism plays a critical role in hepatocarcinogenesis by promoting tumor initiation, progression, metastasis, and drug resistance. This review provides a comprehensive overview of the molecular mechanisms underlying lipid metabolic reprogramming in HCC, highlights key therapeutic targets, and discusses emerging inhibitors with potential for future drug development. **Methods**: A comprehensive literature search was conducted by critically reviewing published research articles, review papers, and clinical studies on lipid metabolism in liver cancer. Current advances were systematically evaluated, focusing on lipid metabolic pathways, associated molecular targets and signaling mechanisms, as well as small-molecule inhibitors, natural products, and clinically relevant therapeutic agents. **Results**: Dysregulated lipid metabolism is a hallmark of HCC, contributing to cancer cell proliferation, survival, angiogenesis, metastasis, immune evasion, and resistance to conventional therapies. Alterations in de novo lipogenesis, fatty acid uptake, fatty acid oxidation, cholesterol biosynthesis, and phospholipid metabolism are frequently observed in HCC. Key enzymes and regulatory proteins, including fatty acid synthase (FASN), acetyl-CoA carboxylase (ACC), stearoyl-CoA desaturase-1 (SCD1), ATP citrate lyase (ACLY), sterol regulatory element-binding proteins (SREBPs), and peroxisome proliferator-activated receptors (PPARs), have emerged as promising therapeutic targets. Numerous synthetic compounds, natural products, and investigational inhibitors targeting these regulators have demonstrated encouraging preclinical and clinical potential for suppressing HCC progression. **Conclusion**: Targeting aberrant lipid metabolism represents a promising therapeutic strategy for HCC. Improved understanding of lipid metabolic reprogramming and its regulatory networks has enabled the identification of novel molecular targets and therapeutic inhibitors. Future studies integrating lipid metabolism with precision medicine may accelerate the development of effective targeted therapies, facilitate early intervention, and improve clinical outcomes in patients with liver cancer.

***Corresponding Authors**
Leena K Pappachen, Email: leenakpappachen@pharmacy.aims.amrita.edu, ORCID: 0000-0001-8980-2648
Bijo Mathew, Email: bijovilaventgu@gmail.com, ORCID: 0000-0002-6658-4497

Introduction

Liver cancer constitutes a major global health burden and remains one of the leading causes of cancer-related mortality worldwide. It predominantly affects individuals over the age of 50 and exhibits a marked male predominance. Hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) account for the vast majority of primary liver cancers.[1,2] Among these, HCC represents approximately 75–85% of cases and typically arises in the context of chronic liver disease. Epidemiological evidence indicates that liver cirrhosis and chronic hepatitis contribute to nearly 80% of HCC cases, with persistent infection by the hepatitis B virus (HBV) and hepatitis C virus (HCV) serving as major etiological drivers.[3–6] Additional risk factors include excessive alcohol consumption, non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), metabolic syndrome, exposure to environmental toxins, and genetic susceptibility. At the molecular level, hepatocarcinogenesis is a multistep process driven by chronic inflammation, fibrosis, and sustained regenerative signaling, which together promote genomic instability and malignant transformation. Recurrent activation of oncogenic pathways including VEGF-mediated angiogenesis, EGFR and FGFR signaling, PI3K/AKT/mTOR, Wnt/β-catenin, Hippo–YAP/TAZ, and TGF-β signaling plays a central role in tumor initiation, progression, immune evasion, and therapeutic resistance. In parallel, alterations in tumor metabolism, epigenetic regulation, and the tumor microenvironment further reinforce malignant phenotypes. These mechanistic insights have provided the biological rationale for the development of targeted and immune-based therapies in liver cancer.[7]

Clinically, liver cancer is frequently asymptomatic in its early stages, resulting in delayed diagnosis. As the disease advances, patients may present with nonspecific symptoms such as unexplained weight loss, abdominal pain, fatigue, anorexia, jaundice, and ascites. Diagnostic evaluation relies on a combination of imaging modalities (ultrasound, computed tomography, and magnetic resonance imaging) and serological biomarkers, enabling tumor detection, staging, and treatment stratification. Therapeutic decision-making is influenced by tumor stage, hepatic functional reserve, and patient performance status. Current standard treatment modalities include surgical resection, liver transplantation, loco regional therapies (ablation and trans arterial chemoembolization), radiotherapy, systemic targeted therapies, and immunotherapy.[8] Despite this expanding therapeutic armamentarium, overall survival improvements in HCC have lagged behind those achieved in other malignancies, largely due to tumor heterogeneity, underlying cirrhosis, and adaptive resistance mechanisms. Emerging evidence highlights the critical role of liver cancer stem cells (CSCs) in tumor initiation, metastasis, immune escape, and post-therapy recurrence. CSCs are maintained by dysregulated developmental and survival pathways such as Wnt, Notch, Hedgehog, Hippo/YAP, and TGF-β, rendering them intrinsically resistant to conventional chemotherapy and targeted agents that primarily eliminate differentiated tumor cells.[9] Consequently, contemporary research is increasingly focused on mechanism-driven therapeutic strategies aimed at selectively targeting CSC populations, modulating the tumor microenvironment, and restoring antitumor immunity while preserving normal hepatic stem cell function. In this review, we comprehensively discuss the etiological factors, molecular mechanisms, and signaling pathways underlying liver cancer pathogenesis, with particular emphasis on therapeutic targets and their mechanisms of action. By integrating advances in targeted therapy, immunotherapy, metabolic regulation, and CSC biology, this article aims to provide a mechanistic framework to guide future drug development and improve clinical outcomes in liver cancer.

1. Targeting altered lipid metabolism as a therapeutic target for liver cancer:

Reprogramming of lipid metabolism is a defining feature of HCC and represents a promising therapeutic vulnerability. Lipid metabolic reprogramming in HCC evolves in a stage-dependent manner, initially supporting tumor initiation, subsequently sustaining proliferative and biosynthetic demands during progression, and ultimately conferring adaptive metabolic plasticity that facilitates therapeutic resistance[10]. During tumor initiation, oncogenic signaling pathways (e.g., PI3K/AKT/mTOR) activate the lipogenic transcriptional program, primarily mediated by SREBP1. At these early stages of hepatocarcinogenesis, metabolic flux is redirected toward de novo lipogenesis, with ATP citrate lyase(ACLY) and acetyl-CoA(ACC)acting as key metabolic gatekeepers that generate cytosolic acetyl-CoA and malonyl-CoA, respectively. Beyond its role in membrane biogenesis, acetyl-CoA functions as a critical substrate for epigenetic regulation through histone acetylation, linking metabolic rewiring to transcriptional reprogramming and malignant transformation. As tumors progress, sustained activation of lipogenic pathways drives the upregulation of downstream enzymes such as FASN, which catalyzes the synthesis of long-chain fatty acids required for rapid cellular proliferation, membrane expansion, and lipid-mediated signaling[11]. In parallel, SCD1 introduces double bonds into saturated fatty acids, generating monounsaturated fatty acids that are essential for maintaining membrane fluidity, preventing lipotoxicity, and modulating redox balance. Additional regulators, including CD147, further potentiate lipogenesis through activation of the Akt/mTOR axis, thereby reinforcing tumor growth, angiogenesis, and metastatic dissemination. In the context of therapeutic resistance, lipid metabolism underlies metabolic plasticity and adaptive stress responses. Elevated activity of SCD1 mitigates endoplasmic reticulum stress and lipid peroxidation, promoting cell survival under therapeutic pressure[12]. Simultaneously, HCC cells exhibit compensatory metabolic adaptations, including enhanced lipid uptake and increased fatty acid β-oxidation, to circumvent inhibition of de novo lipogenesis. Regulatory nodes such as AMPK function as central metabolic sensors that modulate the balance between anabolic and catabolic processes, thereby influencing therapeutic responsiveness. Furthermore, the KLF4–MGLL regulatory axis may contribute to metastatic adaptation through modulation of lipid turnover and bioactive lipid signaling. Collectively, this stage-resolved model underscores that fatty acid synthesis enzymes are not merely overexpressed in HCC but are functionally integrated into distinct phases of tumor evolution: ACLY and ACC initiate metabolic reprogramming, FASN and SCD1 sustain proliferative and biosynthetic demands, while SCD1, together with broader lipid metabolic plasticity, underpins adaptive resistance[13]. This framework provides a mechanistic basis for the rational design of stage-specific and combination therapeutic strategies targeting lipid metabolism in HCC. Among lipid metabolic pathways, the Sterol Regulatory Element-Binding Protein 1 (SREBP1)-Acetyl-CoA Carboxylase (ACC)- Fatty Acid Synthase (FASN)- Stearoyl-CoA Desaturase (SCD) axis has emerged as a central driver, supplying essential lipids for membrane biosynthesis and generating signaling intermediates that activate oncogenic pathways such as PI3K/AKT/mTOR[14].

Pharmacological inhibition of key lipogenic enzymes has demonstrated the ability to suppress tumor growth and sensitize HCC cells to standard treatments, highlighting this pathway as a core metabolic target. Beyond lipid synthesis, targeting cholesterol biosynthesis-particularly through repurposed agents such as statins, offers translational potential due to their established clinical safety and emerging roles in modulating tumor signaling and the immune microenvironment. Similarly, inhibition of fatty acid uptake pathways (e.g., CD36) may prevent metabolic compensation and reduce metastatic potential, while targeting fatty acid oxidation (FAO) can disrupt

energy homeostasis under stress conditions[15]. Emerging strategies also focus on lipid peroxidation and ferroptosis, exploiting tumour cells' dependence on tightly regulated lipid composition to induce cell death. However, the therapeutic targeting of lipid metabolism is challenged by significant metabolic plasticity, as tumor cells can switch between lipid synthesis, uptake, and oxidation to maintain homeostasis. This adaptability often limits the efficacy of single-agent therapies and underscores the need for combination approaches integrating metabolic inhibitors with tyrosine kinase inhibitors or immune checkpoint blockade[16]. The most promising lipid metabolism targets for combination strategies in HCC are SREBP1 (regulatory hub), FASN and ACC (flux-controlling enzymes), and SCD1 (stress adaptation mediator), particularly when integrated with targeted therapies or immunotherapies to simultaneously disrupt tumour metabolism, overcome adaptive resistance, and enhance anti-tumor immune responses[17].

1.1 Fatty acids (FAs) synthesis in HCC

Dysregulation of FAs production has emerged as an expanding field of study, with numerous research findings pointing to disrupted lipid metabolism as a significant contributor to cancer development.[18,19] Cancer cell survival depends on reprogramming metabolic pathways, as evidenced by the increased metabolic requirements of cancer cells in an environment of decreased nutritional supply. Enhanced de novo lipogenesis is one of them. Lipid production and desaturation have been linked in recent research to the carcinogenesis, development, and survival of HCC.[20,21] Although there has been no comprehensive investigation into the fatty acid (FA) biosynthesis machinery in HCC, various studies have revealed abnormal upregulation of enzymes related to this pathway. These enzymes include ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), and Stearoyl-CoA desaturase-1 (SCD1), which have been recognised in various human tumours, including HCC (Figure 1). Research has demonstrated that inhibiting the FAs production pathway suppresses cancer cells growth. Numerous possible targets on these pathways may be useful pharmacological targets in the context of an HCC treatment. Many FASN inhibitors with preclinical anticancer potential have been identified over decades of research, including **C75**, **GSK837149A**, **orlistat**, **GSK2194069**, and **TVB-2640**. **ND-654** and **sorafenib** are used in HCC treatment through inhibition of acetyl-CoA carboxylase activity. Although enhanced fatty acid (FA) synthesis is a recognized metabolic feature of hepatocellular carcinoma (HCC), therapeutic targeting of this pathway faces several limitations. HCC cells exhibit pronounced metabolic flexibility, enabling compensation through increased lipid uptake or activation of alternative lipid metabolic pathways. In addition, tumor heterogeneity and etiological diversity influence dependence on FA synthesis, potentially limiting uniform clinical responses. Given the central role of the liver in lipid metabolism, on-target toxicity and disruption of physiological lipid homeostasis remain important concerns. Furthermore, adaptive resistance mechanisms and the lack of validated predictive biomarkers may restrict the effectiveness of FA synthesis inhibitors as monotherapies, thereby supporting the need for rational combination strategies.[22]

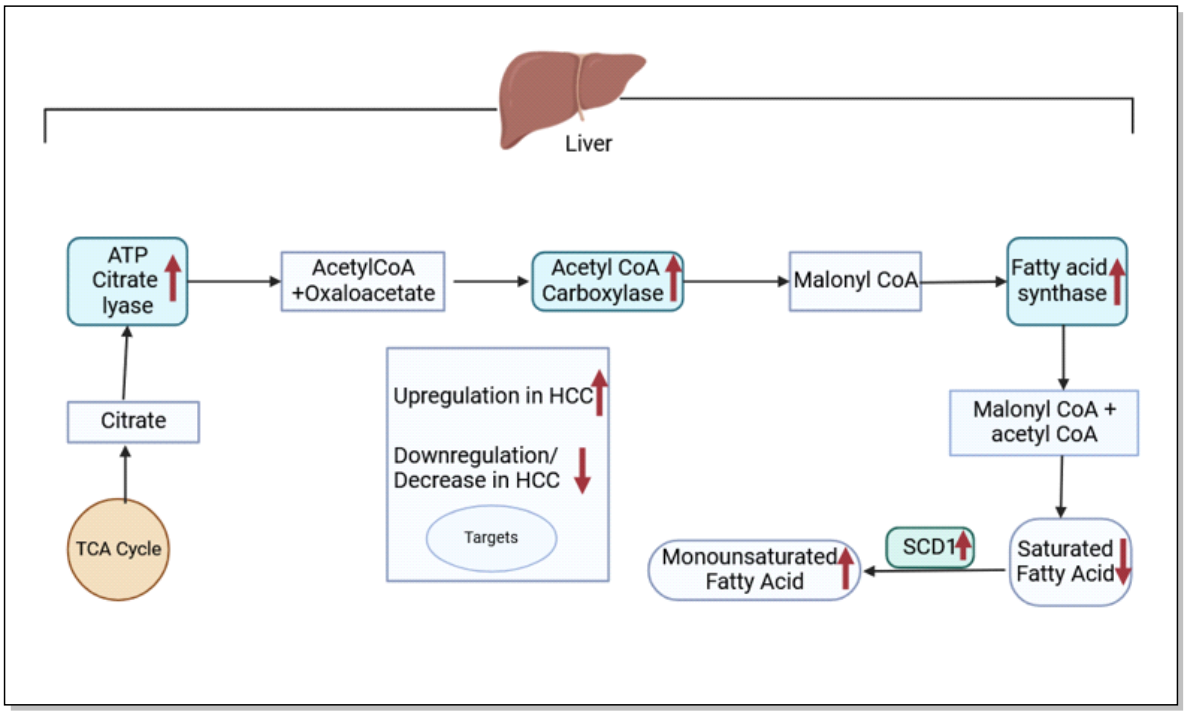

Figure 1. Fatty acid biosynthesis in HCC.

1.1.1 ATP citrate lyase (ACLY)

The enzyme ACLY situated in the cytosol is accountable for converting citrate and coenzyme A into oxaloacetate and acetyl-coenzyme A (acetyl-CoA).[23] Acetyl-CoA is essential for several processes related to metabolism. It is used as a precursor for the production of acetoacetyl-CoA and malonyl-CoA in the mevalonate pathway of cholesterol synthesis, the initial step in the production of FAs. Additionally, acetyl-CoA is crucial for protein-modifying acetylation events, like histone acetylation.[24] Studies involving ligand-dependent conformational alterations in the ACLY tetramer and associated biological protumorigenic effects have discovered several potential targets inside the ACLY protein. ACLY is an enzyme that connects the glycolysis and lipidic metabolism, which are essential for tumor formation, and is positioned strategically during intracellular metabolic processes. Due to its central position at the intersection of two vital metabolic processes, as well as the critical role that acetyl-CoA plays in cellular and lipid metabolism, ACLY is a crucial biomolecule in the survival and physiology of cancer cells, thereby serving a potential therapeutic target. The chemical **SB-204990** is a potent inhibitor of ACLY. To explore the potential of the ACLY inhibitor SB-204990 as a cancer treatment, researchers tested its effectiveness on three human tumour cell lines from the NIH 60 panel. The *in vitro* susceptibility of these cells to SB-204990-induced ACL inhibition and their capacity to develop tumours in nude mice were assessed. In addition, using the A549 cell line identified via RNA interference, the cell lines PC3 and SKOV3 were also examined. All three cell lines exhibited sensitivity to SB-204990's inhibition of ACL, with suppression occurring in a dose- and time-dependent manner.[25] Acetyl-CoA levels were measured after a brief treatment with SB-204990. Total acetyl-CoA levels in treated cells were consistently and significantly lower than in controls (17% decrease; $p < 0.001$; $n = 12$).

1.1.2 Stearoyl-CoA desaturase-1(SCD1)

SCD is an endoplasmic reticulum enzyme that introduces double bonds into fatty acids.[26] In particular, it catalyzes the conversion of stearoyl-CoA into oleoyl-CoA and palmitoyl-CoA into palmitoleoyl-CoA. SCD operates as the rate-limiting enzyme in this enzymatic cascade; it converts saturated fatty acids (SFAs) into monounsaturated fatty acids (MUFAs) by the introduction of a double bond in cis form at the ninth position of the carbon chain. SCD is positioned immediately downstream of fatty acid synthase (FASN).[27] Two of the five identified SCD isoforms (SCD1 and SCD5) are expressed in humans. Although their enzymatic function is retained, each isoform exhibits different tissue distribution and expression patterns. Initial *in vivo* studies conducted on mice with a specific mutation in the SCD1 gene revealed a reduction in body adiposity, improved insulin sensitivity, and resistance to weight gain stimulated by diet. These findings underscore the pivotal role of SCD in regulating fatty acids and metabolic disorders. A promising therapeutic approach for managing diabetes and obesity was modulation of SCD. As potential medicines, researchers have created novel SCD1 inhibitors using various techniques. An SCD inhibitor having a modest bioavailability in a variety of animal species is **MK-8245** (Merck & Co.). Phase I human investigation of the drug for diabetes treatment found that it was generally safe and tolerable. In multiple mouse in vivo studies, including those on prostate, breast, liver, kidney, and lung malignancies, it has been shown that SCD1 inhibitors can slow the growth of tumors. Von Roemeling *et al*., synthesised and assessed an innovative computational-based drug discovery method to design a new SCD1 inhibitor, representing one of the recently discovered SCD1 inhibitors.[28] To examine compound activity and selectivity, the team used cell-based assays and enzymatic testing and quantitative structure-activity relationship (QSAR) studies. By comparing the computational matching outcomes with those of two established SCD1 inhibitors, **A939572** and **ChEMBL375265**, researchers identified SSI-1, SSI-2, SSI-3, and SSI-4 as novel inhibitors of SCD. The newly discovered inhibitors showed no significant cytotoxicity in normal cell lines, including ovarian, renal, and breast cells. However, they inhibited cell proliferation in several cancer cell lines in breast, colon, liver, thyroid, endometrial, prostate, ovarian and lung.

