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Review

Noncoding RNAs: Key Modulators of the Hippo Pathway in Hepatocellular Carcinoma Progression

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Abstract

The Hippo signaling system plays a vital role in controlling cell proliferation, apoptosis, and organ size. Disruption of this pathway strongly correlates with the growth and progression of hepatocellular carcinoma (HCC). Noncoding RNAs (ncRNAs), including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), play a crucial role in regulating Hippo signaling and have a significant impact on different aspects of liver tumor development. This paper thoroughly investigates the functions of ncRNAs in regulating the Hippo pathway, specifically in liver cancer. We examine how certain miRNAs and lncRNAs engage with Hippo signaling components, influencing cellular processes like growth regulation, programmed cell death, the spread of cancer cells, and resistance to chemotherapy. Developing an understanding of these interactions offers valuable knowledge about the intricate regulatory networks that control liver cancer and identifies possible targets for therapeutic intervention. Our study shows how important it is for ncRNA to control Hippo signaling in liver cancer. It also suggests possible directions for future research that focuses on creating ncRNA-based diagnostic and therapeutic methods.

1. Introduction

HCC is one of the most common cancers worldwide [1,2]. Various treatment modalities, such as surgical interventions and organ transplantation, have the potential to improve the overall well-being of individuals suffering from HCC [3]. Nevertheless, due to the present constraints of available medications and the ineffectiveness of early detection, the rate of survival of individuals with HCC is dismal [4]. Therefore, it is crucial to conduct a comprehensive examination of the molecular mechanisms contributing to the progression of liver cancer to discover new and effective treatment approaches [5-7].

The pathogenesis of liver carcinoma (LC) is highly intricate, encompassing the sequential impact of numerous signals that finally result in alterations in crucial molecular consequences in vivo and the development of tumors [8]. The Hippo pathway represents an evolutionarily conserved signaling cascade [9]. It is involved in a range of biological tasks, including cellular proliferation and organ growth [10]. The Hippo pathway is known to control the processes of liver regeneration, development, and metabolism. Disruptions in this system can lead to liver disorders, such as LC [11].

Non-coding RNAs (ncRNAs) are a type of RNA molecule that does not code for proteins [12]. They have been shown to have a role in the development and advancement of different types of malignancies by influencing the biological activities of tumor cells, particularly in HCC [13]. Over 85% of the genome exhibits transcriptional activity, encompassing a wide range of non-coding RNAs. Non-coding RNAs, including miRNAs, lncRNAs, and circRNAs, are plentiful and durable [14]. miRNAs, the most abundant and investigated group of ncRNAs, regulate almost 30% of genes in the genome of humans [15]. miRNAs exert control over gene expression by forming complexes with DNA, RNA, or proteins, thereby modulating a range of biological processes [16]. LncRNAs are RNA molecules that are linear in structure and have a transcript length of more than 200 nucleotides. They exhibit a wider range of functions compared to miRNAs, as the involvement of lncRNAs in cell physiology and pathology, particularly in terms of their spatial and temporal effects, has been increasingly understood. They can function as signals, scaffolds, decoys, or guides. Even lncRNAs of the same type may operate through distinct pathways [17,18]. Recent findings suggest that circRNAs are a type of non-coding RNAs that are associated with many clinical conditions. CircRNAs differ from linear RNAs in that they are formed through a process called back-splicing, resulting in closed-loop structures [19-21]. CircRNAs demonstrate notable properties such as high number, diversity, structural conservation across various species, tissue specificity, stability, and dependence on the stage of tumor development [22,23]. These tasks are performed by interacting with RNA-binding proteins, absorbing miRNAs, converting to peptides or proteins, controlling gene transcription, and interacting with conventional splicing [24].

New research has revealed the important functions of ncRNAs in impacting the YAP/TAZ signaling pathway in the setting of liver cancer [25-27]. These roles involve the control of the transcription process, the localization, and the stability of YAP/TAZ regulators. Furthermore, there is compelling evidence indicating that YAP/TAZ itself could act as an upstream regulator of ncRNAs in liver cancer [28]. This review explores the complex interplay between YAP/TAZ and ncRNAs, focusing on their distinct biological functions about liver cancer. There is a suggestion that non-coding RNAs associated with the YAP/TAZ pathway could become important therapeutic targets and predictive indicators in liver cancer.

2. The Hippo Signaling Pathway: Core Components and Mechanisms of Action

The Hippo signaling system and its constituents were initially discovered in Drosophila melanogaster as a pivotal controller of cellular proliferation, the dimension of organs and tissues, and apoptosis [29]. In subsequent years, researchers found and defined the roles of mammal homology in the fly Hippo signaling system [30]. The primary signaling pathway in vertebrates involves the MST1/2 and LATS1/2 kinase cassettes, which phosphorylate and inhibit the transcriptional regulators YAP and TAZ in conjunction with WW45 (the mammalian counterpart of Salvator) and MOB1 [31,32]. YAP is an essential transcription coactivator that regulates organ growth and is considered a potential oncogene. The activation of YAP is stringently regulated by the kinase cascade of the Hippo pathway, specifically by LATS1/2. The 14-3-3 protein is the critical signal that retains YAP in the cytoplasm by phosphorylating it at Ser 127 [33].