1.1.3 Fatty acid synthase (FASN)

In lower eukaryotes such as fungi and mammals, the entire reaction sequence from palmitoyl CoA and palmitate to acetyl-CoA and malonyl CoA is carried out on a single multifunctional polypeptide chain, also known as FASN type I, which is encoded by a single gene. On the other hand, the procedure is referred to as FASN type II fatty acid biosynthesis in both plants and microorganisms, where it occurs within separate polypeptide chains. Both mechanisms are active in some bacteria, including *Mycobacterium tuberculosis*, which produces exceptionally long FAs. The mitochondria of several species, including humans, have been revealed to include a third system that is similar to the FASN type II system. The 270 kDa protein, identified as animal FASN, consists of two similar subunits aligned head-to-tail in a specific spatial configuration crucial for FASN functionality. FASN activity is lost due to the dimer's dissociation into its component monomers. Numerous research has examined the mechanism of FASN overexpression in cancer, although the overall picture is still poorly understood. The "lipogenic set" of enzymes' up-regulation appears coordinated in many instances. Keratinocyte growth factor, Epidermal growth factor (EGF), and HER2/neu are a few examples of growth factors and their receptors that are involved. Cellular signals are additionally relayed via the PI3K-PKB/Akt and MAP kinase pathways. For instance, it is well known that HER2/neu overexpression causes FASN activity to be upregulated, aiding in tumor cell

growth, survival, chemoresistance, and metastasis. Conversely, pharmacologically inhibiting FASN or siRNA silencing the FASN gene in cancer cells prevents lipogenesis from happening, which inhibits HER2/neu's oncogenic activity and ultimately results in apoptotic tumor cell death, indicating the potential use of FASN inhibitors as treatments for tumors overexpressing HER2. Additionally, it was discovered that in vitro overexpression of FASN can promote cell growth in non-cancerous epithelial cells, resulting in an invasive cancer-like phenotype with decreased response to the tyrosine kinase inhibitors gefitinib (a HER1 inhibitor) and lapatinib (a HER1/HER2 dual inhibitor). Moreover, Jin *et al.* reported that in breast cancer cells FASN is phosphorylated upon forming a complex with HER2 supporting the hypothesis that this interaction enhances signaling and promotes tumor progression. The role of FASN in liver carcinogenesis, and specifically in HCC metabolism, is still not fully understood. Likewise, SCD1, FASN's critical role in catalysing the synthesis of endogenous fatty acids in cells has led to its identification as a possible target in HCC.[29,30] Decades of research have identified various FASN inhibitors with preclinical anticancer potential, including **C75**, **orlistat**, **GSK2194069**, **GSK837149A**, and **TVB-2640**.[31,32]

1.1.4 Acetyl CoA carboxylase (ACC)

Acetyl -CoA carboxylase (ACC) is recognised as a fundamental enzyme in the classical lipid metabolism of both animals and humans.[33,34] ACC functions as a rate-determining enzyme, converting acetyl-CoA into malonyl-CoA during the standard de novo fatty acid synthesis. Mammals express two ACC isoforms, ACC1 and ACC2.ACC1 is predominantly expressed in lipogenic tissues such as liver, adipose, and nursing mammary glands, whereas ACC2 is mainly present in oxidative tissues including the heart and muscle.[35] Various ACC inhibitors have recently been identified, such as novel spiropentacylamide derivatives, **ND-654**, and **sorafenib**, used in cancer treatment. Likewise, laboratory experiments conducted with human glioblastoma cells (U87 EGFRvIII) revealed that exposure to a dual ACC inhibitor not only boosted cellular metabolic rate and reduced de novo lipid synthesis but also heightened apoptotic activity and reduced the efficiency of mitochondrial ATP synthesis. Svensson *et.al.* exhibited antitumor synergy, tumour regression, and survival advantages by employing a potent ACC inhibitor in combination with carboplatin in animal models of non-small cell lung cancer.[36] Limited data are currently available regarding specific targets in hepatocellular carcinoma (HCC) models. However, various studies have explored ACC inhibition across multiple preclinical studies involving various cancer cell lines. Wei *et al.* used rat models of liver cirrhosis and HCC to evaluate the effectiveness of ND-654, a hepatoselective *(*3000:1 liver-to-muscle exposure) allosteric inhibitor of ACC1 and ACC2. Following the development of cirrhosis and during the early stages of HCC progression, rats were administered daily oral gavage treatments with either (1) a vehicle control, (2) sorafenib, (3) ND-654, or (4) a combination of ND-654 and sorafenib. Intriguingly, sorafenib monotherapy alone (57% reduction, $p < 0.01$) were comparable to those achieved with the dual ACC inhibition of ACC1 and ACC2, leading to a significant 41% reduction in HCC incidence ($p < 0.05$). When sorafenib and ND-654 were combined, they remarkably reduced the incidence of HCC by 81% ($p < 0.001$).[37]

1.1.5 CD147 (basigin or emmprin)

CD147 is a transmembrane glycoprotein highly produced on the cell surface of the malignant tumour cells. It has been implicated in wide range of biological processes, including spermatogenesis, immunologic differentiation and development, and functions within the sensory and neurological systems, particularly in photoreceptor activity.[38] It has been shown that CD147 explicitly affects lipid metabolism, increasing lipogenesis and reducing

FA oxidation, making it a crucial element to research in cancer, particularly HCC. Indeed, considerable tumour growth, metastasis, and angiogenesis are linked to elevated expression of CD147. Through the activation of the Akt/mTOR signalling pathway, CD147 enhances the levels of ACC1 and FASN, both crucial lipogenic enzymes. In addition, it upregulates the expression of SREBP1c, a transcription factor associated with lipogenesis, which directly stimulates the transcription of these lipogenic genes, thereby amplifying de novo lipid synthesis. A novel therapeutic antibody that targets CD147 and is attached to a ^{131}I radioisotope (**^{131}I-Metuximab**) has been evaluated in at least one human study for HCC. In preclinical models,treatment with the ^{131}I-Metuximab antibody dramatically increased survival in a rabbit model of HCC. Additionally, inhibition in the ^{131}I-Metuximab therapy group were tumor development and metastasis. Patients received radiofrequency ablation (RFA) plus (^{131}I) metuximab or RFA alone in a later human clinical study. The combination therapy group had a greater survival rate in the CD147 positive population at 1- and 2-year intervals as compared to the RFA group alone. For patients receiving combination therapy, the benefits on survival and recurrence rates were more significant. In the combination group, one- and two-year incidence rates were 31.8% and 58.5%, respectively, whereas in the RFA group, they were 56.3% and 70.9%. In addition, the combination group's median time to complete tumour recurrence was 17 months, whereas the RFA group was 10 months (P = 0.03).

1.1.6 Kruppel-like Factor 4 (KLF4) and monoglyceride lipase (MGLL)

MGLL contributes to the metabolism of lipids by hydrolyzing monoacylglycerides to produce free fatty acids (FFAs) and glycerol. Yang *et al.* investigated the clinical relevance of HCC patients because it has been revealed that MGLL is downregulated in HCC. Their findings indicated that, MGLL was often suppressed in HCC specimens, particularly in regions associated with tumour invasion and metastasis. It was further demonstrated that the zinc finger transcription factor KLF4 was directly linked to the MGLL promoter and enhanced MGLL expression, which inhibited the migration of HCC cells. In HCC tissues, KLF4 expression levels are associated with MGLL expression, indicating that KLF4 is a crucial MGLL regulator.[39] Studies looking at monoacylglycerol (MAGL) synthesis inhibitors have shown impacts on several malignancies by preventing cell migration and invasiveness, although the available data remain limited. By regulating FA release for the formation of tumorigenic signaling lipids, MAGL inhibitors such as **Pristimerin**, **OMDM169**, and **URB602** have shown promising anti-cancer activity.

1.1.7 AMP-activated protein kinase (AMPK)

AMP-activated protein kinase (AMPK) plays a central role in lipid metabolism, by regulating the levels of circulating FFAs through modulation of fatty acid oxidation (FAO) and suppressing lipolysis and lipid synthesis, thereby acting as a multidimensional participant in cellular metabolic processes. In the context of fatty acid metabolism AMPK promotes FAs uptake and FAO while concurrently inhibiting the de novo production of FAs, triglycerides (TG) and cholesterol.[40] By triggering the inhibitory phosphorylation of two crucial participants in this process, ACC and Sterol Regulatory Element-binding protein 1 (SREBP1), AMPK inhibits the formation of FAs. Particularly in HCC, AMPK has been recognized as a potential therapeutic target, with AMPK activators like **simvastatin** and **metformin** exhibiting notable inhibitory effects on the growth of HCC and inducing cell cycle arrest. The commonly used hypoglycemic medication for diabetes, metformin, activates AMPK and can cause apoptosis in HCC cells. In one study, metformin administration resulted in increased expression of p53 and AMPK phosphorylation. Furthermore, activation of the AMPK/p53 signaling axis was shown to induce microRNA-23a production, which subsequently enhanced the activity of the transcription factor FOXA-1.

2.0. NASH and platelet GPIbα:

Platelets, derived from megakaryocytes within the bone marrow, serve a fundamental role in the process of haemostasis.[41] Beyond their essential function in maintaining haemostasis and wound healing following vascular injury, platelets play a vital role in various pathophysiological diseases and conditions related to cytotoxic T lymphocyte-mediated liver injury.[42] Malehmir *et al.* demonstrated that Kupffer cells are essential regulators of intrahepatic platelet acceptance in both the initial and late stages of non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), and borderline NASH.[43] Early NAFL and borderline NASH are also associated with hyaluronan and CD44 binding. These findings suggest that the rise in immune cell-attracting chemokines and cytokines is directly or indirectly associated with the quantity and activation status of intrahepatic platelets. This study revealed the crucial role of GPIbα in the advancement of experimental "autoimmune encephalomyelitis" (EAE), where it directs the movement of immune cells to the inflamed central nervous system (CNS). This function parallels GPIbα's equally crucial role in NASH.[44] In line with the EAE findings, the study results challenged the essential role of cognate interaction partners of GPIbα, including P-selectin, vWF, and Mac-1[45], and they emphasize the proinflammatory role of granules in intrahepatic immune cell recruitment. Furthermore, the authors demonstrated that prevention of NASH using two different antiplatelet agents, ticagrelor and Asp/Clo, in hIL4r/GP1b-Tg mice, effectively halted the progression of subsequent HCC. This suppression primarily occurred because of the absence of procarcinogenic NASH-related conditions, such as intrahepatic inflammation, signalling, and hepatocyte damage. Furthermore, NASH was therapeutically eliminated by anti-GPIbα antibody therapy or Kupffer cell depletion. These methods could significantly affect chemo preventive treatments, which are presently missing in NASH treatment. Researchers' findings endorse the use of antiplatelet therapies (APTs) and P2Y12 antagonists like **Ticagrelor, Prasugrel, and Clopidogrel**, which directly target platelet-derived GPIbα or related pathways. Patients with NASH may benefit from these drugs, which not only attempt to prevent or reverse NASH but also to stop its development into HCC.[46] While platelet GPIbα has emerged as a mechanistic link between NASH-associated inflammation and hepatocellular carcinoma, several limitations remain. Platelet adhesion and activation are regulated by redundant receptor pathways, which may attenuate the therapeutic impact of GPIbα inhibition. Moreover, systemic targeting of GPIbα may compromise physiological haemostasis, raising safety concerns. The heterogeneous nature of NASH-driven HCC and the current lack of robust clinical validation further complicate patient stratification and translational applicability.

3.0 CCT3 function as an upstream of YAP and TFCP2, putative target and tumor biomarker in liver cancer:

There are multiple yes-associated protein (YAP) control methods that are independent of Hippo pathway.[47] In liver cancer, YAP can be regulated in large tumor suppressor kinases (LATS) and serine-threonine kinases mammalian Ste20-like kinases (MST)-independent manner.[47] Surprisingly, tumor growth is not caused by the genetic reduction of Hippo-specific components.[48] It has been reported that CCT3 stimulates YAP production through the 28-member homologous to the E6-AP Carboxyl Terminus (HECT) E3 family, all of which may interact with poly(rC) binding protein 2 (PCBP2) (Figure 2). Investigation of the relationship between YAP/ transcription factor CP2 (TFCP2), PCBP2, and E3 ligase is necessary. In this context, inhibition of CCT3 has been shown to reduce the capacity of liver cancer cells. Additional support for targeting CCT-related tumours is provided by CT20p, a therapeutic peptide demonstrating specific cytotoxicity against cancer growth by inhibiting

CCT proteins.[49] Notably, studies have linked YAP and CCT3, indicating that CCT3 therapy may be advantageous for liver cancer associated with YAP. In liver cancer cells, CCT3 has been recognised as an upstream stimulus that enhances the protein stability of YAP and TFCP2. Importantly, CCT3 may serve as a potential serum biomarker and possible therapeutic target, opening up possibilities to innovative methods for the diagnosis and treatment of liver cancer. Although CCT3 has been implicated as an upstream regulator of YAP and TFCP2 signalling in liver cancer, several limitations should be considered. CCT3 is a core component of the TRiC/CCT chaperonin complex, essential for normal protein folding, raising concerns regarding potential on-target toxicity upon systemic inhibition. The mechanistic specificity of CCT3–mediated regulation of YAP/TFCP2 regulation remains incompletely defined, and functional redundancy among CCT subunits may further limit therapeutic selectivity. Furthermore, the clinical validity of CCT3 as a predictive biomarker and its utility across heterogeneous HCC subtypes require further validation in large, well-characterized patient cohorts.[50]

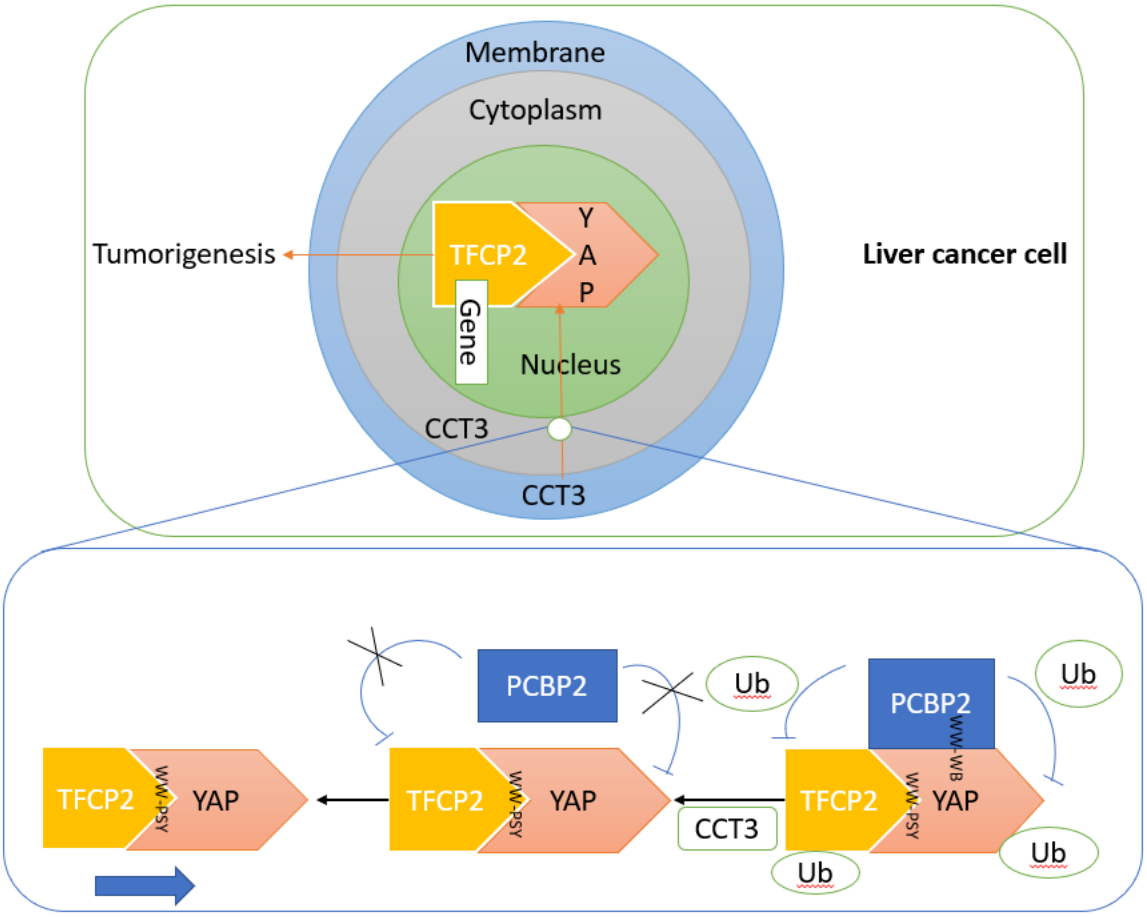

Figure 2. Diagrammatic representation of the process by which CCT3 stimulates YAP and TFCP2 in liver cancer.