The phosphorylation of Serine 397 generates a “phosphodegron” motif that facilitates the binding of SCF-β-TRCP E3 ubiquitin ligase [34]. This binding event triggers the ubiquitination of YAP and its subsequent destruction by the proteasome [33]. Moreover, the phosphorylation of Ser 381 is essential for triggering the activation of a phosphodegron in YAP through CK1δ/ε (Casein Kinase 1), which is then followed by the recruiting process of SCF-β-TRCP E3 ubiquitin ligase [33]. YAP can be phosphorylated by AKT, AMPK, and LATS1/2 to control apoptosis in response to cellular injury and regulate glucose homeostasis [35]. The Hippo pathway has two core kinases: MST1/2 and LATS1/2. Several kinases and regulators, including the MAP4K family, RASSF1A, AMPK (PRKKA1/PRKKA2), TAOK1-3, PKA, PKC, NF2, PP2, RhoA, and Ajuba LIM proteins, all control their activity [36].

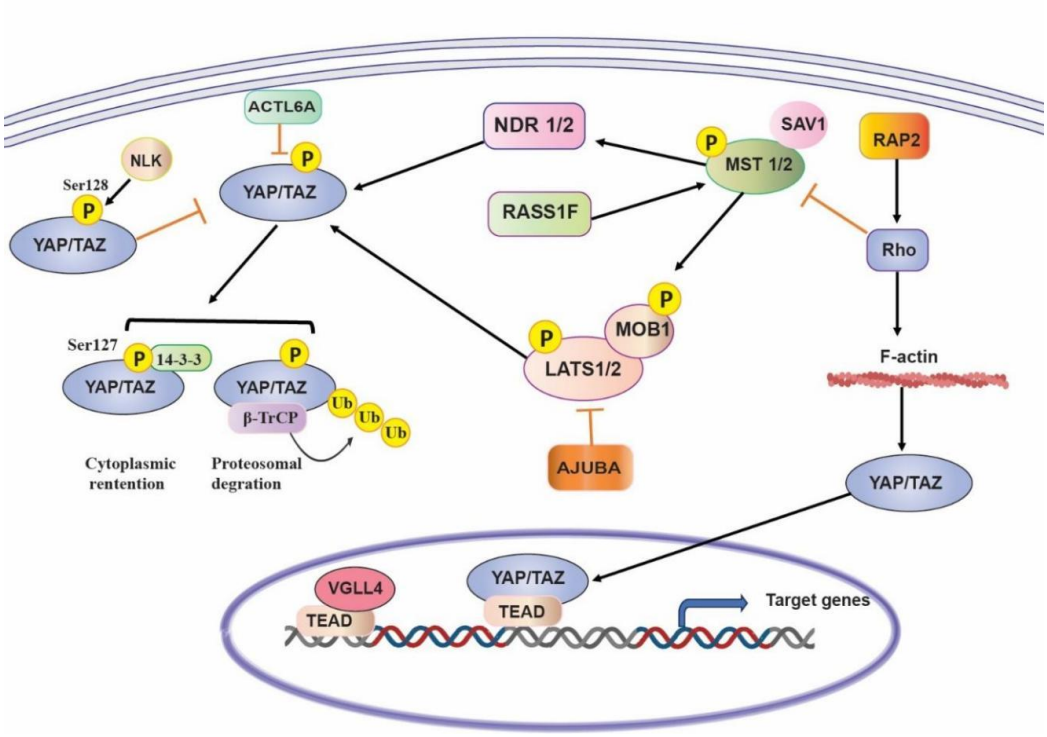

Figure 1. Regulation of YAP/TAZ signaling through pathway crosstalk.

The MST1/2-SAV1 complex is an essential component of the canonical Hippo pathway because it stimulates the LATS1/2-MOB1A/B complex through phosphorylation. After that, this combination makes YAP and TAZ inactive by phosphorylating them. The cascade's core kinases are MST1/2 and LATS1/2, and adaptor proteins SAV1 and MOB1A/B enhance MST1/2 and LATS1/2's activation and phosphorylation [37]. The deactivation of YAP and TAZ, controlled by phosphorylation, occurs through the sequester of phosphorylated YAP/TAZ in the cytoplasm via 14-3-3 proteins, as well as via the degradation of phosphorylated YAP/TAZ by the proteasome [33,38]. Deleting genes *MST1/2*, *LATS1/2*, *SAV1*, or *MOB1A/B* results in higher concentrations of YAP and TAZ in the nucleus, leading to greater activity as transcriptional coactivators. On the other hand, overexpression of *MST1/2*, *LATS1/2*, *SAV1*, or *MOB1A/B* leads to enhanced cytoplasm localization and destruction

of YAP and TAZ. Consequently, the measurement of YAP/TAZ protein levels and their location inside cells is frequently employed to assess the functioning of the Hippo pathway (Figure 1) [10].

YAP/TAZ activity is predominantly controlled by the Hippo signaling cascade. This pathway is triggered when MST1/2 and LATS1/2 kinases, along with their cofactors SAV1 and MOB, are phosphorylated, causing YAP/TAZ to be retained in the cytoplasm and ultimately degraded. Conversely, when kinase activity is inactive, YAP/TAZ accumulates in the nucleus and interacts with transcription factors to activate gene expression. The Hippo pathway encompasses various additional regulatory elements. Moreover, YAP/TAZ are modulated by mechanotransduction, responding to mechanical signals via the actin cytoskeleton, underscoring their role in merging biochemical and mechanical signals in cellular activities.

2.1 The Role of the Hippo Pathway in HCC

YAP has been consistently linked to the development of HCC for a significant period of time. Yap is excessively produced and necessary for advancement in c-Myc and Akt1-driven HCC [39]. Overexpression of *YAP* specifically in hepatocytes is also enough to cause the development of hepatocellular carcinoma [40]. Similarly, the induction of *Yap* or *TAZ* by hydrodynamic tail injection can induce the development of HCC [41]. The Hippo pathway plays a crucial function in preventing the growth of liver cancer. When Mst1/2, Sav1, Nf2, Mob1a/b, or Kibra are downregulated, it is enough to trigger the formation of HCC, cholangiocarcinoma (CC), or a combination of both [10]. Moreover, it was demonstrated that the activation of Yap is an essential and initial occurrence in the development of liver cancer induced by carcinogens in rats [42].

Moreover, Yap has a crucial role in other types of liver tumors. *YAP* has extensive expression in individuals with hepatoblastomas and is necessary for the growth of hepatoblastoma cell lines. Moreover, the overexpression of *YAP* and *β-catenin* in the liver of adult mice is enough to cause the formation of hepatoblastoma, and the removal of activated YAP in existing hepatoblastoma leads to the regression of the tumor [43-45]. These findings are especially intriguing considering the fact that people with genetic mutations in APC and a family history of polyposis adenomatous had a greater possibility of developing hepatoblastoma [46]. APC-deficient adenomas in the intestinal tract were examined in investigations, revealing that APC has an independent negative regulatory effect on both YAP and β-catenin [47]. Furthermore, a type of tumor called epithelioid hemangioendothelioma, which originates from endothelial cells in blood vessels, is frequently found in the liver. This tumor is characterized by specific fusion genes resulting from chromosomal translocation, including TAZ-CAMTA1 and YAP-TFE3. These fusion genes are believed to remove the normal suppression mechanism controlled by the Hippo pathway and activate a gene program similar to YAP/TAZ [48,49].

It is believed that activated YAP/TAZ plays a role in promoting the expression of crucial TEAD-dependent targets that support the growth and survival of different types of liver malignancies. YAP/TAZ stimulates the production of the antiapoptotic gene *BIRC5*, which is necessary for the persistence of liver cancerous cells [40]. YAP has been found to target the AMPK protein family member NUAK2 in the liver. NUAK2 is necessary for the growth of liver cancer, which is dependent on YAP, and it helps to maintain the activation of YAP [50]. YAP also induces the production of genes related to the Notch pathway, such as *Notch2*. The stimulation of Notch is necessary for YAP-dependent reprogramming of hepatocytes [51]. In addition, a gene signature involving *YAP/TAZ* has been constructed to accurately predict a negative prognosis in patients. However, it is still unclear how many of these genes, including established *YAP/TAZ* targets like Ctgf, contribute to the genesis and progression of liver cancer [52].

Although there is convincing genetic proof connecting the Hippo pathway and the transcriptional regulatory proteins, YAP and TAZ, to liver cancer, the specific approaches by which the Hippo signaling is dysregulated are still not fully understood [50,53]. Elevated levels of YAP and TAZ are associated with a negative prognostic in liver cancer, since a significant number of patients demonstrate an excessive production of these proteins [54-56]. Genetic modifications in genes including *ARID1A*, *KRAS*, and *TP53*, together with epigenetic alterations, have been linked to the disruption of the Hippo pathway [57,58]. Recent research indicates that cell competition, in which the activation of YAP/TAZ in adjacent hepatocytes could inhibit the progression of tumors, is a significant factor in the dynamics of cancer [59,60]. Therefore, it is the relative amounts of YAP/TAZ in tumors compared to adjacent tissue that could potentially accelerate the progression of cancer.

2.2 Influence of Noncoding RNAs on the Hippo Signaling Pathway in HCC

NcRNAs constitute the endogenous RNA molecules that make up about 98% of the transcribed genome [61]. They were previously considered "dark matter" due to their inability to produce proteins [62]. After extensive investigation, it has been discovered that they play a crucial role as molecules of signaling in the control of vital physiological pathways, such as Hippo signaling [63]. Their presence is plentiful and consistent, mostly consisting of miRNAs, lncRNAs, and circRNAs. NcRNAs play a role in regulating various cancers, including hepatocellular carcinoma [64].

2.2.1 MiRNAs: Key Regulators of Gene Expression

MicroRNAs are a class of small, noncoding RNA molecules that play a pivotal role in regulating gene expression at the post-transcriptional level. MiRNAs play crucial roles in the development of cancer, and their characteristics vary among healthy tissues and different types of cancer [65]. Dysregulation of miRNA biogenesis and expression has a significant impact on the occurrence and advancement of liver cancers [66]. miRNAs may serve as tumor suppressors or oncogenes

based on the specific mRNAs they regulate and the phenotypic changes these interactions induce within cells [67].

2.2.1.1 MiRNAs: Precise Regulators of the Hippo Pathway in HCC

Moreover, miRNAs can interact with parts of the Hippo-YAP/TAZ signaling pathway. MiRNAs play crucial roles in the development of cancer, and their characteristics vary among healthy tissues and different types of cancer [65]. They change many cellular functions, such as migration, proliferation, apoptosis, and differentiation, by carefully controlling gene expression through post-transcriptional mechanisms [65]. Their capacity to pinpoint critical elements of signaling cascades renders them crucial to cancer biology. Within the framework of HCC, miRNAs are especially significant for their interactions with the Hippo-YAP/TAZ signaling pathway. Various malignancies, including HCC, disrupt this pathway, an essential regulator of organ growth and tissue homeostasis [66].