4.0 TAZ and YAP:

Oncogenes Yes associated protein (YAP) and WW domain containing transcription regulator 1 (TAZ/WWTR1) play distinct roles in tumorigenesis, specific to different cell types. For example, TAZ has been found to be more essential for the emergence of breast cancer, whereas YAP serves as a critical oncogene in hepatocarcinogenesis.[51] Remarkably, chromatin immunoprecipitation (ChIP) sequencing studies have indicated that YAP and TAZ share a significant portion of their transcriptional program. This raises an important question of whether and how much these factors affect the formation and development of various tumor types. For several reasons, addressing this

issue is crucial to developing therapeutic strategies. First, the loss of one element, such as YAP, may be functionally made up for by another, such as TAZ. Second, because TAZ/YAP is essential for regeneration in various organs, blocking both transcriptional regulators may have unfavorable side effects for cancer patients with chronic illnesses.[52] Therefore, a comprehensive understanding of the partially overlapping and mutually incompatible TAZ and YAP effector mechanisms is required. This information not only aids in distinguishing the specific characteristics of TAZ and YAP but also enables the determination of downstream effectors, potentially indicating therapeutic targets. By comparing the expression of these transcriptional regulators in various cell lines of human liver cancer, researchers were able to directly investigate the biology of YAP and TAZ in HCC cells. While some cell lines exhibited similarly high levels of YAP and TAZ expression (such as HLF and HLE), others (such as HuH6 for YAP and SNU182 for TAZ) show preferential expression of one component under conditions of moderate cell density. HLF cells, with comparable YAP/TAZ levels, were chosen to facilitate a more comprehensive functional analysis of tumour cell characteristics. The simultaneous knockdown of both genes, as well as individual inhibition using RNA interference (RNAi), was implemented to study the impact of TAZ and YAP on HCC cell biology. Following the inhibition of either TAZ or YAP individually, cell viability was reduced by approximately 37 to 50%. It's interesting to note that simultaneous YAP/TAZ silencing did not result in a further decline in cell viability. As there was no evidence of functional compensation or cumulative effects observed after combined inhibition, these findings suggested that TAZ and YAP sustain cell survival and proliferation through similar molecular processes. Despite this, regular alterations in apoptosis were not noticed, suggesting that a rise in cell death was not the cause of the decline in cell viability. To assess cell mobility, lateral migration into a predefined cell-free space was measured. In the presence of the cell proliferation inhibitor mitomycin C, individual knockdown of TAZ and YAP reduced cell mobility, with a 40 to 50% decrease in gap closure. This ruled out the possibility that cell mitosis had any effect on this phenotype. After combined inhibition of TAZ and YAP, the effects on lateral migration were slightly more robust in the samples. The capacity of HCC cell to invade ECM was evaluated as these results suggested that TAZ and YAP mediated pathways in HCC mobility were only partially independent.[53] Although aberrant activation of YAP and TAZ is strongly implicated in liver tumorigenesis, several limitations hinder their direct therapeutic targeting. YAP/TAZ function as transcriptional co-activators lacking enzymatic activity, making them intrinsically challenging drug targets. In addition, pathway complexity and crosstalk with multiple upstream signals may enable compensatory activation mechanisms. Given their roles in normal liver regeneration and tissue homeostasis, systemic inhibition of YAP/TAZ raises concerns regarding on-target toxicity. Moreover, context-dependent activation and tumor heterogeneity complicate patient stratification and prediction of therapeutic response.[54]

5.0 TGFβ gene:

Bevant *et al.* discovered that liver cancer has been associated with transforming growth factor beta (TGF). The effects of TGF on tumour growth can differ depending on the phase of the tumour, indicating that its mechanism of action is complex.[55] It can either repress or promote tumor growth. TGF has cytostatic characteristics in its early stages, which strongly induce the epithelial to mesenchymal transition (EMT); it later stimulates cell proliferation and metastasis. In this study, researchers investigated DNA methylation as a potential molecular mechanism for turning on tumor-promoting factor TGF activity in HCC. Researchers found that the transcriptional response of SNU449 HCC cells to TGF is significantly impaired by **decitabine,** a demethylating drug previously

employed in clinical settings to treat several malignancies. Decitabine was also found to enhance the expression of transcription factors associated with EMT, like SNAI1/2 and ZEB1/2.[55]

6.0 SPAG9/MKK3/p38 axis:

Many studies have revealed that increased cell proliferation and resistance to apoptosis assist in the emergence of liver cancer.[56] Although there is evidence that sperm-associated antigen 9 (SPAG9) plays a role as a tumor inducer in some forms of cancer, the exact mechanisms are yet unknown. Luo *et al.* found how SPAG9 encouraged liver cancer.[57] First, they observed that 16 out of 20 (80%) of the liver cancer samples they analyzed, were overexpressed SPAG9. Immunohistochemistry demonstrated that the protein was either not expressed or only sporadically in nearby non-cancerous tissues. This discovery supports a previously postulated role for SPAG9 in developing liver cancer.[58] According to reports, SPAG9 is found in the cytoplasm of tumor cells.[59] Its employee's cellular immunofluorescence and immunohistochemistry techniques to identify the presence of SPAG9 in the cytoplasm and nucleus of HepG2 cells. Additionally, they found that inhibiting SPAG9 expression halted the proliferation of HepG2 cells, promoting apoptosis and led to the cell cycle arrest (Figure 3).[60] Remarkably, the previous study revealed that when SPAG9 was suppressed in QGY-7703 cells, it led to cell cycle arrest occurred specifically in G1 and G2 phase.[61] Nevertheless, in HepG2 cells, the cell cycle arrest occurred during the S phase. They postulated that this difference might be attributed to the distinct types of liver cancer origins of these two cell lines: HepG2 cells originated from hepatoblastoma, whereas QGY-7703 cells originated from hepatocellular carcinoma.[62] Further extensive research is essential to unravel the exact regulatory role of SPAG9 in cell cycle and apoptosis. It has been discovered that SPAG9 is highly expressed in both cell lines derived from liver tumours and the tissues from individuals with liver cancer. Consequently, in-depth investigations are imperative to comprehend SPAG9's biological function fully and explore its potential clinical applications. A signaling system known as Mitogen Activated Protein Kinase (MAPK) is linked to cell growth, differentiation, migration, invasion, and death.[63] SPAG9 functions as a scaffold protein by engaging with JNK and other p38 signalling modules through its JNK binding domain.[64] Moreover, it has been proven to engage in the stimulation of the MAPK signaling pathway. Scaffold proteins have the ability to assemble components of the MAPK cascade, guiding the phosphorylation process and facilitating pathway activation.[65] In a previous study, it was discovered that SPAG9 is implicated in osteosarcoma proliferation and invasion by positively regulating JNK-mediated signalling.[66] Researchers' findings showed that SPAG9 is a factor in liver cancer. It has demonstrated that JNK expression was markedly downregulated when SPAG9 was silenced. JNK and SPAG9 interacted with the HepG2 cells generated from liver cancer; this connection was previously seen in an ovarian cancer cell line.[67] JNK is a kinase that phosphorylates protein kinases and scaffolds proteins, and its overexpression promotes the development of cancer and apoptosis.[68] Researchers' findings indicate that SPAG9 and JNK interact directly to control the proliferation and death of liver cancer cell.[69] The MAP kinase p38 regulates a pathway for signaling initiated by stress.[70] It controls mechanisms related to cell survival and death during both normal development and carcinogenesis. This pathway can be triggered by diverse extracellular signals, including oxidative stress, ischemia, hypoxia, UV irradiation, and cytokines. Elevated phosphorylation of p38 serves as an indicator of an unfavourable prognosis in individuals with liver cancer. Moreover, deactivation of p38 can induce apoptosis in liver cancer cells. p38 plays a significant role in the development of liver cancer.[71] By activating the SPAG9/p38 signaling pathway, SPAG9 potentially governs the survival and death mechanisms in tumor cells. Research has shown that this pathway influences the expression of proteins responsible for

regulating the cell cycle and initiating the epithelial- mesenchymal transition.[72] The activation of p38 requires a three-tiered signaling cascade involving MAP-kinase kinase kinases (MAPKKKs), MAP-kinase kinases (MKKs), and MAP-kinases (MAPKs). Specifically, the kinases MKK3 and MKK6 operate upstream of p38 in this signaling pathway.[73] Researchers discovered that silencing of SPAG9 dramatically reduced the expression of p38 and MKK3 but had no significant effect on MKK6[71]. According to Stramucci et *al.*, blocking upstream kinases may disrupt p38-mediated signaling, obstructing pro-tumorigenic signals but not tumor suppressive signals.[73] Nevertheless, MKK3 is thought to be a target for cancer therapy. Researchers' findings showed that the SPAG9/MKK3/p38 axis controlled the activation of p38 in liver cancer (Figure 3), and elements associated with this unique route may be therapeutic targets for liver cancer.

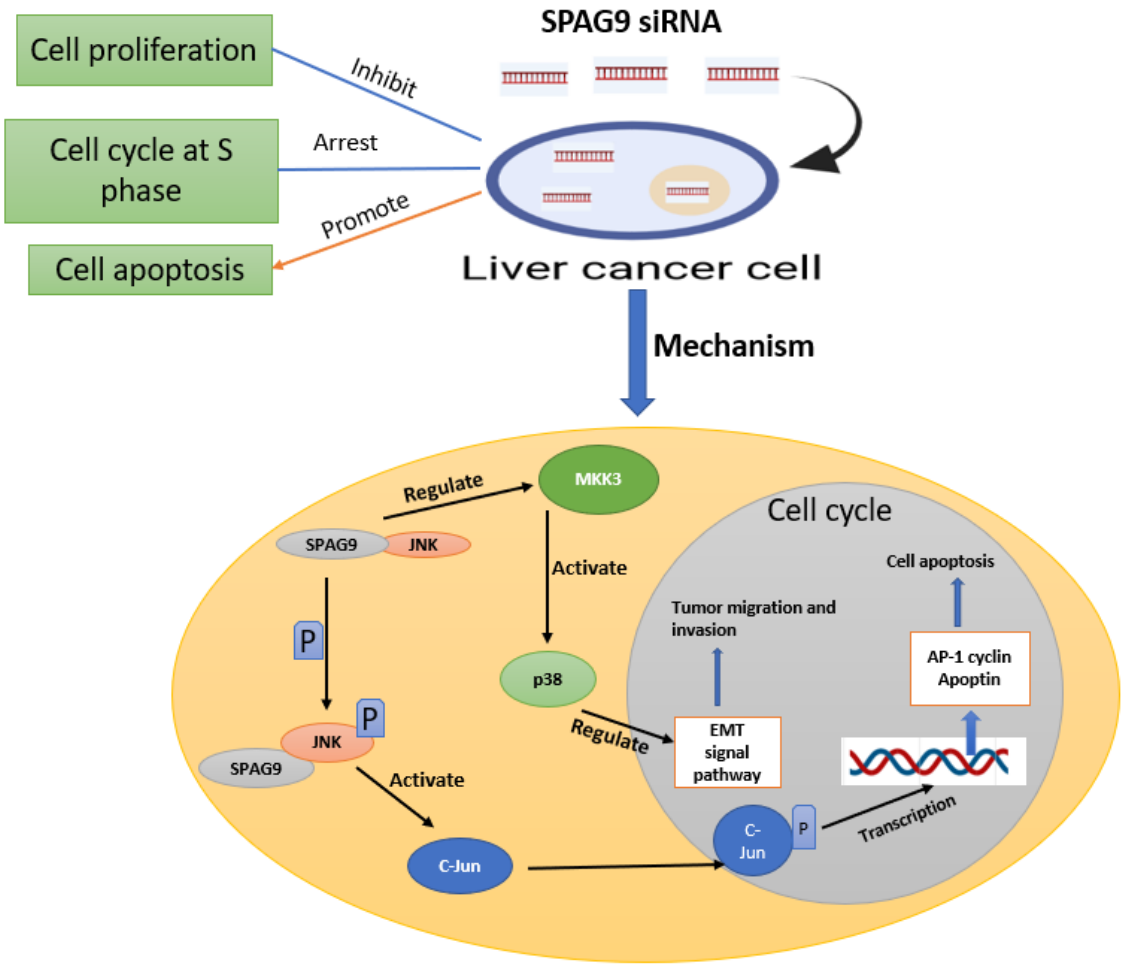

Figure 3. The role of SPAG9 in the progression of liver cancer

7.0 Glypican-3 antibodies:

Glypican-3, a member of the glypican family, is also referred to as DGSX, GTR2-2, MXR7, OCI-5, SDYS, SGB, SGBS, or SGBS1. It binds to the cell surface through a glycosylphosphatidylinositol (GPI) anchor. Glypican-3 is also known as a heparan sulfate proteoglycan (HSPG).[74] Simpson-Golabi-Behmel syndrome (SGBS), a rare X-linked overgrowth disorder resulting from loss-of-function mutations, is a condition in which

GPC3 was initially identified in a patient. GPC3-deficient animals exhibit developmental overgrowth and several SGBS-specific defects.[75] Overexpression of GPC3 in transgenic mice inhibits liver regeneration and hepatocyte proliferation. Several growth factors, including Wnts[76], Hedgehogs[77], fibroblast growth factors (FGFs), and bone morphogenetic proteins[78], may bind to GPC3 and act as co-receptors or storage sites within cells. This function allows GPC3 to regulate the interactions of these growth factors with their respective cell surface receptors. This could explain the finding in the following two experiments in which cell surface GPC3 increased the development of HCC cells (Figure 4). The majority of the mouse monoclonal antibodies (mAbs) against GPC3 that have been created so far target a peptide generated from GPC3.[79] However, none of these antibodies have demonstrated the capacity to stop the growth of HCC cells or trigger apoptosis. Except for GC33, which is being investigated as a potential therapeutic drug, they are therefore employed as research tools. For the treatment of liver cancer, four GPC3 antibodies, GC33, YP7, HN3, and MDX-1414 are being developed. In order to treat individuals with HCC, therapeutic antibodies targeting GPC3 are a desirable target. However,its structure-function relationship remains unclear, nevertheless. Except for HN3, most GPC3-targeting antibodies do not promptly halt HCC cell proliferation. Feng *et al.,* found that HN3 and functional epitope of GPC3 is directly dependent to tumor growth inhibition.[80] Hence, further exploration of GPC3's structural biology holds the potential to facilitate the development of new antibodies with enhanced tumor-suppressive properties.

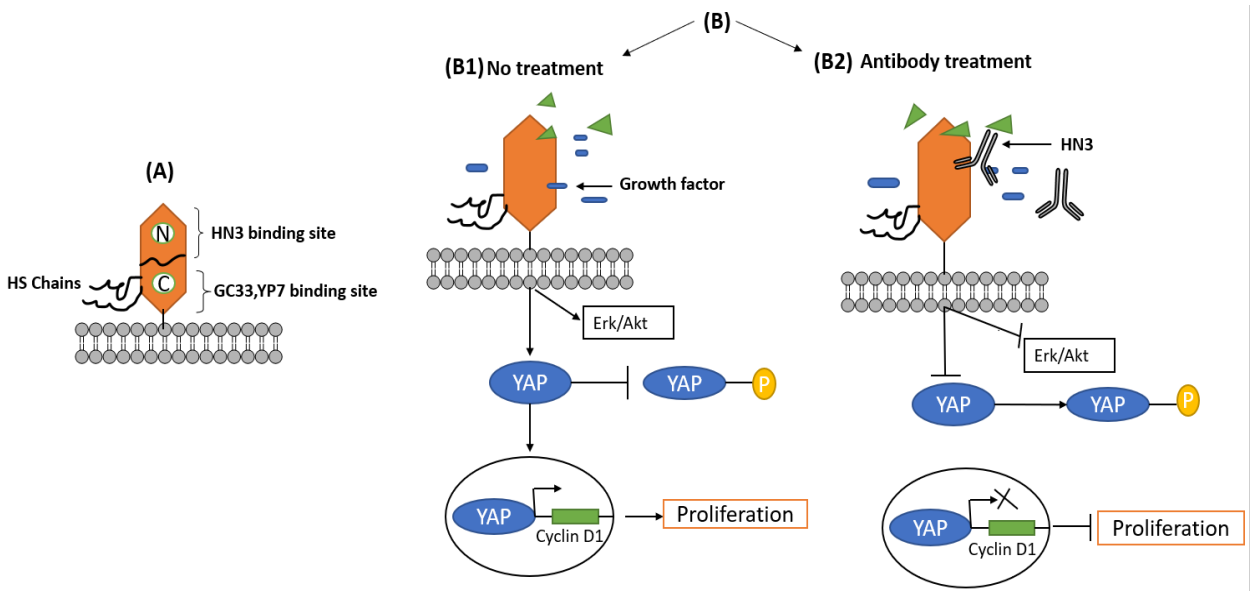

Figure 4. Therapeutic antibodies that target GPC3 are being used to treat liver cancer. (A) Schematic representation of the binding sites of the existing antibodies and the structure of GPC3. N represents amino acids domain. C is the domain of the carboxyl-terminal. Heparan sulphate, or HS. (B) The mechanism by which the HN3 antibody works. (B1) Growth factors bind to GPC3 in the absence of HN3 and encourage cell division. (B2) When HN3 is present, it inhibits growth factor binding and initiates intracellular signaling, which in turn causes YAP to become inactive and inhibits HCC cell proliferation.

8.0 BIRC3:

Yao Fu *et al*. found that baculoviral IAP repeat-containing 3 (BIRC3) upregulates MAP3K7, causing ERK1/2 phosphorylation and triggering EMT marker transcription, which in turn increases HCC cell motility and metastasis. In patients with HCC undergoing curative resection, BIRC3 serves as a distinctive prognostic predictor. For the treatment of HCC metastasis and recurrence, targeted therapy against BIRC3 may provide a unique therapeutic approach.[81] The researchers objective was to investigate the impact of BIRC3 on the

proliferation, migration, and invasion capabilities of HCC cells. They used wound healing tests to assess the cell migration in these cells. Their findings demonstrated that, in comparison to the control, BIRC3 overexpression significantly increased cell migration. However, the specific siRNA considerably slowed LM3 migration by depleting BIRC3. Remarkably, the cell line with high metastatic potential (LM3) exhibited increased cell migration compared to the cell line with low metastatic potential. The results from an apoptosis assay revealed that BIRC3 overexpression led to a reduction in tumour cell apoptosis, whereas BIRC3 knockdown increased tumour cell apoptosis. They used the selective BIRC3 inhibitor **AT406** and evaluated its possible impact on the HCC xenograft model to further investigate the beneficial effect of targeting BIRC3 *in vivo*. One mg/kg of AT-406 was administered daily by oral gavage. The subcutaneous tumour model using BIRC3 knockdown LM3 cell lines demonstrated that BIRC3 knockdown can directly reduce tumour growth. In mice implanted with HCC xenografts, AT-406 therapy dramatically reduced lung metastasis relative to the control. In conclusion, we found that BIRC3 may be a valuable potential target for liver cancer.

9.0 Bromodomain-containing protein BRPF1:

Epigenetic abnormalities, along with gene mutations, contribute to the development of cancer. Epigenetic regulators are frequently dysregulated in human HCC. Histone methyltransferases EZH2, SUV39H1, SETDB1, G9a, and HELLS have been characterised for their pathogenic functions in liver carcinogenesis, demonstrating the significant impact that epigenetic abnormalities play in the emergence of HCC. Cheng *et al*. discovered that the increased expression of the bromodomain-containing protein BRD4 plays a significant role in the abnormal formation of super-enhancers in HCC.[82] Furthermore, they observed that the genetic removal or pharmacological suppression of BRD4 effectively eliminated super-enhancer-driven oncogene inhibition, leading to the suppression of HCC growth.[83] The importance of bromodomain-containing proteins in cancer development is highlighted by these findings, which also suggest that targeting bromodomain-containing proteins may be a new approach to treating cancer. The functions of other bromodomain-containing proteins in liver carcinogenesis, besides BRD4, are still unknown. Researchers identified BRPF1 as the gene most commonly overexpressed in human HCC (Figure 5).[82] BRPF1 is part of the MOZ-MORF acetyltransferase complex, which is notably concentrated at the HOXA9 promoter. According to reports, MOZ-MORF frequently fuses with EP300, CBP, or TIF2, which causes mistargeted acetylation and accelerates the development of leukaemia.[84] Through MOZ-dependent histone acetyltransferase activity, BRPF1 depletion decreased MOZ-TIF2 location on the HOX genes and decreased HOX expression in acute myeloid leukaemia, indicating that BRPF1 and the MOZ/MORF complex are oncogenic. BRPF1 expression in medulloblastoma is significantly reduced compared to non-tumour tissues. However, a recent study demonstrated that BRPF1 acts as a tumour suppressor gene. It revealed that truncated BRPF1 interacts with smoothened, promoting adult sonic hedgehog (SHH) medulloblastoma.[85] The authors did not demonstrate that reintroducing the normal BRPF1 gene hampers cancer development when BRPF1 is truncated. Nor did they establish that the enhanced activity of the truncated BRPF1 protein is responsible for BRPF1's oncogenic role. Additionally, BRPF1 expression is downregulated in medulloblastoma, but their analysis shows that it is elevated in a number of cancer types. It suggests that BRPF1 might serve a specific purpose for different cell types. In general, the pathogenic function of BRPF1 in cancer growth is still largely unknown. Their research showed that BRPF1 overexpression was significantly associated with clinicopathological characteristics. In HCC patients, higher levels of BRPF1 expression were linked to lower rates of both overall and disease-free survival. Additionally, discovered as a possible tissue biomarker for HCC diagnosis was discovered as BRPF1. They experimentally demonstrated that BRPF1 gene ablation decreased the rate of cell proliferation and the

growth of orthotopic xenograft tumours in mice. *In vivo*, **GSK5959** inhibited HCC cell proliferation and showed promise as a treatment. More significantly, BRPF1 increased the expression of stem cell factors and supported the capacity for self-renewal, which contributed to the stemness of liver cancer. As a key regulator, BRPF1 promotes the expression of many important oncogenes that are involved in multiple processes that lead to cancer. They also identified two widely recognised oncogenes, E2F2 and EZH2, as downstream targets of BRPF1. EZH2 acts as an H3K27 methyltransferase, leading to the transcriptional silencing of genes associated with differentiation. On the other hand, E2F2 serves as a transcriptional activator, governing the expression of genes related to cell cycle progression. Furthermore, their earlier research demonstrated that inhibiting EZH2 effectively hindered the progression of HCC in both laboratory experiments *in vitro* and *in vivo* models. H3K9ac, H3K14ac, and H3K23ac are only a few of the histone acetylation marks that the MOZ/MORF complex controls. Their findings showed that inhibition of BRPF1 did not affect the overall levels of acetylation at H3K9, H3K14, and H3K23 but that MOZ/MORF inhibition resulted in an notable reduction. **GSK5959** showed promise as a treatment *in vivo* by inhibiting the development of HCC cells. Additionally, **WM1119** significantly lessened MOZ chromatin binding in comparison to GSK5959. These findings suggest= that MOZ-MORF is partially BRPF1-independent in its chromatin binding and regulatory function of histone acetylation. According to reports, MOZ-MORF controls transcriptional activity in carcinogenesis by interacting with several transcriptionl factors, including RUNX and NRF2.[86,87] RUNX1 has a binding site in the E2F2 promoter region, which is interesting. It remains unclear whether RUNX1 or other transcription factors impact the MOZ-MORF complex's function independently of BRPF1 or its genomic positioning. Their research indicates that the collaboration between MOZ-MORF and BRPF1 enhances the expression of E2F2 and EZH2 by promoting H3K14 acetylation at their promoter regions, rather than H3K9 or H3K23. The MOZ-MORF complex controlled the levels of a certain histone marks in various genes and cell types. For instance, in the mouse embryo, MOZ controlled the expression of the HOX gene through H3K9 acetylation but not H3K14 acetylation.[88] Another study found that the levels of H3K9 and H3K14 acetylation were unaffected by the BRPF1 mutation, while H3K23 acetylation was deregulated.[89] They found that histone acetylation is regulated by the MOZ-MORF complex in a cell-type and gene-specific manner. Additional studies are required to unravel the specific mechanisms by which the MOZ-MORF complex selectively governs its target genes via distinct histone acetylation patterns. Their research has shed light on the vital roles played by BRPF1 and the MOZ-MORF acetyltransferase complex in liver carcinogenesis. It has also highlighted the precise regulatory control exerted by the MOZ-MORF complex over histone acetylation marks on the promoters of its target genes. Their discoveries underscore the emerging approach of targeting bromodomain-containing proteins as a novel method for treating cancer. Furthermore, their research demonstrates the therapeutic potential of BRPF1 inhibitors in the treatment of HCC.[90]

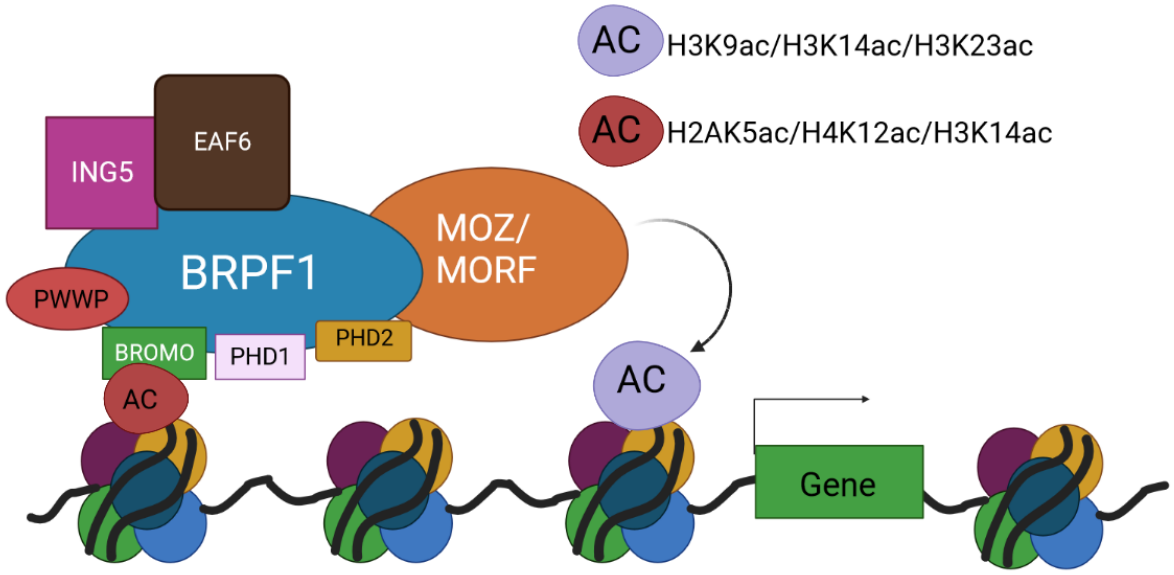

Figure 5. The MOZ/MORF histone acetyltransferase complex, which controls the acetylation of H3K9, H3K14, and H3K23 for gene activation, contains the core subunit BRPF1.

10.0 A MYC aurora kinase A protein complex represents a viable therapeutic target in p53-altered liver cancer:

The transcription factors MYC (also referred to as c-MYC), MYCN, and MYCL are closely related and have been connected to the growth of tumors. Within these networks, MYC stands out as a pivotal node situated downstream of signaling pathways frequently activated in various solid tumors. Due to its role in the development and maintenance of tumors, MYC is a prime candidate for cancer therapy. Notably, HCCs reliant on MYC often exhibit genetic alterations in p53 (Trp53 in mice and TP53 in humans), which are associated with a dismal prognosis. The role of p53 is to suppress cell growth in response to DNA damage or abnormal oncogene activation. Tumor suppressor protein $p19^{ARF}$ activates p53 after oncogenic stress.[91] In Trp53-altered hepatocytes under oncogenic stress after activation by $p19^{ARF}$, and through transcriptional activation of aurora kinase A (AURKA), it induces G2/M cell cycle arrest. Selection for high MYC expression was necessary for tumorigenesis from G2/M-arrested Trp53-altered hepatocytes, and the survival of the resultant tumors depended on AURKA- mediated MYC stabilization. Although the MYC oncogene is overexpressed in over 50% of human malignancies, its complex structure poses challenges for manipulation. Dauch *et al.* found that MYC and AURKA, two proteins shown to regulate one another at the transcriptional level, also interact physically in TP53-affected cells.[92] They also found that treating cells with AURKA inhibitors, which alter the conformation of the protein, effectively disrupts the formation of the MYC-AURKA complex. This disruption ultimately results in the degradation of MYC. All initiatives over the past ten years to find efficient, targeted molecular treatments for HCC have failed. They also revealed that HCC acquires resistance to sorafenib through the activation of MAPK14 (p38α) signaling. Sorafenib currently stands as the only systemic therapy available for patients with terminal liver cancer.[93] This discovery

was made possible through the utilization of cutting-edge *in vivo* shRNA-based screening technology. The pharmacological inhibition of MAPK14 restored sorafenib sensitivity. Nevertheless, their study demonstrates that AURKA inhibitors, even when used as a standalone treatment, have the potential to decelerate tumor development and enhance the overall survival rate in 50% of mice afflicted with aggressive liver carcinomas. Researchers found that there is currently no other therapy in mouse models that exhibits comparable therapeutic efficacy, reflecting the therapy resistance observed in human HCC.[94] Importantly, their xenograft studies suggest that AURKA inhibitors could potentially be effective against TP53-mutated human HCC. Epidemiological statistics confirm that the most significant risk factor for liver cancer development is chronic liver injury, often leading to hepatic cirrhosis. Nevertheless, the molecular mechanisms underlying how chronic liver injury and compensatory liver regeneration promote liver cancer growth remain poorly understood. The research provides valuable insights: liver injury followed by compensatory regeneration drives carcinogenesis through the activation of MYC. This activation enables the evasion of $p19^{ARF}$- and AURKA- mediated G2/M cell cycle arrest in hepatocytes with Trp53 alterations. The compound **MLN8237** or other AURKA inhibitors, capable of changing protein conformation, should be explored in clinical trials for managing advanced TP53-altered HCCs.

11.0 Hypoxia as a potential target for drug combination therapy of liver cancer:

Transarterial chemoembolization (TACE), which delivers localized doxorubicin in combination with tumor embolization, represents the standard treatment for intermediate-stage HCC. However, embolization-induced hypoxia can promote the survival and dissemination of cancer cells that have adapted to low-oxygen conditions.[95] Hypoxia-inducible factor 1 (HIF1) is the transcriptional modulator that coordinates responses to hypoxia. Combining medical therapy with HIF-1 targeting offers the potential to enhance HCC treatment outcomes. HepG2 cells were cultured under both normoxic and hypoxic settings to evaluate viability and the expression of hypoxia-induced HIF1 in both settings. Subsequently, the cells were subjected to treatment with **doxorubicin**, **rapamycin**, and various combinations of these therapies. An ectopic xenograft mouse model of HCC was used in pilot research to assess the antitumor effects of various drug combinations given by drug-eluting beads *in vivo*. In combination with the minimal effective dose of rapamycin for both normoxic and hypoxic HepG2 cells, a therapeutic concentration of doxorubicin was determined. This concentration not only inhibits the survival of normoxic and hypoxic HepG2 cells but also surpasses the threshold beyond which hypoxic cells develop resistance to chemotherapy. Doxorubicin alone was less effective than combinations of rapamycin and doxorubicin. The buildup of HIF1 caused by hypoxia is inhibited by both doxorubicin and rapamycin, according to Western blotting[95].

12.0 C-X-C motif chemokine ligand 5 (CXCL5):

Recent research demonstrates that CXCL5 silencing or antibody-mediated blockade suppresses tumour growth, proliferation, migration, and invasion, supporting CXCL5 as a potential therapeutic target in liver cancer. (Figure 6). Experimental data indicated that the tyrosine kinase inhibitor **gefitinib** could be more effective when combined with CXCL5 antibody to decrease tumor growth without increasing side effects in lung cancer patients.[96] CXCL5 limits the development of certain malignancies. As a crucial adjuvant antiangiogenic therapy against cancer, targeting CXCL5 may have therapeutic advantages for immunotherapy or chemotherapy for cancer. However, the development and practical application of CXCL5- target-specific medications present various challenges. These drugs must attain the utmost levels of specificity, efficacy, and minimal toxicity. Considering the complexity of molecular pathways and interactions involving targeted chemokines/receptors, the specificity of CXCL5 as a

therapeutic target for particular cancer types and its duration should be carefully and comprehensively examined. The effectiveness of CXCL5 needs to be consistently demonstrated because there is still debate over whether it functions as a protective factor in some malignancies. CXCL5-targeted medicines for liver cancer may have unexpected toxicities or side effects due to the broad biological roles and involvement of CXCL5 and its receptor. Local delivery of CXCL5 inhibitors, such as through the hepatic artery or portal vein, may maximize therapeutic effects within the liver while minimizing potential damage. Determining the efficacy of CXCL5 therapy requires clear guidelines for monitoring measurements. It is essential to establish specific criteria to assess the effectiveness of CXCL5 inhibitors. Additionally, it should be investigated whether the sensitivity of cancer to CXCL5 inhibitors varies based on the disease severity. Addressing these aspects is crucial for the development and successful application of CXCL5-targeted therapies[96].

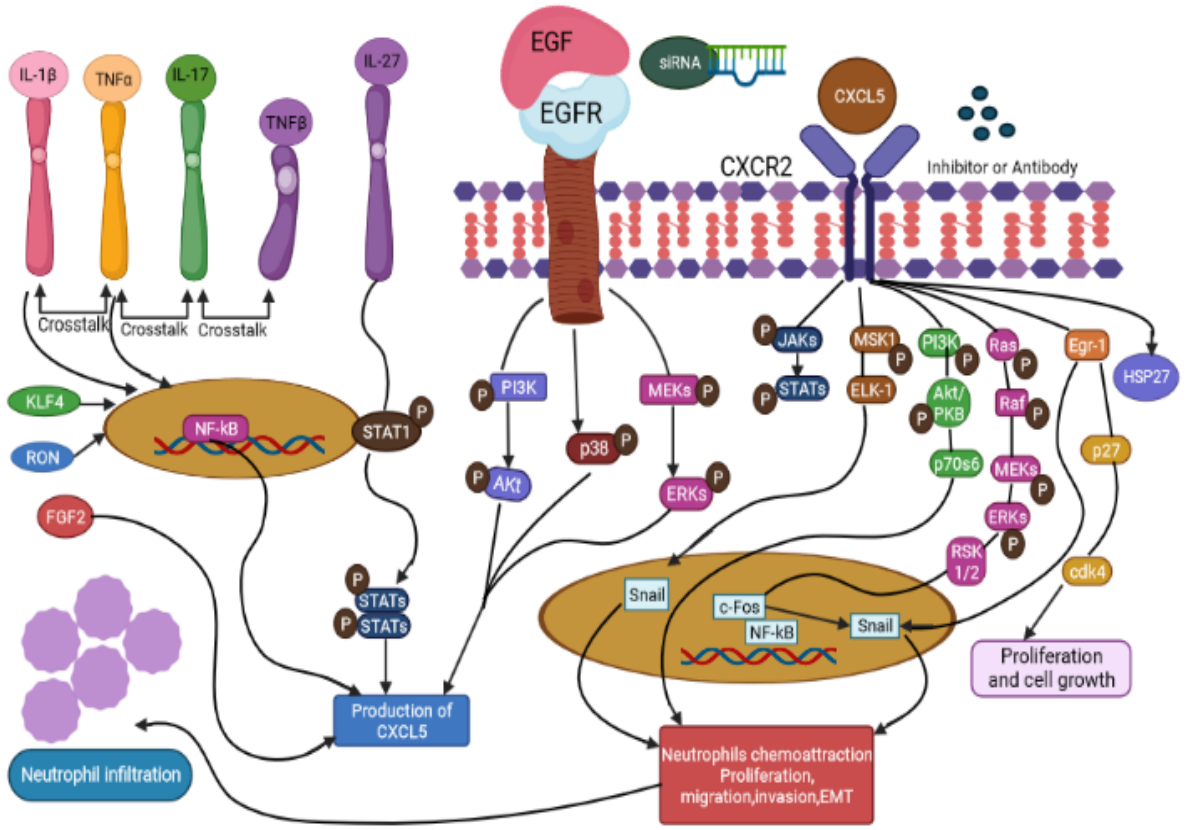

Figure 6. CXCL5 signaling pathways that up-regulates transcript factors, such as Snail and NF-kB, to stimulate proliferation, migration, invasion, and neutrophil chemo attraction.