MiRNAs specifically bind to target mRNAs to control the stability and translation of important parts of the Hippo pathway, such as MST1/2, LATS1/2, and YAP/TAZ. These interactions can enhance or inhibit oncogenic signals, rendering miRNAs essential for preserving the balance between normal and malignant cellular behavior. MiRNAs can either stop or grow tumors, depending on the cell type. This shows how diverse and complicated miRNAs are in controlling cancer. [66]. This regulatory accuracy highlights the potential of miRNAs as therapeutic targets and diagnostic indicators in HCC. Their extensive dysregulation in liver cancer provides an opportunity for innovative therapy techniques that seek to restore normal Hippo pathway function and impede tumor advancement.

2.2.1.1.1 Targeting YAP: Tumor Suppressor and Oncogenic miRNAs

Liu et al. discovered that microRNA-375 specifically targets the Hippo-signaling mediator YAP in liver cancer, effectively suppressing the tumor's characteristics. The expression of miR-375 was markedly reduced in carcinoma of the liver tissues in comparison to adjacent non-tumor tissues [68]. The overexpression of miR-375 reduced the transcriptional function of *YAP* and inhibited its normal protein level. Functional experiments confirmed that miR-375 suppressed the growth and infiltration of HCC cells, indicating a possible therapeutic utilization for the treatment of HCC. Furthermore, YAP activation is the first step in the development of liver cancer and is associated with miR-375 reduction. When Verteporfin (VP) was given, the number of preneoplastic foci declined and cell proliferation decreased. This was caused by interfering with the YAP-TEAD complex, which highlights the important role of miR-375 in controlling the overproduction of *YAP* and suggests a possible treatment for liver cancer [69]. In fibrolamellar carcinoma (FLC), an uncommon form of liver cancer, cells when miR-375 was overexpressed, reduced cell migration and proliferation via inhibiting proteins in the Hippo signaling pathway [70]. Moreover, the regulation of *IL-6* and *TGF-β* expression by the miR-375/Yes-associated protein (YAP) axis is one factor that leads to cisplatin resistance in liver cancer cells. In cisplatin-resistant cells, elevated levels of *YAP* and its nuclear localization were associated with reduced miR-375 levels, which in turn led to elevated levels of *IL-6* and *TGF-β*. It is suggested that targeting the miR-375/YAP axis could be useful in overcoming chemoresistance in liver cancer, as suppressing YAP restored cisplatin sensitivity [71].

Linked to alterations in DNA and histone methylation, de Conti et al. discovered that prolonged furan exposure in Fischer 344 rats led to an irreversible down-regulation of miR-375 in the liver [72]. YAP1, an important player in liver carcinogenesis, was up-regulated as a result of this down-regulation. The results point to the involvement of epigenetic changes and non-genotoxic processes in furan's hepatotoxicity and carcinogenesis.

The interaction between the Hippo and PI3K-mTOR pathways is facilitated by YAP through the inhibition of PTEN via miR-29. The activation of mTOR by YAP is mediated by the decrease in expression of *PTEN*, which is done by the suppression of *PTEN* translation induced by miR-29. This interaction leads to the modification of the PI3K-mTOR pathway, which affects the size of cells, growth of tissues, and hyperplasia. These findings demonstrate a functional connection between the Hippo and PI3K-mTOR pathways in the regulation of organ growth [73]. Specifically, miRNA-186 inhibits HCC development and Hippo signaling by targeting YAP1. The migration, invasion, and proliferation of HCC cells were reduced when miR-186 was overexpressed, which led to a decrease in YAP1 mRNA and protein levels [74]. Through its targeting of *YAP1* expression, miRNA-590-5p was discovered to inhibit chemoresistance in HCC. miR-590-5p decreases stemness indicators and ATP-binding cassette transport proteins by downregulating *YAP1*, a critical molecule in chemoresistant HCC cells. Patients with HCC who did not respond well to transarterial chemoembolization (TACE) had higher *YAP1* levels, suggesting that the miR-590-5p/YAP axis could be a possible target for HCC chemoresistance treatment [75].

Researchers discovered that miR-506 inhibits hepatocellular proliferation by interacting with the 3'UTR of the YAP mRNA. HCC tissues had much lower levels of miR-506, and this was associated with a negative correlation with YAP expression. Hepatoma cell lines showed a decrease in cell growth when miR-506 inhibited YAP and the genes it targets, *c-Myc* and *CTGF*. Based on these findings, miR-506 is an essential regulator of HCC growth by interacting with YAP [76]. Similarly, Lei et al. found that hsa-miR-132 inhibits the growth of hepatic carcinoma cells by targeting YAP [77]. miR-132 decreases *YAP* expression at both mRNA and protein levels, leading to increased apoptosis and reduced cell proliferation and invasion. This indicates that miR-132 could be a potential therapeutic target for liver cancer.