13.0 The autotaxin-lysophosphatidic acid pathway:

HCC remains a leading cause of cancer-related mortality worldwide. The overall 5-year survival rate is below 15% and is strongly influenced by disease stage and underlying clinical factors. Early-stage detection remains challenging, with most patients diagnosed at advanced stages when potentially curative options such as surgical resection or liver transplantation are no longer feasible. Moreover, HCC exhibits marked resistance to conventional chemotherapeutic agents, underscored by the limited clinical benefit of sorafenib, which has remained the only FDA-approved systemic therapy for advanced HCC for nearly a decade. Immunotherapy is

showing positive early results, but response rates are still about 20%. Because of these factors, improving screening efforts may not be the most promising approach to minimize mortality related to the poor prognosis of HCC at this stage of chemoprevention. In recent research, two animal models of non-alcoholic steatohepatitis (NASH) were used: the Stelic Mouse Animal Model (STAM), created by the Stelic Institute, and a high-fat, choline-deficient, L-amino acid-defined diet (CDAHFD), comprising 0.1% methionine and 60% calories from fat. It was found that the enzyme autotaxin (ATX), also known as ectonucleotide pyrophosphatase-phosphodiesterase 2 (ENPP2), is crucial in HCC.[97] The secreted enzyme ATX converts lysophosphatidylcholine (LPC) to lysophosphatidic acid (LPA), a biologically active phospholipid. LPA receptors 1-6 (LPAR1-LPAR6) are a set of six G protein-coupled receptors that mediate LPA signalling. Signaling through these receptors, affecting cell proliferation, migration, and survival, has been linked to the emergence of cancer and fibrosis in various organs.[98] In recent studies, it has been shown that the expression of ATX increases in individuals infected with HCV, aiding viral replication. Moreover, persistent elevation of blood ATX levels has been observed in chronic HCV patients, where it correlates with the stage of fibrosis, a well-known risk factor for HCC. However, until recently, the function of ATX-LPA signaling in liver cancer had not been studied. In order to identify pan etiology targets for HCC chemoprevention, Erstad *et al.* synthesized genome wide transcriptional profiles of clinical fibrotic /cirrhotic liver tissue (n = 523) and performed regulatory gene network modelling.[99] The transcriptome meta-analysis identified three key hub modules and two large groupings of 31 strongly regulated gene modules. A higher chance of recurrent de novo HCC was associated explicitly with activation of one of these central hub modules. They systematically analyzed the enrichment of experimentally induced genetic perturbation transcriptome patterns using an unbiased small hairpin RNA (shRNA) library, which targeted the deletion of 5,272 genes (NIH Library of Integrated Cellular Signatures [LINCS] project). This analysis aimed to determine the functional regulators for this particular module. Researchers found that the HCC risk gene module is closely correlated with five upstream regulator genes, one of which is LPAR1. LPAR1 exhibited high expression levels in the collagen-secreting hepatic stimulated stellate cells of the liver. However, ATX expression is primarily confined to hepatic cells in the liver, highlighting a crucial relationship among different cell types that contribute to HCC and liver fibrosis. The administration of either an ATX inhibitor **(AM063)** or an LPAR1 antagonist **(AM095)** to rats in a DEN model of hepatic fibrosis and HCC, which has been demonstrated to closely mimic human disease, resulted in a decrease in histological fibrosis and a reduction in the development of HCC, demonstrating for the first time a link between hepatocarcinogenesis and ATX-LPA signaling. It was demonstrated more recently that ATX-deficient mice, specifically in hepatocyte are protected against the development of liver injury in response to several CCl_4 doses and a single DEN injection, as well as against the development of fibrosis in response to CCl4. Recently, two studies on LPA receptor antagonists have been completed though the results have not yet been released. One involved the LPAR1-selective antagonist **BMS-986020** in the treatment of idiopathic pulmonary fibrosis (NCT01766817), and the other antagonist **SAR100842** in the treatment of systemic sclerosis (NCT01651143). Additionally, a phase II trial for idiopathic-pulmonary fibrosis (NCT02738801) is investigating the ATX inhibitor **GLPG1690**.[100]

14.0 TNF-dependent Signalling Pathways in Liver Cancer:

A cytokine called tumor necrosis factor (TNF) is produced by monocytes and other immune, parenchymal, and other cells. When TNF binds to its receptors, it activates a variety of signaling cascades, including the pro-apoptotic caspase cascade, as well as stress- and inflammation-related pathways, such as NF-κB, p38MAPK, and c-Jun-(N)-terminal kinase (JNK) pathways. TNF's significance in cancer is debatable because it has been linked

to both pro-carcinogenic and anti-carcinogenic effects (Figure 7). Recently, researchers have investigated its potential role in hepatocarcinogenesis using genetically modified animal models. Findings in genetically modified mouse models have a significant impact on the current understanding of TNF's role in the development of liver cancer. It is intriguing to observe that mice with a constitutive deletion of TNF or its receptors, TNFRI and TNFRII, are still viable. This viability enables *in vivo* experiments to be conducted on adult mouse livers.[101,102] These investigations have shown that different TNF-dependent signalling pathways contribute differently to the development of hepatocarcinogenesis, although some findings remain debatable and highly dependent on the experimental model system. However, a better understanding of this complex pathway in hepatocarcinogenesis may be gained by carefully interpreting results from mouse models and critically evaluating their limitations. This could help to identify the TNF pathway's most potent targets and the ideal clinical contexts for chemopreventive or therapeutic approaches to treat HCC in the future. It's interesting to note that palliative care settings are being used in current clinical studies testing, for example, MEK (MAPK kinase) inhibitors such as **GSK1120212** and **Cobimetinib/GDC-0973** or STAT3 inhibitors. Despite their therapeutic potential, TNF-dependent signaling pathways in liver cancer present several challenges. TNF signaling is highly pleiotropic and tightly regulated, mediating not only tumor-promoting inflammation but also immune surveillance and tissue homeostasis. As a result, systemic inhibition may lead to immune dysregulation or unintended hepatotoxic effects. Furthermore, extensive pathway redundancy and crosstalk with NF-κB, JNK, and apoptotic signaling networks can enable adaptive resistance, thereby limiting the long-term efficacy of TNF-targeted therapeutic strategies.[103]

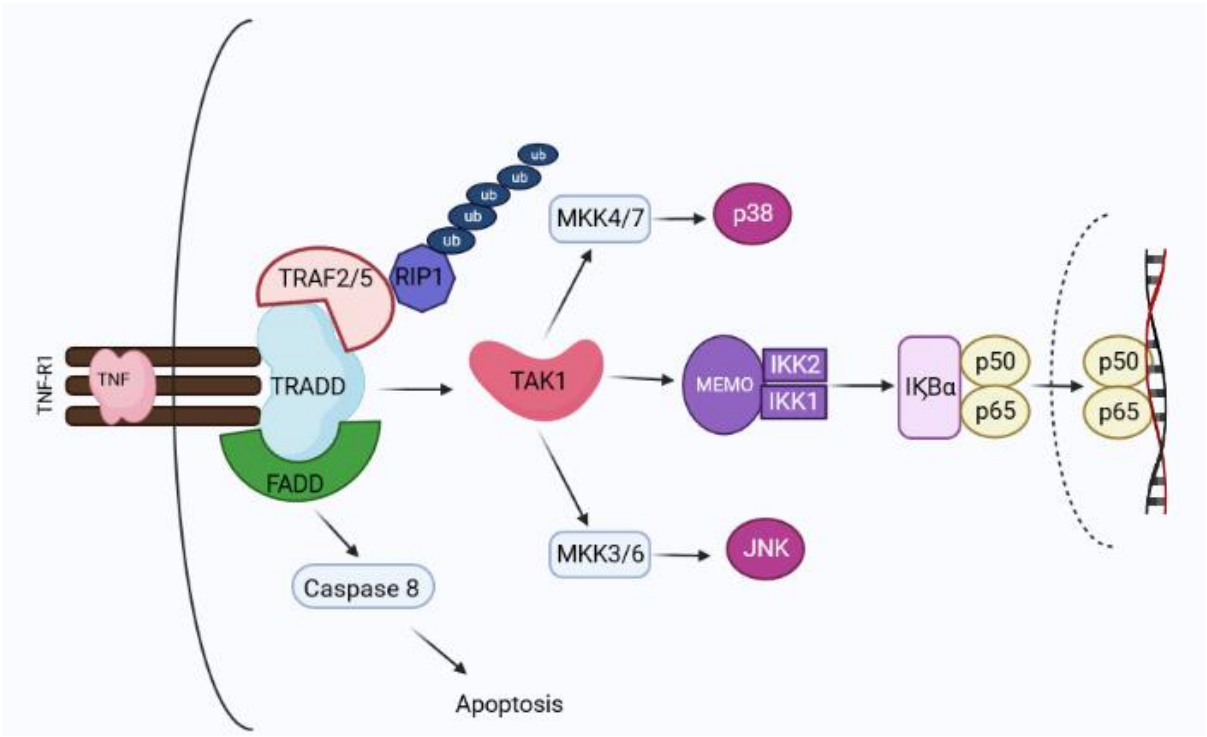

Figure 7. A streamlined TNF pathway model. TNF promotes various intracellular signalling cascades, including the NF-κB pathway, JNK, p38MAPK, and caspase cascade, after connecting to its receptors. IKK stands for I\B kinase; ub stands for ubiquitin; p50/p65 is the most prevalent NF-κB heterodimer.

15.0 Tyrosine kinase inhibitors:

15.1 Tyrosine kinase inhibitors (TKIs) that target PDGFR and VEGFR pathways

Hepatocarcinogenesis is linked to three important pro-angiogenic factors, namely "platelet-derived growth factor" (PDGF), "fibroblast growth factor" (bFGF), and "vascular endothelial growth factor" (VEGF). Indeed, these inflammatory processes significantly contribute to the invasiveness, neovascularization, and metastatic potential of HCC. In HCC, elevated levels of VEGF are associated with postoperative recurrence, poor prognosis, and shortened overall survival. Dysplastic nodules show VEGF expression, which increases during hepatocarcinogenesis. There is evidence that PDGF overexpression contributes to HCC's higher risk of metastasizing.[104] Endothelial cells express the VEGFR 1 and VEGFR2, which help these cells survive by sending signals. Microvascular sprouting endothelial cells respond to PDGF as an angiogenic factor. PDGF receptors (PDGFRs) are essential for the migration of smooth muscle cells and pericytes to the area around nascent vascular sprouts. Endothelial cells become more vulnerable to VEGF suppression when PDGFRs are inhibited because pericyte detachment from the endothelium is a known consequence of this process. Inhibitors targeting VEGF and PDGF signalling pathways have emerged as promising therapeutic agents for HCC treatment, as their expression is linked to the degree of microvessel density and the ability of cancer cells to spread. Sorafenib, for example, hampers VEGF and PDGF-dependent angiogenesis in HCC by not only inhibiting Raf kinase in tumour cells but also by targeting pericytes and endothelial cells by inhibiting VEGFR1-3 and PDGFR-ß Another oral multikinase inhibitor, TSU-68, targeting VEGFR, PDGFR, and FGFR, was administered to 35 patients with Child-Pugh A/B HCC in a Phase II trial at a daily dose of 400 mg. Results showed six patients achieved stable conditions for over six months, three individuals exhibited partial responses, and one patient had to discontinue treatment due to toxicity.

15.2 TKIs that target the FGFR and VEGFR pathways

In patients with HCC, high levels of bFGF and FGF-2 expression have been found. The extracellular matrix releases proteases, integrins, and collagenases, which combine to produce growing microvascular networks, and these become more active in the presence of bFGF.[105] Heparanase expression with bFGF promotes the tumor's growth, invasion, and angiogenesis. A high preoperative serum bFGF level was found to be associated with an aggressive tumor and an early postoperative recurrence in a clinical investigation of patients undergoing HCC resection. Furthermore, VEGF-mediated HCC growth and angiogenesis have been synergistically enhanced by bFGF. Through an autocrine mechanism, it acts as a mitogen to promote the growth of HCC cells, and by binding to FGFR1, it quickens the development and spread of HCC. **Brivanib** inhibited the development of liver cancer xenografts in vivo and displayed potent and specific inhibition of VEGFR and FGFR-1 tyrosine kinases.

15.3 TKIs that target the EGFR pathway

EGFR is highly expressed in HCCs, and activation of EGFR by TGF-a or EGF is required for HCC cell proliferation.[106] EGFR serves as a therapeutic target for the treatment of HCC. EGFR inhibitors like **cetuximab**, **panitumumab**, **gefitinib**, **erlotinib**, and **lapatinib** have demonstrated their ability to suppress HCC cells.

15.4 Threonine/tyrosine kinase inhibitors that target the Raf/MEK/ERK pathway

The Raf/MEK/ERK pathway appears to be one of the major cellular signaling routes implicated in the start and development of numerous cancers, including HCC. Tyrosine kinase receptors that are bound to ligands, including c-Met, PDGFR, EGFR, IGFR, and VEGFR utilize this pathway to transmit extracellular signals to the nucleus. The activation of the Raf/MEK/ERK cascade controls various processes such as drug resistance, angiogenesis, cellular motility, extracellular matrix remodeling, apoptosis resistance, and cell cycle progression. Numerous

molecular processes contribute to the activation of this system, which has been widely demonstrated to have increased activity in HCC cells, HCC models, and HCC patient tissues.[107] The HCV core protein has the ability to directly mediate the Raf/MEK/ERK cascade. Studies have shown that inhibiting MEK kinase increases apoptosis in existing HCC tumors in mice and hinders the growth of HCC. Another study found that MEK inhibitor treatment reduced the growth of HCC xenografts in a dose-dependent manner. In preclinical models of human HCC, **AZD6244** combined with **rapamycin** treatment displayed anticancer and antiangiogenic effects, according to a recent study.[108]

15.5 TKIs that target the PI3K/Akt/mTOR pathway

One of the main signaling pathways connected to RTKs (Receptor Tyrosine Kinase) found in cancer cells is the PI3K/Akt/mTOR protein cascade. Activation of RTKs triggers the PI3K/AKT/mTOR pathway, which is linked to a poor prognosis in HCC (Figure 8).[109] Patients who have phosphoinositide-3 kinase catalytic domain mutations frequently have increased Akt expression, which then activates mTOR. Human HCC shows mTOR phosphorylation and its downstream targets. “Phosphatase and tensin homolog” (PTEN), diminished or missing in nearly 50% of the examined hepatocellular carcinomas, negatively regulates PI3K function. Additionally, animals with hepatocyte-specific abrogation of PTEN expression developed HCC. These findings imply that targeting the PI3K/Akt/mTOR pathway could be an effective treatment for HCC. It is possible to block the PI3K/AKT/mTOR pathway to a certain extent. In animal models of HCC, PI3K inhibitors, including **wortmannin**, **LY294002**, and **FTY720**, have shown some anticancer efficacy.[110]

15.6 TKIs that target the Jak/Stat pathway

More than 40 cytokines and growth factors activate the Jak/Stat pathway, which is involved in various cell processes, including differentiation, proliferation, and apoptosis. The Janus tyrosine kinases (Jak1, 2, and 3, Tyk2) are phosphorylated by the cytokines, activating Stat1 – 6.[111] The Jak/Stat pathway can be activated by Hepatitis B and C viruses. In HCC, tyrosine kinase phosphorylation by Jak1, Jak2, and Tyk3 was significantly elevated compared to healthy livers, increasing from nearby non-neoplastic livers to hepatocellular carcinomas. Tumours exhibited significantly higher levels of Stat1, Stat3, and Stat5 than adjacent liver tissues, and Stat3 phosphorylation was notably higher in HCCs with a poor prognosis compared to those with a better prognosis. Most HCCs exhibited elevated levels of Jak/Stat target genes such as Bcl-xL, Mcl-1, cyclin D1, and c-Myc. Furthermore, inducing apoptosis in hepatoma cells was achieved by combining a Jak/Stat inhibitor with demethylating drugs. These findings suggest the use of Jak/Stat inhibitors, like **AZD1480,** for treating human hepatocellular carcinoma and highlight the significance of the Jak/Stat pathway in developing HCC.

15.7 TKI that targets c-met and VEGFR pathways

The receptor c-Met, which binds to hepatocyte growth factor (HGF), has a special role in the development, survival, and invasion of tumor cells, according to a wealth of experimental and clinical data. The interaction between HGF and c-Met activates both the ERK and PI3K signaling pathways. In HCC, point mutations in MET have been found, but it is still unclear exactly how c-Met/HGF imbalance contributes to the development of HCC.[112,113] **Foretinib** (GSK-1363089, formerly known as XL-880) is an oral kinase inhibitor that acts on the VEGF and c-Met receptors.

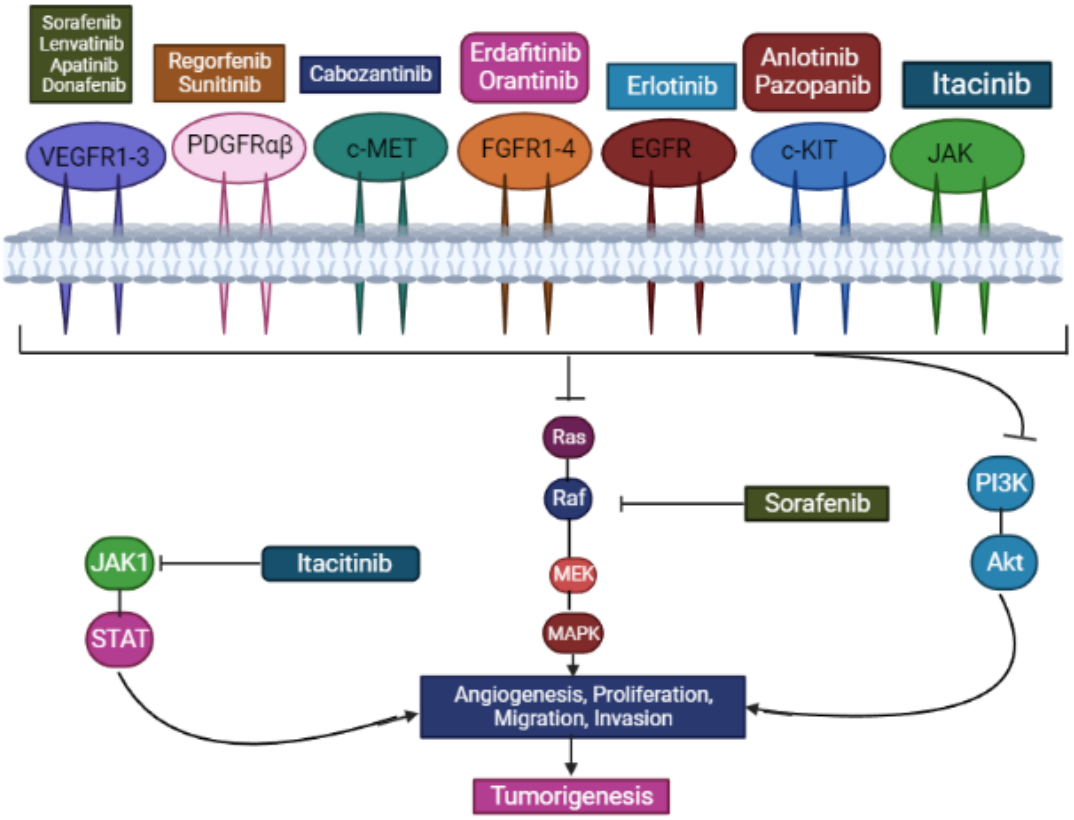

Figure 8. TKI targets and tyrosine kinase-mediated signaling pathways in the development of HCC tumors. TKIs attach to matching kinases in their substrates to phosphorylate tyrosine residues. This inhibits the activation of downstream signaling pathways (JAK-STAT, PI3K-AKT, and RAS-MAPK), which stops HCC cells from proliferating, migrating, invading, and forming angiogenesis.

16.0 Liver cancer stem cells: implications for a new therapeutic target:

HCC therapy first line of treatment is liver transplantation or resection.[114,115] Unfortunately, 80% of HCC patients are too advanced to be treated using current surgical techniques. Chemotherapy, which can be given as systemic therapy or transarterial chemoembolization, is the second-line treatment; however, due to the cancer's resistance to chemotherapy, the overall response rate is poor.[116,117] In addition to conventional systemic chemotherapy, targeted therapy may be an additional treatment option for individuals with advanced-stage HCC. Clinical research has recently examined molecular targets linked to multiple critical mechanisms that contribute to the growth of HCC, such as downstream signaling cascades of vascular endothelial growth factor and epidermal growth factor. However, targeted treatments and systemic chemotherapy primarily target differentiated, fast-proliferating HCC cancer cells.[118] The discovery of cancer stem cells (CSCs) in a variety of solid tumors, such as brain, colon, prostate, breast, pancreatic, melanoma, and head and neck cancers, has introduced a new avenue for therapeutic strategies in treating malignancies, including liver cancer. The premise behind the current theory of CSCs is that cancer tissue contains stem cells, a subset of the cell hierarchy, in the same way as healthy tissues do (Figure 9). As stated in different ways, CSCs are found in cancerous tissues in the same way as normal tissues. CSCs are pathological, tumour-initiating cells that sustain cancer growth and resistance, whereas therapeutic stem cells are normal, carefully regulated cells intentionally used to restore tissue function and treat disease.[119] CSCs take part in tissue regeneration in the same manner as regular stem cells. Many genes related to self-renewal appear to be linked to cancer, prompting efforts to elucidate the mechanism of cancer formation from the standpoint of a stem

cell hierarchy. This theory is being examined to identify the origin of CC and HCC using isolated liver stem/progenitor cells. We will first discuss the possible biological origins of liver stem/progenitor cells in this review section, as well as how they may be involved in the development of liver cancer.

16.1 Liver stem cells: hepatocytes

Bipotential progenitor cells are mainly derived from the fetal liver, as shown by the cells' significant colonization of the affected rat liver.[120] Hepatocytes can live for more than a year on average under typical conditions. As a result, the liver rarely regenerates, with only 0.01% of hepatocytes engaged in an active cell cycle at any given moment.[121] Hepatocytes possess the ability to self-replicate in response to the loss of parenchymal cells, allowing them to replace the original liver mass. In rodents, if two-thirds of the liver is removed through partial hepatectomy, the liver can regenerate its mass within approximately ten days. The specific processes governing this regenerative process have been thoroughly studied in previous years.[122,123]

16.2 Liver stem cells: oval cells

Oval cells are small cells that first appear in the periportal area and then infiltrate the bile canaliculi. They stand out for having an oval nucleus and a large ratio of nucleus to cytoplasm size.[124] Oval cells are bipotent, that means they can differentiate into either cholangiocytes or hepatocytes.[125–127] To decrease hepatocyte replication in response to regenerative stimuli, such as partial hepatectomy or injection of carbon tetrachloride, a carcinogen was used in the animal system, where stimulation of oval cells has been thoroughly studied.[128]

16.3 Liver stem cells: bone marrow cells

The idea that oval cell reactions originate from the canal of Hering was disputed by Sell *et al*.[129] Research has shown that intraportal stem cells contribute to the liver's response to periportal necrosis produced by allyl alcohol, indicating an alternative cell source outside the Hering canal. Additionally, studies increasingly provide evidence that oval cells and hepatocytes sometimes originate from bone marrow cells (BMCs) following liver injury, demonstrated through a lethally exposed and sex-mismatched bone marrow transplant rat model.[130] Approximately 1-2% of the hepatocytes in the murine liver were found to be potentially derived from the bone marrow without any liver injury using a similar transplantation method in mice, indicating that bone marrow participates in the normal hepatocyte turnover.[131]

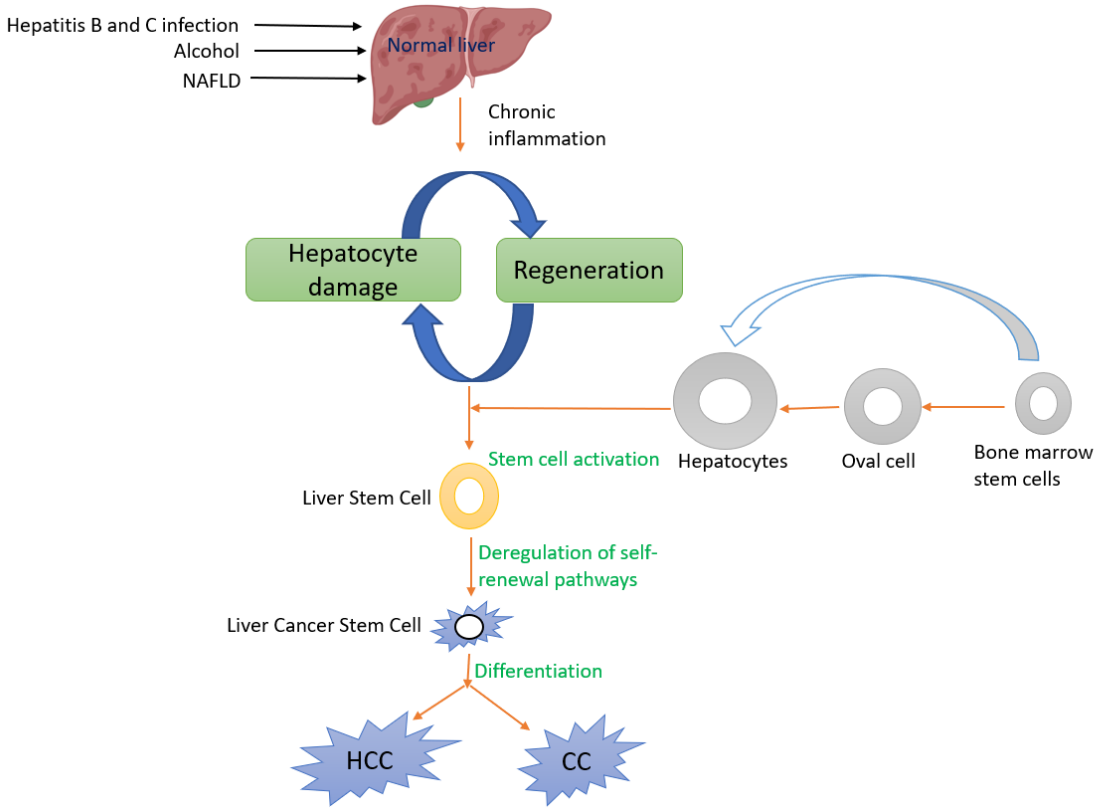

Figure 9. Model for multistep hepatocarcinogenesis using stem cells. Normal liver regeneration occurs as a result of hepatic injury in response to chronic inflammation due to hepatitis B and hepatitis C virus infections, alcohol, and other non-alcoholic fatty liver disorders (NAFLD). Hepatocytes or oval cells are examples of intrahepatically or extrahepatically activated normal liver stem cells (bone marrow cells). It is thought that normal liver stem or progenitor cells with excessive and persistent self-renewal undergo genetic changes, giving rise to liver cancer stem cells. Hepatocarcinogenesis may involve all three types of cells. Put another way, liver cancer stem cells may differentiate into HCC or CC.

Table-1 Comparison table of Targets of liver cancer, mechanism of action and their limitation.

Target / Pathway	**Mechanism of Liver Cancer**	**Inhibitor / Therapeutic Examples**	**Preclinical vs Clinical Status**	**Key Limitations**
Fatty Acid (FA) Synthesis (HCC/NASH)[132]	Upregulation of de novo lipogenesis (FASN, ACC, SCD1) supports membrane biosynthesis, energy supply, and oncogenic signaling	FASN inhibitors (TVB-2640), ACC inhibitors (PF-05221304)	Preclinical and early clinical (mainly metabolic diseases; limited HCC trials)	Metabolic toxicity, systemic lipid dysregulation, tumor heterogeneity
Platelet GPIbα[133]	Platelet–tumor interaction promotes metastasis, immune evasion, and angiogenesis	Anti-GPIbα antibodies, platelet inhibitors	Preclinical	Bleeding risk, lack of tumor specificity
CCT3–YAP–TFCP2 Axis[134]	CCT3 stabilizes YAP, enhancing transcriptional programs for proliferation and survival	Indirect YAP inhibitors (verteporfin), chaperonin targeting (experimental)	Preclinical	No direct CCT3 inhibitors, pathway redundancy
YAP/TAZ (Hippo pathway)[135]	Nuclear YAP/TAZ drive oncogenic	Verteporfin, TEAD	Preclinical to early clinical	Context-dependent effects, toxicity due

	transcription, stemness, and drug resistance	inhibitors (VT3989, IK-930)		to role in tissue regeneration
TGFβ Signaling[136]	Dual role: tumor suppressor early, pro-tumorigenic later via EMT, fibrosis, immune suppression	Galunisertib (LY2157299), anti-TGFβ antibodies	Clinical trials in HCC	Stage-dependent effects, systemic toxicity
SPAG9/MKK3/p38 Axis[137]	Activates stress kinases promoting proliferation, invasion, and survival	p38 inhibitors (SB203580 – experimental)	Preclinical	p38 has tumor-suppressive roles; off-target effects
Glypican-3 (GPC3)[138]	Oncofetal protein enhancing Wnt/β-catenin signaling in HCC	Codrituzumab, GPC3-CAR T cells	Clinical trials	Limited efficacy as monotherapy, antigen heterogeneity
BIRC3[139]	Inhibits apoptosis, promotes NF-κB signaling and survival	SMAC mimetics (birinapant)	Preclinical to early clinical	Resistance mechanisms, compensatory survival pathways
BRPF1[140]	Epigenetic regulator affecting histone acetylation and oncogene expression	BRPF inhibitors (OF-1, experimental)	Preclinical	Epigenetic toxicity, lack of selectivity
MYC–Aurora Kinase A Complex (p53-altered HCC)[141]	Stabilizes MYC, promotes mitosis and genomic instability	Aurora A inhibitors (alisertib)	Clinical trials	Toxicity, adaptive resistance
Hypoxia (HIF signaling)[142]	Hypoxic microenvironment induces angiogenesis, glycolysis, therapy resistance	HIF inhibitors, combination with TKIs (e.g., sorafenib)	Preclinical and clinical (combination strategies)	Difficult to target directly, systemic effects
CXCL5[143]	Chemokine-driven tumor proliferation, angiogenesis, immune cell recruitment	Anti-CXCL5 antibodies, CXCR2 inhibitors	Preclinical	Redundant chemokine networks
Autotaxin–LPA Pathway[144]	LPA signaling promotes proliferation, migration, fibrosis	Autotaxin inhibitors (GLPG1690)	Preclinical / early clinical (fibrosis)	Broad physiological roles of LPA
TNF-dependent Signaling[145]	Chronic inflammation via NF-κB, JNK promotes hepatocarcinogenesis	Anti-TNF agents (infliximab – indirect relevance)	Limited/indirect clinical relevance	Risk of immunosuppression, infection
Tyrosine Kinase Pathways[146]	Aberrant VEGFR, PDGFR, FGFR signaling drives angiogenesis and growth	Sorafenib, Lenvatinib, Regorafenib	Approved clinical therapies	Modest survival benefit, resistance
Liver Cancer Stem Cells (CSCs)[147]	CSCs drive recurrence, metastasis, drug resistance	Wnt, Notch, Hedgehog inhibitors	Preclinical to early clinical	Marker heterogeneity, toxicity to normal stem cells

17. Context on Clinical Success Rates:

Despite the identification of numerous molecular targets in hepatocellular carcinoma (HCC), only a limited number of systemic therapies, most notably multikinase inhibitors (sorafenib, lenvatinib, regorafenib) and immune checkpoint inhibitor–based combinations, have demonstrated consistent clinical benefit. This translational attrition reflects several biological and clinical constraints. First, tumor heterogeneity and etiologic diversity (viral hepatitis, NASH, alcohol-related disease) dilute the impact of single-target agents that show efficacy in genetically or metabolically restricted preclinical models.[148] Second, many targets exert context-dependent or dual roles (e.g., TGFβ, p38, Hippo signaling), functioning as tumor suppressors in early disease while promoting progression in advanced stages, complicating patient selection and trial design.[149] Third, adaptive resistance and pathway redundancy rapidly bypass single-node inhibition, limiting durability of response observed in early-phase trials.[150] Fourth, liver-specific toxicity and impaired hepatic reserve restrict dose intensity and therapeutic windows, particularly in cirrhotic patients.[151] Finally, the success of approved therapies underscores the importance of pleiotropic pathway modulation (angiogenesis, proliferation, immune evasion) and biomarker-enriched strategies, as exemplified by immunotherapy combinations that integrate tumor-intrinsic and microenvironmental targeting. Collectively, these factors explain why broad-spectrum or combinatorial approaches have translated more effectively than highly specific targets, despite strong preclinical rationale.

18. Integration With Immunotherapy

Contemporary management of HCC increasingly incorporates immune checkpoint–based therapies, either as monotherapy or in combination with targeted agents. PD-1/PD-L1 inhibitors restore antitumor T-cell activity by overcoming tumor-induced immune exhaustion and have demonstrated clinically meaningful survival benefits, particularly when combined with anti-angiogenic agents. CTLA-4 inhibitors further enhance immune priming by promoting T-cell activation and clonal expansion, providing a complementary mechanism that strengthens antitumor immunity.[152] Importantly, combination strategies integrating immunotherapy with tyrosine kinase inhibitors (TKIs) exploit synergistic effects, whereby TKIs modulate the tumor microenvironment by reducing immunosuppressive signaling, normalizing tumor vasculature, and enhancing immune cell infiltration.[152] This integrative approach addresses both tumor-intrinsic oncogenic pathways and immune evasion mechanisms, contributing to improved response rates and durable disease control compared with single-agent therapies. As a result, immunotherapy-based combinations now represent a central therapeutic paradigm in advanced HCC and provide a rational framework for incorporating emerging molecular targets into future treatment strategies.

Conclusion:

Hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) represent the two principal forms of primary liver cancer, with HCC accounting for the majority of cases and remaining a leading cause of cancer-related mortality worldwide. Although surgical resection and liver transplantation offer curative potential, their applicability is limited, as over 80% of patients are diagnosed at intermediate or advanced stages, when curative interventions are no longer feasible. Locoregional approaches, including transarterial chemoembolization (TACE), and systemic chemotherapy have historically constituted the mainstay of treatment; however, intrinsic chemoresistance, underlying liver dysfunction, and tumor heterogeneity have collectively constrained their clinical efficacy.

The past decade has witnessed a paradigm shift toward molecularly targeted therapies and immunotherapy-based strategies. Multikinase inhibitors targeting angiogenic and growth factor–driven pathways, such as VEGF, EGFR,

and FGFR signaling, have demonstrated modest survival benefits, while recent advances in immune checkpoint inhibition, particularly PD-1/PD-L1 and CTLA-4–based combinations, have significantly improved clinical outcomes in selected patient populations. Nevertheless, these therapies primarily target rapidly proliferating, differentiated tumor cells, and their long-term effectiveness is frequently undermined by adaptive resistance mechanisms, pathway redundancy, and immune evasion.

Accumulating evidence indicates that liver cancer stem cells (CSCs) play a central role in tumor initiation, therapeutic resistance, metastasis, and disease recurrence. Conventional systemic therapies often fail to eradicate these CSC populations, thereby enabling tumor regrowth even after initial clinical responses. Consequently, emerging therapeutic strategies are increasingly focused on selective targeting of CSC-associated signaling pathways, metabolic dependencies, epigenetic regulators, and tumor–microenvironment interactions, while preserving normal hepatic stem cell function. In parallel, the integration of CSC-directed agents with immunotherapy, anti-angiogenic drugs, and metabolic modulators represents a promising avenue for achieving durable tumor control. In summary, this review synthesizes current therapeutic modalities, molecular targets, and mechanistic insights underlying liver cancer progression and treatment resistance. A deeper understanding of tumor heterogeneity, immune regulation, and CSC biology, coupled with rational combination therapies and biomarker-driven patient stratification, is expected to accelerate drug development and improve clinical outcomes. Such advances hold substantial promise for transforming liver cancer management and ultimately reducing the global burden of this aggressive and life-threatening disease.

Author Contribution: S. B., V. B., and A. S. N; writing original draft, S. K., K. M. S., L. K. P, review editing, supervision, investigation, conceptualization**.** All authors approved the final version of the manuscript.

Competing Interests

The authors declare that they have no competing interests.