Through its targeting of *YAP1*, Jung et al. found that miR-194 stimulates hepatocytic differentiation of progenitor cells [78]. During this differentiation, there was a significant upregulation of miR-194, which improved hepatocytic markers and characteristics. Human embryonic stem cells and progenitor cells overexpressing miR-194 reduced pluripotent factors and sped up differentiation. Identification of miR-194 as an important regulator of liver cell differentiation through YAP1 was confirmed by its induction of differentiation in response to miR-194 targeting YAP1, which was counteracted by *YAP1* overexpression. Furthermore, miR-199a-3p directly interacts with YAP1, restricting cell growth and inducing apoptosis in HCC. This tumor-suppressive miRNA shows significantly lower expression in HCC tissues and cell lines, whereas YAP1 levels are substantially higher. By targeting YAP1, miR-199a-3p effectively curtails proliferation and promotes programmed cell death in liver cancer cells [72]. Another study displayed that miR-21-3p is markedly increased in HCC and associated with reduced survival and advanced tumor stages. It facilitates HCC advancement by directly affecting SMAD7, a negative regulator of the TGF-β pathway, resulting in YAP1 overexpression and increased tumor migration and invasion. The restoration of SMAD7 expression somewhat mitigates these consequences, underscoring the miR-21-3p/SMAD7/YAP1 axis as a crucial epigenetic process and a prospective therapeutic target in HCC [79].

Research has also shown that miR-345 can prevent the spread of HCC by interacting with YAP-1. In both HCC tissues and cell lines, reduced miR-345 expression was associated with a poor outcome. In vitro, miR-345 overexpression prevented HCC cell motility and invasion, and in vivo, miR-345 knockdown increased lung metastasis. It was found that miR-345 affects the behavior of HCC cells through YAP1, a downstream target of the microRNA. A possible therapeutic target for reducing HCC metastasis could be miR-345, according to these data [80].

2.2.1.1.2 Influencing TAZ: Modulating Cancer Cell Dynamics

The study revealed that microRNA-9-3p functions as a tumor suppressor in HCC cells by specifically targeting TAZ (WWTR1). A negative relationship between miR-9-3p and TAZ expression was discovered in both HCC cell lines and clinical samples. Administration of miR-9-3p mimics resulted in a decrease in TAZ expression and suppression of cell proliferation, whereas miR-9-3p inhibitors led to an increase in TAZ expression and enhanced cell growth. These findings emphasize miR-9-3p as a promising therapeutic target in HCC [81]. HCC carcinogenesis is accelerated when HBV preS2 enhances TAZ expression via miRNA-338-3p. Overexpression of PreS2 suppressed miRNA-338-3p expression, which in turn increased TAZ protein levels. Since miRNA-338-3p mimics downregulated TAZ and miRNA-338-3p inhibitors restore TAZ expression, it was confirmed that miRNA-338-3p directly targets TAZ. TAZ overexpression increased HCC cell proliferation and migration, whereas TAZ knockdown decreased these processes [82]. Through its targeting of TAZ, miR-125b inhibits HCC cell migration and invasion. Both HCC tissues and cell lines showed a decrease in miR-125b expression. Inhibiting miR-125b enhanced motility and invasion of HCC cells, whereas overexpressing miR-125b decreased these characteristics. Overexpression of TAZ, which was found to be a downstream target of miR-125b, rendered miR-125b ineffective. These results point to miR-125b as a possible therapeutic target in HCC through its suppression of TAZ [83].

2.2.1.1.3 Regulating LATS1/2: Controlling Cell Growth and Apoptosis

A crucial component of the Hippo signaling system, LATS2, is directly inhibited by miR-103, which in turn increases metastasis and EMT in HCC. Poor outcomes and greater metastasis were associated with miR-103 overexpression in HCC cells. Targeting the miR-103/LATS2 axis may be an effective treatment strategy for HCC, according to clinical data which demonstrated that low E-cadherin and LATS2 expression was associated with high miR-103 expression [84]. Through its regulation of LATS1 methylation and targeting of DNMT3B, miR-29c-3p was discovered to prevent tumor development in HCC. Tumor growth and overall survival are both negatively correlated with miR-29c-3p downregulation in HCC. Reduced migration, proliferation, and tumor formation are observed in HCC cells when miR-29c-3p is overexpressed. HCC patients may benefit from targeting miR-29c-3p because it inhibits DNMT3B, which in turn affects LATS1 methylation and renders the Hippo signaling pathway inactive [85]. Via the Wnt/β-catenin and Hippo/YAP signaling pathways, it was discovered that MEIS2C and MEIS2D increase the advancement of HCC. A worse prognosis was associated with higher levels of MEIS2C/D expression in HCC tissues. Cell migration, invasion, and proliferation were all suppressed when MEIS2C/D was knocked down. CDC73 triggered the Wnt/β-catenin pathway through MEIS2C, and the miR-1307-3p/LATS1 axis enhanced YAP nuclear translocation through MEIS2D. This suggests that MEIS2C/D could be therapeutic targets for HCC [86]. According to research by Li et al., microRNA-15b in extracellular vesicles of macrophages treated with arsenite speeds up the growth of HCC via targeting and reducing LATS1, therefore blocking the Hippo pathway. Increased migration, invasion, and cell proliferation are effects of miR-15b transfer [28]. Based on these results, miR-15b may be a therapeutic target since it promotes the advancement of HCC.

In addition, miR-650 inhibits LATS2, which in turn increases metastases and the epithelial-mesenchymal transition (EMT) in HCC. HCC tissues showed an upregulation of miR-650, which was linked to unfavorable clinical outcomes. It targets LATS2 and increases HCC cell motility, invasion, and multiplication. Because tumors with high miR-650 levels and low LATS2 levels have a poor prognosis, we can use the miR-650/LATS2 pathway as a diagnostic marker for HCC prognosis and as a therapeutic target [87]. Interestingly, FOXA2 activates the GREM2/LATS2/YAP

axis and suppresses miR-103a-3p, which in turn limits the migration and invasion of liver cancer cells. In liver cancer samples, miR-103a-3p was overexpressed, but GREM2 and FOXA2 were downregulated. Cellular invasion and migration were decreased under overexpression of FOXA2, which increased GREM2, improved LATS2 activity, and phosphorylated YAP. By influencing the miR-103a-3p as well as GREM2/LATS2/YAP pathways, these results point to FOXA2 as a potential treatment option for liver cancer [88]. By focusing on LATS2, Yang et al. discovered that miR-195 induces cell death in HCC cells. A decrease in miR-195 was observed in drug-resistant HCC cells, whereas an increase in its expression led to an overexpression of LATS2 and an increase in cell death [89]. Alternatively, LATS2 levels were decreased when miR-195 was inhibited. These results suggest that miR-195 could be a potential therapeutic option for enhancing HCC cellular apoptosis.

2.2.1.1.4 Targeting Other Components of the Hippo Pathway in Liver Cancer

Researchers discovered that miR-135b enhances the development of HCC tumors by interacting positively with the Hippo pathway. A correlation between advanced stages of HCC and poor survival is the upregulation of miR-135b in HCC tissues. As a transcriptional target of the Hippo system, miR-135b increases HCC cell proliferation and migration by suppressing MST1, a critical component of the Hippo pathway. Because of this, miR-135b may be a useful therapeutic target and predictive biomarker for HCC [90]. Similarly, miR-3910 targets MST1 and activates YAP signaling to increase HCC growth and migration. HCC tissues and cell lines increased miR-3910, promoting cell proliferation and migration. In a mouse model, miR-3910 knockdown decreased HCC metastasis, suggesting it may be a therapeutic target [91].

Importantly, research has shown that deubiquitinase YOD1 can increase YAP/TAZ activities while decreasing LATS levels by stabilizing ITCH, an E3 ligase of LATS. miR-21 controls YOD1, which in turn modulates YAP/TAZ levels to cell density. There is some evidence that YOD1 could be a therapeutic target for liver cancer. In a transgenic mouse model, YOD1 caused hepatocyte proliferation and hepatomegaly, which is consistent with YAP expression in patients with liver cancer [92]. Recent research has uncovered that extracellular vesicles (EVs) produced by M2 macrophages play a critical role in inducing CD8+ T cell dysfunction in HCC via the miR-21-5p/YOD1/YAP/β-catenin signaling axis. These EVs transport miR-21-5p into HCC tissues, where it inhibits YOD1, thereby activating the YAP/β-catenin pathway. This activation diminishes the proliferation and cytotoxic capabilities of CD8+ T cells, enabling immune evasion by the tumor. Significantly, blocking miR-21-5p or increasing YOD1 expression can mitigate these effects, making this pathway a promising target for therapeutic intervention in HCC [93]. Through downregulating PAX5, miR-1254 activates the Hippo-YAP signaling pathway, which in turn accelerates the growth of HCC. Increased levels of miR-1254 in HCC tissues promote tumor growth and metastasis by enhancing cell motility, invasion, and proliferation. According to these results, miR-1254 may be an effective target for managing HCC [94]. Lin et al. displayed that exosomal miR-4800-3p targets STK25 and inhibits the Hippo signaling pathway, which accelerates the growth of HCC [95]. High quantities of miR-4800-3p in exosomes derived from TGF-treated HCC cells and patient blood improve cell proliferation, migration, invasion, and EMT. It appears that miR-4800-3p could be a possible target for HCC, as lowering its levels inhibited these tumor-promoting actions.

Overall, in HCC, studies have demonstrated that microRNAs have a substantial impact on the Hippo signaling system. By focusing on parts of this pathway like YAP, TAZ, and LATS1/2, changes in miRNAs can affect how cells move, invade, and fight chemotherapy. They can also work as tumor suppressors or oncogenes. These studies' findings highlight the therapeutic potential of microRNAs in HCC treatment. Finally, these studies show that microRNAs are important for regulating liver cancer progression by influencing certain components of the Hippo pathway (Table 1).

2.2.1.2 Clinical Relevance of miRNAs Targeting the Hippo-YAP/TAZ Pathway in HCC

HCC remains a challenging disease to diagnose in its early stages, as it often progresses without noticeable symptoms. Consequently, detection typically occurs at advanced stages, significantly limiting therapeutic options and reducing survival rates [96]. While liver biopsy is considered the gold standard for diagnosis, its invasive nature and associated risks restrict its use to select cases [97]. Current blood-based biomarkers lack the sensitivity and specificity necessary for effective early detection and disease stratification, underscoring the need for improved diagnostic tools [98].

Circulating miRNAs have emerged as promising candidates for non-invasive biomarkers, given their detectability in various body fluids, including plasma, serum, saliva, urine, and breast milk [99]. Unlike cellular RNAs, circulating miRNAs exhibit exceptional stability, maintaining their structure and functionality under extreme conditions such as heat, pH variation, and repeated freeze-thaw cycles [100,101]. This inherent resilience makes circulating miRNAs particularly advantageous for diagnostic applications.