Funding

There is no funding is available

References-

1. Farazi PA, DePinho RA. Hepatocellular carcinoma pathogenesis: from genes to environment. *Nat Rev Cancer* 2006;6(9):674-87. doi: 10.1038/nrc1934
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer Statistics, 2008. *CA Cancer J Clin* 2008;58(2):71-96. doi: 10.3322/CA.2007.0010
3. Bosch FX, Ribes J, Cléries R, Díaz M. Epidemiology of Hepatocellular Carcinoma. *Clin Liver Dis* 2005;9(2):191-211. doi: 10.1016/j.cld.2004.12.009
4. El-Serag HB. Hepatocellular Carcinoma. *J Clin Gastroenterol* 2002;35:S72-8. doi: 10.1097/00004836-200211002-00002
5. Plaz Torres MC, Jaffe A, Perry R, Marabotto E, Strazzabosco M, Giannini EG. Diabetes medications and risk of HCC. *Hepatology* 2022;76(6):1880-97. doi: 10.1002/hep.32439

6. Anzola M. Hepatocellular carcinoma: role of hepatitis B and hepatitis C viruses proteins in hepatocarcinogenesis. *J Viral Hepat* 2004;11(5):383-93. doi: 10.1111/j.1365-2893.2004.00521.x

7. Alqahtani A, Khan Z, Alloghbi A, S. Said Ahmed T, Ashraf M, M. Hammouda D. Hepatocellular Carcinoma: Molecular Mechanisms and Targeted Therapies. *Medicina (B Aires)* 2019;55(9):526. doi: 10.3390/medicina55090526

8. Gan C, Yuan Y, Shen H, Gao J, Kong X, Che Z, et al. Liver diseases: epidemiology, causes, trends and predictions. *Signal Transduct Target Ther* 2025;10(1):33. doi: 10.1038/s41392-024-02072-z

9. Gallage S, García-Beccaria M, Szydlowska M, Rahbari M, Mohr R, Tacke F, et al. The therapeutic landscape of hepatocellular carcinoma. *Med* 2021;2(5):505-52. doi: 10.1016/j.medj.2021.03.002

10. An L, Li Z. Molecular network of metabolic reprogramming and precision diagnosis and treatment of hepatocellular carcinoma. *Biomark Res* 2025;13(1):124. doi: 10.1186/s40364-025-00844-5

11. Pope ED, Kimbrough EO, Vemireddy LP, Surapaneni PK, Copland JA, Mody K. Aberrant lipid metabolism as a therapeutic target in liver cancer. *Expert Opin Ther Targets* 2019;23(6):473-83. doi: 10.1080/14728222.2019.1615883

12. Burchat N, Akal T, Ntambi JM, Trivedi N, Suresh R, Sampath H. SCD1 is nutritionally and spatially regulated in the intestine and influences systemic postprandial lipid homeostasis and gut-liver crosstalk. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 2022;1867(9):159195. doi: 10.1016/j.bbalip.2022.159195

13. Xue M, Zhou C, Zheng Y, Zhang Z, Wang S, Fu Y, et al. The association between KLF4 as a tumor suppressor and the prognosis of hepatocellular carcinoma after curative resection. *Aging* 2020;12(15):15566-80. doi: 10.18632/aging.103592

14. Li N, Li X, Ding Y, Liu X, Diggle K, Kisseleva T, et al. SREBP Regulation of Lipid Metabolism in Liver Disease, and Therapeutic Strategies. *Biomedicines* 2023;11(12):3280. doi: 10.3390/biomedicines11123280

15. Wong TL, Kong Y, Ma S. Lipid metabolism in cancer cells: Its role in hepatocellular carcinoma progression and therapeutic resistance. *Hepatol Commun* 2025;9(11). doi: 10.1097/HC9.0000000000000837

16. Wu Y, Li H, Yue K, Jing C, Duan Y. Ferroptosis in cancer: metabolism, mechanisms and therapeutic prospects. *Mol Cancer* 2025;24(1):303. doi: 10.1186/s12943-025-02520-6

17. Su F, Koeberle A. Regulation and targeting of SREBP-1 in hepatocellular carcinoma. *Cancer and Metastasis Reviews* 2024;43(2):673-708. doi: 10.1007/s10555-023-10156-5

18. Santos CR, Schulze A. Lipid metabolism in cancer. *FEBS J* 2012;279(15):2610-23. doi: 10.1111/j.1742-4658.2012.08644.x

19. Menendez JA, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nat Rev Cancer* 2007;7(10):763-77. doi: 10.1038/nrc2222

20. Falvella FS. Stearoyl-CoA desaturase 1 (Scd1) gene overexpression is associated with genetic predisposition to hepatocarcinogenesis in mice and rats. *Carcinogenesis* 2002;23(11):1933-6. doi: 10.1093/carcin/23.11.1933

21. Muir K, Hazim A, He Y, Peyressatre M, Kim DY, Song X, et al. Proteomic and Lipidomic Signatures of Lipid Metabolism in NASH-Associated Hepatocellular Carcinoma. *Cancer Res* 2013;73(15):4722-31. doi: 10.1158/0008-5472.CAN-12-3797

22. Park S, Hall MN. Metabolic reprogramming in hepatocellular carcinoma: mechanisms and therapeutic implications. *Exp Mol Med* 2025;57(3):515-23. doi: 10.1038/s12276-025-01415-2

23. Verschueren KHG, Blanchet C, Felix J, Dansercoer A, De Vos D, Bloch Y, et al. Structure of ATP citrate lyase and the origin of citrate synthase in the Krebs cycle. *Nature* 2019;568(7753):571-5. doi: 10.1038/s41586-019-1095-5

24. Zaidi N, Swinnen J V., Smans K. ATP-Citrate Lyase: A Key Player in Cancer Metabolism. *Cancer Res* 2012;72(15):3709-14. doi: 10.1158/0008-5472.CAN-11-4112

25. Hanai J, Doro N, Sasaki AT, Kobayashi S, Cantley LC, Seth P, et al. Inhibition of lung cancer growth: ATP citrate lyase knockdown and statin treatment leads to dual blockade of mitogen-activated protein Kinase (MAPK) and Phosphatidylinositol-3-kinase (PI3K)/AKT pathways. *J Cell Physiol* 2012;227(4):1709-20. doi: 10.1002/jcp.22895

26. Igal RA. Stearoyl-CoA desaturase-1: a novel key player in the mechanisms of cell proliferation, programmed cell death and transformation to cancer. *Carcinogenesis* 2010;31(9):1509-15. doi: 10.1093/carcin/bgq131

27. Liu X, Strable MS, Ntambi JM. Stearoyl CoA Desaturase 1: Role in Cellular Inflammation and Stress. *Advances in Nutrition* 2011;2(1):15-22. doi: 10.3945/an.110.000125

28. von Roemeling CA, Caulfield TR, Marlow L, Bok I, Wen J, Miller JL, et al. Accelerated bottom-up drug design platform enables the discovery of novel stearoyl-CoA desaturase 1 inhibitors for cancer therapy. *Oncotarget* 2018;9(1):3-20. doi: 10.18632/oncotarget.21545

29. Arif M, Klevstig M, Benfeitas R, Doran S, Turkez H, Uhlén M, et al. Integrative transcriptomic analysis of tissue-specific metabolic crosstalk after myocardial infarction. *Elife* 2021;10. doi: 10.7554/eLife.66921

30. Buckley D, Duke G, Heuer TS, O'Farrell M, Wagman AS, McCulloch W, et al. Fatty acid synthase – Modern tumor cell biology insights into a classical oncology target. *Pharmacol Ther* 2017;177:23-31. doi: 10.1016/j.pharmthera.2017.02.021

31. Flavin R, Peluso S, Nguyen PL, Loda M. Fatty Acid Synthase As a Potential Therapeutic Target in Cancer. *Future Oncology* 2010;6(4):551-62. doi: 10.2217/fon.10.11

32. Carroll RG, Zasłona Z, Galván-Peña S, Koppe EL, Sévin DC, Angiari S, et al. An unexpected link between fatty acid synthase and cholesterol synthesis in proinflammatory macrophage activation. *Journal of Biological Chemistry* 2018;293(15):5509-21. doi: 10.1074/jbc.RA118.001921

33. Wakil SJ, Abu-Elheiga LA. Fatty acid metabolism: target for metabolic syndrome. *J Lipid Res* 2009;50:S138-43. doi: 10.1194/jlr.R800079-JLR200

34. Wang L, Zhang T, Wang L, Cai Y, Zhong X, He X, et al. Fatty acid synthesis is critical for stem cell pluripotency via promoting mitochondrial fission. *EMBO J* 2017;36(10):1330-47. doi: 10.15252/embj.201695417

35. Flavin R, Peluso S, Nguyen PL, Loda M. Fatty Acid Synthase As a Potential Therapeutic Target in Cancer. *Future Oncology* 2010;6(4):551-62. doi: 10.2217/fon.10.11

36. Svensson RU, Parker SJ, Eichner LJ, Kolar MJ, Wallace M, Brun SN, et al. Inhibition of acetyl-CoA carboxylase suppresses fatty acid synthesis and tumor growth of non-small-cell lung cancer in preclinical models. *Nat Med* 2016;22(10):1108-19. doi: 10.1038/nm.4181

37. Lambrecht J, Tacke F. Acetyl-CoA Carboxylase Inhibition as a Therapeutic Tool in the Battle Against NASH: Hitting More Than Just One Mechanism? *Cell Mol Gastroenterol Hepatol* 2020;10(4):859-61. doi: 10.1016/j.jcmgh.2020.07.002

38. Muramatsu T. Basigin (CD147), a multifunctional transmembrane glycoprotein with various binding partners. *J Biochem* 2016;159(5):481-90. doi: 10.1093/jb/mvv127

39. El–Serag HB, Rudolph KL. Hepatocellular Carcinoma: Epidemiology and Molecular Carcinogenesis. *Gastroenterology* 2007;132(7):2557-76. doi: 10.1053/j.gastro.2007.04.061

40. Jeon SM. Regulation and function of AMPK in physiology and diseases. *Exp Mol Med* 2016;48(7):e245-e245. doi: 10.1038/emm.2016.81

41. Michelson AD. How Platelets Work: Platelet Function and Dysfunction. *J Thromb Thrombolysis* 2003;16(1-2):7-12. doi: 10.1023/B:THRO.0000014586.77684.82

42. George JN. Platelets. *The Lancet* 2000;355(9214):1531-9. doi: 10.1016/S0140-6736(00)02175-9

43. Malehmir M, Pfister D, Gallage S, Szydlowska M, Inverso D, Kotsiliti E, et al. Author Correction: Platelet GPIbα is a mediator and potential interventional target for NASH and subsequent liver cancer. *Nat Med* 2022;28(3):600-600. doi: 10.1038/s41591-022-01693-7

44. Starossom SC, Veremeyko T, Yung AWY, Dukhinova M, Au C, Lau AY, et al. Platelets Play Differential Role During the Initiation and Progression of Autoimmune Neuroinflammation. *Circ Res* 2015;117(9):779-92. doi: 10.1161/CIRCRESAHA.115.306847

45. Wang Y, Gao H, Shi C, Erhardt PW, Pavlovsky A, Soloviev DA, et al. Correction: Corrigendum: Leukocyte integrin Mac-1 regulates thrombosis via interaction with platelet GPIbα. *Nat Commun* 2017;8(1):16124. doi: 10.1038/ncomms16124

46. Malehmir M, Pfister D, Gallage S, Szydlowska M, Inverso D, Kotsiliti E, et al. Platelet GPIbα is a mediator and potential interventional target for NASH and subsequent liver cancer. *Nat Med* 2019;25(4):641-55. doi: 10.1038/s41591-019-0379-5

47. Wang J, Tang X, Weng W, Qiao Y, Lin J, Liu W, et al. The membrane protein melanoma cell adhesion molecule (MCAM) is a novel tumor marker that stimulates tumorigenesis in hepatocellular carcinoma. *Oncogene* 2015;34(47):5781-95. doi: 10.1038/onc.2015.36

48. Totaro A, Panciera T, Piccolo S. YAP/TAZ upstream signals and downstream responses. *Nat Cell Biol* 2018;20(8):888-99. doi: 10.1038/s41556-018-0142-z

49. Carr AC, Khaled AS, Bassiouni R, Flores O, Nierenberg D, Bhatti H, et al. Targeting chaperonin containing TCP1 (CCT) as a molecular therapeutic for small cell lung cancer. *Oncotarget* 2017;8(66):110273-88. doi: 10.18632/oncotarget.22681

50. Liu Y, Zhang X, Lin J, Chen Y, Qiao Y, Guo S, et al. CCT3 acts upstream of YAP and TFCP2 as a potential target and tumour biomarker in liver cancer. *Cell Death Dis* 2019;10(9):644. doi: 10.1038/s41419-019-1894-5

51. Cordenonsi M, Zanconato F, Azzolin L, Forcato M, Rosato A, Frasson C, et al. The Hippo Transducer TAZ Confers Cancer Stem Cell-Related Traits on Breast Cancer Cells. *Cell* 2011;147(4):759-72. doi: 10.1016/j.cell.2011.09.048

52. Patel SH, Camargo FD, Yimlamai D. Hippo Signaling in the Liver Regulates Organ Size, Cell Fate, and Carcinogenesis. *Gastroenterology* 2017;152(3):533-45. doi: 10.1053/j.gastro.2016.10.047

53. Rausch V, Hansen CG. The Hippo Pathway, YAP/TAZ, and the Plasma Membrane. *Trends Cell Biol* 2020;30(1):32-48. doi: 10.1016/j.tcb.2019.10.005

54. Zhang S, Zhou D. Role of the transcriptional coactivators YAP/TAZ in liver cancer. *Curr Opin Cell Biol* 2019;61:64-71. doi: 10.1016/j.ceb.2019.07.006

55. Bévant K, Desoteux M, Abdel Wahab AHA, Abdel Wahab SA, Metwally AM, Coulouarn C. DNA Methylation of TGFβ Target Genes: Epigenetic Control of TGFβ Functional Duality in Liver Cancer. *Cells* 2021;10(9):2207. doi: 10.3390/cells10092207

56. LIU W, XU C, WAN H, LIU C, WEN C, LU H, et al. MicroRNA-206 overexpression promotes apoptosis, induces cell cycle arrest and inhibits the migration of human hepatocellular carcinoma HepG2 cells. *Int J Mol Med* 2014;34(2):420-8. doi: 10.3892/ijmm.2014.1800

57. Luo S, Ren B, Zou G, Liu J, Chen W, Huang Y, et al. SPAG9/MKK3/p38 axis is a novel therapeutic target for liver cancer. *Oncol Rep* Published online January 30, 2019. doi: 10.3892/or.2019.6987

58. Yan Q, Lou G, Qian Y, Qin B, Xu X, Wang Y, et al. SPAG9 is involved in hepatocarcinoma cell migration and invasion via modulation of ELK1 expression. *Onco Targets Ther* Published online March 2016:1067. doi: 10.2147/OTT.S98727

59. Xie C, Fu L, Liu N, Li Q. Overexpression of SPAG9 correlates with poor prognosis and tumor progression in hepatocellular carcinoma. *Tumor Biology* 2014;35(8):7685-91. doi: 10.1007/s13277-014-2030-x

60. Qiao L, Zhang L, Wang H. SPAG9 Expression Predicts Good Prognosis in Patients with Clear-Cell Renal Cell Carcinoma: A Bioinformatics Analysis with Experimental Validation. *Genes (Basel)* 2023;14(4):944. doi: 10.3390/genes14040944

61. Ren B, Zou G, He J, Huang Y, Ma G, Xu G, et al. Sperm-associated antigen 9 is upregulated in hepatocellular carcinoma tissue and enhances QGY cell proliferation and invasion inï¿½vitro. *Oncol Lett* Published online October 26, 2017. doi: 10.3892/ol.2017.7270

62. Marin JJG, Cives-Losada C, Asensio M, Lozano E, Briz O, Macias RIR. Mechanisms of Anticancer Drug Resistance in Hepatoblastoma. *Cancers (Basel)* 2019;11(3):407. doi: 10.3390/cancers11030407

63. Rohrabaugh S, Kesarwani M, Kincaid Z, Huber E, Leddonne J, Siddiqui Z, et al. Enhanced MAPK signaling is essential for CSF3R-induced leukemia. *Leukemia* 2017;31(8):1770-8. doi: 10.1038/leu.2016.376

64. Lee CM, Onésime D, Reddy CD, Dhanasekaran N, Reddy EP. JLP: A scaffolding protein that tethers JNK/p38MAPK signaling modules and transcription factors. *Proceedings of the National Academy of Sciences* 2002;99(22):14189-94. doi: 10.1073/pnas.232310199

65. Raman M, Chen W, Cobb MH. Differential regulation and properties of MAPKs. *Oncogene* 2007;26(22):3100-12. doi: 10.1038/sj.onc.1210392

66. Xiao C, Fu L, Yan C, Shou F, Liu Q, Li L, et al. SPAG9 is overexpressed in osteosarcoma, and regulates cell proliferation and invasion through regulation of JunD. *Oncol Lett* 2016;12(4):2674-9. doi: 10.3892/ol.2016.4920

67. Ha JH, Yan M, Gomathinayagam R, Jayaraman M, Husain S, Liu J, et al. Aberrant expression of JNK-associated leucine-zipper protein, JLP, promotes accelerated growth of ovarian cancer. *Oncotarget* 2016;7(45):72845-59. doi: 10.18632/oncotarget.12069

68. Seki E, Brenner DA, Karin M. A Liver Full of JNK: Signaling in Regulation of Cell Function and Disease Pathogenesis, and Clinical Approaches. *Gastroenterology* 2012;143(2):307-20. doi: 10.1053/j.gastro.2012.06.004

69. Luo S, Ren B, Zou G, Liu J, Chen W, Huang Y, et al. SPAG9/MKK3/p38 axis is a novel therapeutic target for liver cancer. *Oncol Rep* Published online January 30, 2019. doi: 10.3892/or.2019.6987

70. Grossi V. p38α MAPK pathway: A key factor in colorectal cancer therapy and chemoresistance. *World J Gastroenterol* 2014;20(29):9744. doi: 10.3748/wjg.v20.i29.9744

71. Wang S, Lee K, Tsai C, Chen Y, Yeh Y. Phosphorylated p38 and JNK MAPK proteins in hepatocellular carcinoma. *Eur J Clin Invest* 2012;42(12):1295-301. doi: 10.1111/eci.12003

72. Sinha A, Agarwal S, Parashar D, Verma A, Saini S, Jagadish N, et al. Down regulation of SPAG9 reduces growth and invasive potential of triple-negative breast cancer cells: possible implications in targeted therapy. *Journal of Experimental & Clinical Cancer Research* 2013;32(1):69. doi: 10.1186/1756-9966-32-69

73. Stramucci L, Pranteda A, Bossi G. Insights of Crosstalk between p53 Protein and the MKK3/MKK6/p38 MAPK Signaling Pathway in Cancer. *Cancers (Basel)* 2018;10(5):131. doi: 10.3390/cancers10050131

74. Filmus J, Selleck SB. Glypicans: proteoglycans with a surprise. *Journal of Clinical Investigation* 2001;108(4):497-501. doi: 10.1172/JCI13712

75. Pilia G, Hughes-Benzie RM, MacKenzie A, Baybayan P, Chen EY, Huber R, et al. Mutations in GPC3, a glypican gene, cause the Simpson-Golabi-Behmel overgrowth syndrome. *Nat Genet* 1996;12(3):241-7. doi: 10.1038/ng0396-241

76. Song HH, Shi W, Xiang YY, Filmus J. The Loss of Glypican-3 Induces Alterations in Wnt Signaling. *Journal of Biological Chemistry* 2005;280(3):2116-25. doi: 10.1074/jbc.M410090200

77. Capurro MI, Li F, Filmus J. Overgrowth of a mouse model of Simpson– Golabi–Behmel syndrome is partly mediated by Indian Hedgehog. *EMBO Rep* 2009;10(8):901-7. doi: 10.1038/embor.2009.98

78. Hartwig S, Hu MC, Cella C, Piscione T, Filmus J, Rosenblum ND. Glypican-3 modulates inhibitory Bmp2-Smad signaling to control renal development in vivo. *Mech Dev* 2005;122(7-8):928-38. doi: 10.1016/j.mod.2005.03.007

79. Capurro M, Wanless IR, Sherman M, Deboer G, Shi W, Miyoshi E, et al. Glypican-3: a novel serum and histochemical marker for hepatocellular carcinoma. *Gastroenterology* 2003;125(1):89-97. doi: 10.1016/S0016-5085(03)00689-9

80. Feng M, Ho M. Glypican-3 antibodies: A new therapeutic target for liver cancer. *FEBS Lett* 2014;588(2):377-82. doi: 10.1016/j.febslet.2013.10.002