Although direct evidence linking miRNAs involved in Hippo-YAP/TAZ signaling to circulation is scarce, several miRNAs discussed in this study—such as miR-21 [79], miR-375 [68], and miR-590-5p [75]—have been identified in the serum of liver cancer patients. These findings suggest their potential as diagnostic and prognostic markers. For instance, miR-21, known to regulate YOD1 and modulate Hippo signaling, is frequently upregulated in HCC tissues and detectable in circulation, correlating with tumor progression [92,93]. Similarly, miR-375, a tumor-suppressive miRNA that targets YAP, holds significant potential as a diagnostic biomarker and therapeutic agent due to its serum presence [68].

Table 1. The microRNAs involved in the Hippo signaling pathway in HCC

MicroRNA	Target	Sample	Description	Role	Reference
miR-375	YAP	HCC, FLC	A decrease in miR-375 expression contributes to higher YAP activity and promotes chemoresistance in HCC. On the other hand, enhancing miR-375 levels effectively restricts the growth and invasive behavior of HCC cells.	Tumor Suppressor	[68,70,71]
miR-29	PTEN	HCC	miR-29 decreases PTEN, leading to mTOR activation and modification of the PI3K-mTOR pathway.	Oncogene	[73]
miR-186	YAP1	HCC	Upregulation of miR-186 reduces YAP1, decreasing the proliferation and migration of HCC cells.	Tumor Suppressor	[74]
miR-590-5p	YAP1	HCC	miR-590-5p reduces chemoresistance in HCC by downregulating YAP1.	Tumor Suppressor	[75]
miR-506	YAP	HCC	Downregulation of miR-506 leads to increased YAP and HCC cell growth.	Tumor Suppressor	[76]
miR-132	YAP	HCC	miR-132 decreases YAP expression, increasing apoptosis and reducing proliferation and invasion of HCC cells.	Tumor Suppressor	[77]
miR-194	YAP1	HCC	miR-194 promotes hepatocytic differentiation by reducing YAP1.	Tumor Suppressor	[78]
miR-199a-3p	YAP1	HCC	Downregulation of miR-199a-3p leads to increased YAP1 and HCC cell growth.	Tumor Suppressor	[72]
miR-21-3p	YAP1	HCC	Upregulation of miR-21-3p facilitates migration, invasion, and YAP1 expression in hepatocellular carcinoma via targeting SMAD7, hence advancing tumor progression.	Oncogene	[79]
miR-345	YAP1	HCC	Upregulation of miR-345 inhibits HCC cell motility and invasion, reducing metastasis.	Tumor Suppressor	[80]
miR-9-3p	TAZ	HCC	miR-9-3p targets TAZ, reducing cell proliferation and enhancing apoptosis.	Tumor Suppressor	[81]
miR-338-3p	TAZ	HCC	miR-338-3p downregulation increases TAZ, promoting HCC cell proliferation and migration.	Tumor Suppressor	[82]
miR-125b	TAZ	HCC	miR-125b suppresses the migration and invasion of HCC cells by directly targeting TAZ.	Tumor Suppressor	[83]
miR-103	LATS2	HCC	miR-103 downregulates LATS2, enhancing metastasis and EMT in HCC.	Oncogene	[84]
miR-29c-3p	DNMT3B, LATS1	HCC	miR-29c-3p inhibits tumor growth by affecting LATS1 methylation.	Tumor Suppressor	[85]
miR-1307-3p	LATS1	HCC	miR-1307-3p upregulation enhances YAP nuclear translocation, promoting HCC progression through the Hippo/YAP and Wnt/β-catenin signaling pathways.	Oncogene	[86]
miR-15b	LATS1	HCC	miR-15b promotes HCC progression by downregulating LATS1.	Oncogene	[28]
miR-650	LATS2	HCC	miR-650 upregulation increases HCC cell motility, invasion, and proliferation by targeting LATS2.	Oncogene	[87]
miR-103a-3p	LATS2	HCC	miR-103a-3p downregulation increases GREM2/LATS2/YAP activity, promoting HCC progression.	Oncogene	[88]
miR-195	LATS2	HCC	miR-195 induces apoptosis in HCC cells by targeting LATS2.	Tumor Suppressor	[89]
miR-135b	MST1	HCC	miR-135b upregulation enhances HCC cell proliferation and migration by suppressing MST1.	Oncogene	[90]
miR-3910	MST1	HCC	miR-3910 targets MST1, activating YAP signaling to increase HCC growth and migration.	Oncogene	[91]
miR-21	YOD1	HCC	miR-21 regulates YOD1, affecting YAP/TAZ levels and promoting liver cancer cell proliferation.	Oncogene	[92,93]
miR-1254	PAX5	HCC	miR-1254 upregulation activates the Hippo-YAP pathway, accelerating HCC growth and metastasis.	Oncogene	[94]
miR-4800-3p	STK25	HCC	miR-4800-3p inhibits the Hippo signaling pathway, promoting HCC progression.	Oncogene	[95]

Additionally, miRNAs are valuable tools for monitoring therapeutic responses. Evidence indicates that miRNA expression profiles in HCC cells change in response to anticancer treatments, with miRNAs related to the Hippo-YAP/TAZ pathway showing significant alterations [102]. This highlights their potential utility in evaluating treatment efficacy and disease progression.