81. Fu P, Hu B, Ma X, Yang Z, Yu M, Sun H, et al. New insight into BIRC3: A novel prognostic indicator and a potential therapeutic target for liver cancer. *J Cell Biochem* 2019;120(4):6035-45. doi: 10.1002/jcb.27890

82. Cheng CLH, Tsang FHC, Wei L, Chen M, Chin DWC, Shen J, et al. Bromodomain-containing protein BRPF1 is a therapeutic target for liver cancer. *Commun Biol* 2021;4(1):888. doi: 10.1038/s42003-021-02405-6

83. Tsang FH, Law C, Tang TC, Cheng CL, Chin DW, Tam WV, et al. Aberrant Super-Enhancer Landscape in Human Hepatocellular Carcinoma. *Hepatology* 2019;69(6):2502-17. doi: 10.1002/hep.30544

84. Crowley JA, Wang Y, Rapoport AP, Ning Y. Detection of MOZ-CBP fusion in acute myeloid leukemia with 8;16 translocation. *Leukemia* 2005;19(12):2344-5. doi: 10.1038/sj.leu.2403971

85. Ballabio C, Gianesello M, Lago C, Okonechnikov K, Anderle M, Aiello G, et al. Notch1 switches progenitor competence in inducing medulloblastoma. *Sci Adv* 2021;7(26). doi: 10.1126/sciadv.abd2781

86. Pelletier N, Champagne N, Stifani S, Yang XJ. MOZ and MORF histone acetyltransferases interact with the Runt-domain transcription factor Runx2. *Oncogene* 2002;21(17):2729-40. doi: 10.1038/sj.onc.1205367

87. Ohta K, Ohigashi M, Naganawa A, Ikeda H, Sakai M, Nishikawa J ichi, et al. Histone acetyltransferase MOZ acts as a co-activator of Nrf2–MafK and induces tumour marker gene expression during hepatocarcinogenesis. *Biochemical Journal* 2007;402(3):559-66. doi: 10.1042/BJ20061194

88. Voss AK, Collin C, Dixon MP, Thomas T. Moz and Retinoic Acid Coordinately Regulate H3K9 Acetylation, Hox Gene Expression, and Segment Identity. *Dev Cell* 2009;17(5):674-86. doi: 10.1016/j.devcel.2009.10.006

89. Yan K, Rousseau J, Machol K, Cross LA, Agre KE, Gibson CF, et al. Deficient histone H3 propionylation by BRPF1-KAT6 complexes in neurodevelopmental disorders and cancer. *Sci Adv* 2020;6(4). doi: 10.1126/sciadv.aax0021

90. Ullah M, Pelletier N, Xiao L, Zhao SP, Wang K, Degerny C, et al. Molecular Architecture of Quartet MOZ/MORF Histone Acetyltransferase Complexes. *Mol Cell Biol* 2008;28(22):6828-43. doi: 10.1128/MCB.01297-08

91. Dauch D, Rudalska R, Cossa G, Nault JC, Kang TW, Wuestefeld T, et al. A MYC–aurora kinase A protein complex represents an actionable drug target in p53-altered liver cancer. *Nat Med* 2016;22(7):744-53. doi: 10.1038/nm.4107

92. Lu L, Han H, Tian Y, Li W, Zhang J, Feng M, et al. Aurora kinase A mediates c-Myc's oncogenic effects in hepatocellular carcinoma. *Mol Carcinog* 2015;54(11):1467-79. doi: 10.1002/mc.22223

93. Yin D, Wangensteen KJ. Incapacitated Capicua in Sorafenib-Resistant HCC. *Cell Mol Gastroenterol Hepatol* 2020;10(2):428-9. doi: 10.1016/j.jcmgh.2020.03.007

94. Dauch D, Rudalska R, Cossa G, Nault JC, Kang TW, Wuestefeld T, et al. A MYC–aurora kinase A protein complex represents an actionable drug target in p53-altered liver cancer. *Nat Med* 2016;22(7):744-53. doi: 10.1038/nm.4107

95. Bowyer C, Lewis AL, Lloyd AW, Phillips GJ, Macfarlane WM. Hypoxia as a target for drug combination therapy of liver cancer. *Anticancer Drugs* 2017;28(7):771-80. doi: 10.1097/CAD.0000000000000516

96. Kuo P, Huang M, Hung J, Chou S, Chiang S, Huang Y, et al. Synergistic effect of lung tumor-associated dendritic cell-derived HB-EGF and CXCL5 on cancer progression. *Int J Cancer* 2014;135(1):96-108. doi: 10.1002/ijc.28673

97. Bain G, Shannon KE, Huang F, Darlington J, Goulet L, Prodanovich P, et al. Selective Inhibition of Autotaxin Is Efficacious in Mouse Models of Liver Fibrosis. *J Pharmacol Exp Ther* 2017;360(1):1-13. doi: 10.1124/jpet.116.237156

98. Aikawa S, Hashimoto T, Kano K, Aoki J. Lysophosphatidic acid as a lipid mediator with multiple biological actions. *J Biochem* 2015;157(2):81-9. doi: 10.1093/jb/mvu077

99. TAGAYASU Y, YAMADA R, KANEMITSU K, KONDO Y, ITOYAMA R, HAYASHI H, et al. Conversion Surgery Performed Following Durvalumab Combined With Gemcitabine and Cisplatin in Cholangiocarcinoma: A Case Report. *In Vivo (Brooklyn)* 2025;39(3):1724-30. doi: 10.21873/invivo.13974

100. Kaffe E, Katsifa A, Xylourgidis N, Ninou I, Zannikou M, Harokopos V, et al. Hepatocyte autotaxin expression promotes liver fibrosis and cancer. *Hepatology* 2017;65(4):1369-83. doi: 10.1002/hep.28973

101. Baud V, Karin M. Signal transduction by tumor necrosis factor and its relatives. *Trends Cell Biol* 2001;11(9):372-7. doi: 10.1016/S0962-8924(01)02064-5

102. Yamada Y, Kirillova I, Peschon JJ, Fausto N. Initiation of liver growth by tumor necrosis factor: Deficient liver regeneration in mice lacking type I tumor necrosis factor receptor. *Proceedings of the National Academy of Sciences* 1997;94(4):1441-6. doi: 10.1073/pnas.94.4.1441

103. Roderburg C, Gautheron J, Luedde T. TNF-Dependent Signaling Pathways in Liver Cancer: Promising Targets for Therapeutic Strategies? 2012;30(5):500-7. doi: 10.1159/000341700

104. Wei T, Zhang LN, Lv Y, Ma XY, Zhi L, Liu C, et al. Overexpression of platelet-derived growth factor receptor alpha promotes tumor progression and indicates poor prognosis in hepatocellular carcinoma. *Oncotarget* 2014;5(21):10307-17. doi: 10.18632/oncotarget.2537

105. Ingber D. Extracellular matrix and cell shape: Potential control points for inhibition of angiogenesis. *J Cell Biochem* 1991;47(3):236-41. doi: 10.1002/jcb.240470309

106. Harada K, Shiota G, Kawasaki H. Transforming growth factor-α and epidermal growth factor receptor in chronic liver disease and hepatocellular carcinoma. *Liver* 1999;19(4):318-25. doi: 10.1111/j.1478-3231.1999.tb00056.x

107. Villanueva A, Newell P, Chiang D, Friedman S, Llovet J. Genomics and Signaling Pathways in Hepatocellular Carcinoma. *Semin Liver Dis* 2007;27(1):055-76. doi: 10.1055/s-2006-960171

108. Huynh H, Ngo VC, Koong HN, Poon D, Choo SP, Toh HC, et al. AZD6244 enhances the anti-tumor activity of sorafenib in ectopic and orthotopic models of human hepatocellular carcinoma (HCC). *J Hepatol* 2010;52(1):79-87. doi: 10.1016/j.jhep.2009.10.008

109. Rong C, Muller M, Flechtenmacher C, Holzinger D, Dyckhoff G, Bulut OC, et al. Differential Activation of ERK Signaling in HPV-Related Oropharyngeal Squamous Cell Carcinoma. *Cancers (Basel)* 2019;11(4):584. doi: 10.3390/cancers11040584

110. Lee TK, Man K, Ho JW, Sun CK, Ng KT, Wang XH, et al. FTY720 induces apoptosis of human hepatoma cell lines through PI3-K-mediated Akt dephosphorylation. *Carcinogenesis* 2004;25(12):2397-405. doi: 10.1093/carcin/bgh250

111. Rizell M, Andersson M, Cahlin C, Hafström L, Olausson M, Lindnér P. Effects of the mTOR inhibitor sirolimus in patients with hepatocellular and cholangiocellular cancer. *Int J Clin Oncol* 2008;13(1):66-70. doi: 10.1007/s10147-007-0733-3

112. Ueki T, Fujimoto J, Suzuki T, Yamamoto H, Okamoto E. Expression of hepatocyte growth factor and its receptor c- met proto-oncogene in hepatocellular carcinoma. *Hepatology* 1997;25(4):862-6. doi: 10.1002/hep.510250413

113. Zhao Y, Ye W, Wang YD, Chen WD. HGF/c-Met: A Key Promoter in Liver Regeneration. *Front Pharmacol* 2022;13. doi: 10.3389/fphar.2022.808855

114. Carr BI. Hepatocellular carcinoma: Current management and future trends. *Gastroenterology* 2004;127(5):S218-24. doi: 10.1053/j.gastro.2004.09.036

115. Kulik L, Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. *Gastroenterology* 2004;127(5):S277-82. doi: 10.1053/j.gastro.2004.09.042

116. AGUAYO A. Nonsurgical treatment of hepatocellular carcinoma. *Semin Oncol* 2001;28(5):503-13. doi: 10.1016/S0093-7754(01)90143-5

117. Kuvshinoff BW, Ota DM. Radiofrequency ablation of liver tumors: Influence of technique and tumor size. *Surgery* 2002;132(4):605-12. doi: 10.1067/msy.2002.127545

118. Klonisch T, Wiechec E, Hombach-Klonisch S, Ande SR, Wesselborg S, Schulze-Osthoff K, et al. Cancer stem cell markers in common cancers – therapeutic implications. *Trends Mol Med* 2008;14(10):450-60. doi: 10.1016/j.molmed.2008.08.003

119. Chu X, Tian W, Ning J, Xiao G, Zhou Y, Wang Z, et al. Cancer stem cells: advances in knowledge and implications for cancer therapy. *Signal Transduct Target Ther* 2024;9(1):170. doi: 10.1038/s41392-024-01851-y

120. Theise ND, Nimmakayalu M, Gardner R, Illei PB, Morgan G, Teperman L, et al. Liver from bone marrow in humans. *Hepatology* 2000;32(1):11-6. doi: 10.1053/jhep.2000.9124

121. Alison MR. Liver Stem Cells: Implications for Hepatocarcinogenesis. *Stem Cell Rev* 2005;1(3):253-60. doi: 10.1385/SCR:1:3:253

122. Michalopoulos GK, DeFrances MC. Liver Regeneration. *Science (1979)* 1997;276(5309):60-6. doi: 10.1126/science.276.5309.60

123. Fausto N. Liver regeneration and repair: Hepatocytes, progenitor cells, and stem cells. *Hepatology* 2004;39(6):1477-87. doi: 10.1002/hep.20214

124. Marrero JA. Hepatocellular carcinoma. *Curr Opin Gastroenterol* 2005;21(3):308-12. doi: 10.1097/01.mog.0000159817.55661.ca

125. Libbrecht L, De Vos R, Cassiman D, Desmet V, Aerts R, Roskams T. Hepatic Progenitor Cells in Hepatocellular Adenomas. *Am J Surg Pathol* 2001;25(11):1388-96. doi: 10.1097/00000478-200111000-00006

126. Robrechts C, De Vos R, Van den Heuvel M, Van Cutsem E, Van Damme B, Desmet V, et al. Primary liver tumour of intermediate (hepatocyte—bile duct cell) phenotype: a progenitor cell tumour? *Liver* 1998;18(4):288-93. doi: 10.1111/j.1600-0676.1998.tb00168.x

127. Kim H, Park C, Han KH, Choi J, Kim YB, Kim JK, et al. Primary liver carcinoma of intermediate (hepatocyte–cholangiocyte) phenotype. *J Hepatol* 2004;40(2):298-304. doi: 10.1016/j.jhep.2003.10.023

128. Alison M, Golding M, Sarraf C, Edwards R, Lalani E. Liver damage in the rat induces hepatocyte stem cells from biliary epithelial cells. *Gastroenterology* 1996;110(4):1182-90. doi: 10.1053/gast.1996.v110.pm8613008

129. Yin L, Lynch D, Sell S. Participation of different cell types in the restitutive response of the rat liver to periportal injury induced by allyl alcohol. *J Hepatol* 1999;31(3):497-507. doi: 10.1016/S0168-8278(99)80043-9

130. Petersen BE, Bowen WC, Patrene KD, Mars WM, Sullivan AK, Murase N, et al. Bone Marrow as a Potential Source of Hepatic Oval Cells. *Science (1979)* 1999;284(5417):1168-70. doi: 10.1126/science.284.5417.1168

131. Sakaida I. Clinical application of bone marrow cell transplantation for liver diseases. *J Gastroenterol* 2006;41(1):93-4. doi: 10.1007/s00535-006-1746-9

132. Wang M, Han J, Xing H, Zhang H, Li Z, Liang L, et al. Dysregulated Fatty Acid Metabolism in Hepatocellular Carcinoma. *Hepat Oncol* 2016;3(4):241-51. doi: 10.2217/hep-2016-0012

133. Malehmir M, Pfister D, Gallage S, Szydlowska M, Inverso D, Kotsiliti E, et al. Platelet GPIbα is a mediator and potential interventional target for NASH and subsequent liver cancer. *Nat Med* 2019;25(4):641-55. doi: 10.1038/s41591-019-0379-5

134. Liu Y, Zhang X, Lin J, Chen Y, Qiao Y, Guo S, et al. CCT3 acts upstream of YAP and TFCP2 as a potential target and tumour biomarker in liver cancer. *Cell Death Dis* 2019;10(9):644. doi: 10.1038/s41419-019-1894-5

135. Fu M, Hu Y, Lan T, Guan KL, Luo T, Luo M. The Hippo signalling pathway and its implications in human health and diseases. *Signal Transduct Target Ther* 2022;7(1):376. doi: 10.1038/s41392-022-01191-9

136. Deng Z, Fan T, Xiao C, Tian H, Zheng Y, Li C, et al. TGF-β signaling in health, disease and therapeutics. *Signal Transduct Target Ther* 2024;9(1):61. doi: 10.1038/s41392-024-01764-w

137. Luo S, Ren B, Zou G, Liu J, Chen W, Huang Y, et al. SPAG9/MKK3/p38 axis is a novel therapeutic target for liver cancer. *Oncol Rep* Published online January 30, 2019. doi: 10.3892/or.2019.6987

138. Kandil DH, Cooper K. Glypican-3. *Adv Anat Pathol* 2009;16(2):125-9. doi: 10.1097/PAP.0b013e3181992455

139. Fu P, Hu B, Ma X, Yang Z, Yu M, Sun H, et al. New insight into BIRC3: A novel prognostic indicator and a potential therapeutic target for liver cancer. *J Cell Biochem* 2019;120(4):6035-45. doi: 10.1002/jcb.27890

140. Cheng CLH, Tsang FHC, Wei L, Chen M, Chin DWC, Shen J, et al. Bromodomain-containing protein BRPF1 is a therapeutic target for liver cancer. *Commun Biol* 2021;4(1):888. doi: 10.1038/s42003-021-02405-6

141. Dauch D, Rudalska R, Cossa G, Nault JC, Kang TW, Wuestefeld T, et al. A MYC–aurora kinase A protein complex represents an actionable drug target in p53-altered liver cancer. *Nat Med* 2016;22(7):744-53. doi: 10.1038/nm.4107

142. Guo Y, Xiao Z, Yang L, Gao Y, Zhu Q, Hu L, et al. Hypoxia-inducible factors in hepatocellular carcinoma (Review). *Oncol Rep* Published online November 1, 2019. doi: 10.3892/or.2019.7397

143. Tu T, Hong H, Alhousari D, He L, Alba M, Gu Y, et al. Proinflammatory macrophages release CXCL5 to regulate T cell function and limit effects of αPD-1 in steatosis-driven liver cancer. *JHEP Reports* 2025;7(6):101385. doi: 10.1016/j.jhepr.2025.101385

144. She S, Zhang Q, Shi J, Yang F, Dai K. Roles of Autotaxin/Autotaxin-Lysophosphatidic Acid Axis in the Initiation and Progression of Liver Cancer. *Front Oncol* 2022;12. doi: 10.3389/fonc.2022.922945

145. Roderburg C, Gautheron J, Luedde T. TNF-Dependent Signaling Pathways in Liver Cancer: Promising Targets for Therapeutic Strategies? 2012;30(5):500-7. doi: 10.1159/000341700

146. Xue Y, Ruan Y, Wang Y, Xiao P, Xu J. Signaling pathways in liver cancer: pathogenesis and targeted therapy. *Molecular Biomedicine* 2024;5(1):20. doi: 10.1186/s43556-024-00184-0

147. Yamashita T, Wang XW. Cancer stem cells in the development of liver cancer. *Journal of Clinical Investigation* 2013;123(5):1911-8. doi: 10.1172/JCI66024

148. Febbraio MA, Reibe S, Shalapour S, Ooi GJ, Watt MJ, Karin M. Preclinical Models for Studying NASH-Driven HCC: How Useful Are They? *Cell Metab* 2019;29(1):18-26. doi: 10.1016/j.cmet.2018.10.012

149. Xiao Y, Dong J. The Hippo Signaling Pathway in Cancer: A Cell Cycle Perspective. *Cancers (Basel)* 2021;13(24):6214. doi: 10.3390/cancers13246214

150. Labrie M, Brugge JS, Mills GB, Zervantonakis IK. Therapy resistance: opportunities created by adaptive responses to targeted therapies in cancer. *Nat Rev Cancer* 2022;22(6):323-39. doi: 10.1038/s41568-022-00454-5

151. Karsten Dafonte K, Weber L, Chmielewski F, Böhmer AM, Lutz P, Hartmann G, et al. Dose Recommendations for Common Drugs in Patients with Liver Cirrhosis: A Systematic Literature Review. *Clin Drug Investig* 2023;43(7):475-502. doi: 10.1007/s40261-023-01289-0

152. Ruff SM, Manne A, Cloyd JM, Dillhoff M, Ejaz A, Pawlik TM. Current Landscape of Immune Checkpoint Inhibitor Therapy for Hepatocellular Carcinoma. *Current Oncology* 2023;30(6):5863-75. doi: 10.3390/curroncol30060439