Current therapeutic strategies targeting the Hippo-YAP/TAZ signaling pathway demonstrate promise but are constrained by limitations such as toxicity, short half-lives, and adverse effects. For instance, small molecules like pazopanib, dasatinib, and statins activate Hippo signaling and enhance chemosensitivity in HCC models. Verteporfin, a YAP inhibitor, disrupts the interaction between YAP and TEAD, facilitating YAP degradation and improving treatment outcomes in YAP-overexpressing cancers [103]. However, the therapeutic application of these agents is often limited by undesirable side effects and inconsistent efficacy.

miRNA-based therapies offer an alternative with a potentially better safety profile. Preclinical studies have demonstrated that miRNA mimics, such as miR-590-5p, and inhibitors targeting oncogenic miRNAs [75], such as miR-21, can suppress HCC progression by modulating Hippo signaling components [79]. Advances in delivery technologies, particularly nanoparticle-based systems, have improved the targeted delivery of miRNAs to liver tissues, reducing off-target effects and enhancing therapeutic efficiency [104].

For example, MRX34, a liposomal miR-34 mimic, was tested in a phase I clinical trial involving solid tumors, including HCC [105]. While the trial demonstrated dose-dependent regulation of target genes, it also revealed immune-related adverse events in a subset of patients. These findings underscore the necessity for further research to optimize delivery systems and minimize side effects, ensuring the safety and efficacy of miRNA-based therapies. Future efforts should focus on expanding the repertoire of therapeutic miRNAs and refining delivery technologies to realize the full potential of miRNA-based interventions in liver cancer treatment.

2.2.2 lncRNAs: Versatile Modulators of the Hippo Pathway in HCC

The advancement of extensive parallel sequencing technology has revealed the significant involvement of lncRNA in the progression of human HCC [106]. Currently, several long non-coding RNA (lncRNA) abnormalities associated with HCC, such as PVT1, MALAT1, EWSAT1, and lncBRM, have been utilized as predictive biomarkers for diagnosing or predicting the prognosis of human diseases [107-110]. Moreover, there is compelling evidence indicating that lncRNAs are linked to HCC through many signaling pathways, including Hippo signaling.

2.2.2.1 Targeting YAP: Driving Proliferation and Metastasis

To control the progression of liver cancer caused by Malat1 mutations, Wang et al. discovered that YAP and SRSF1 inhibit each other inversely [107]. While SRSF1 blocks YAP, YAP upregulates Malat1, a lncRNA that promotes cancer cell migration and proliferation. The nuclear localization of SRSF1 is decreased by YAP overexpression, which amplifies the effects of Malat1. In liver cancer tissues, lower SRSF1 levels are correlated with higher YAP levels. A novel strategy for treating liver cancer may be to target the connection between YAP and SRSF1. Specially, He et al. discovered that the lncRNA EWSAT1 activates the Src-YAP signaling pathway, which in turn enhances the development of HCC. Aggressive characteristics and poor survival are associated with EWSAT1 being elevated in HCC tissues. Through its binding to YAP, promotion of its phosphorylation and nuclear translocation, and activation of Hippo-YAP target genes, it increases HCC cell proliferation and metastasis. In HCC, EWSAT1 has the potential to be both a predictive biomarker and a therapeutic target [108]. According to research by Zhuo et al., the Hippo signaling system is inhibited by the long noncoding RNA RP11-40C6.2, which is associated with HCC [11]. Overexpression of the lncRNA stabilizes YAP1 by inhibiting its phosphorylation and destruction in HBV-associated HCC. Animal models and cell lines both demonstrate that this YAP1 stability enhances oncogenic consequences. The YAP1/TAZ/TEADs complex binds to the promoter of RP11-40C6.2, which drives transcription.

In liver cancer cells, Runx2 and YAP negatively regulate the tumor suppressor long non-coding RNA MT1DP. Through direct promoter binding, Runx2 and YAP suppress MT1DP expression. An increase in cell death and a decrease in cell proliferation are hallmarks of MT1DP overexpression, suggesting a tumor-suppressing function. Additionally, MT1DP suppresses FoxA1, which in turn raises *YAP* and *RUNX2* expression, which promotes the progression of liver cancer, and inhibits alfa-fetoprotein (AFP) [111]. Consistently, liver cancer stem cells (CSCs) and hepatic cellular carcinoma (HCC) tumors exhibit high expression of lncBRM, a long noncoding RNA. In order for liver CSCs to self-renew and initiate tumors, LncBRM is essential because it activates YAP1 signaling by associating with BRM. The lncBRM and YAP1 signaling targets can be used as biomarkers and therapeutic targets because their expression levels are correlated with tumor severity in HCC patients [109].

Interestingly, HCC tissues show a substantial increase in the expression of the long non-coding RNA PVT1 relative to surrounding healthy tissues, whereas miR-186-5p is decreased. By lowering miR-186-5p's regulatory impact on its target gene *YAP1*, PVT1 enhances HCC cell growth, invasion, and migration. This relationship provides more evidence that PVT1 is an important factor in HCC development and metastases [110]. Additionally, the overexpression of lncRNA-ATB in HCC tissues was found to be associated with bigger tumors, higher tumor necrosis factor (TNM) stages, and worse patient survival rates. LncRNA-ATB enhances autophagy in HCC cells through upregulating the expression of autophagy-related protein 5 (ATG5) and yes-associated protein (YAP). This research demonstrates that lncRNA-ATB has a new function in controlling autophagy, which has a major effect on the development of HCC [112]. Moreover, the expression of a newly discovered long non-coding RNA (lncRNA) called PLK4 is markedly reduced in HCC cells and tissues. The PARP1/2 inhibitor talazoparib causes cellular senescence via increasing lncRNA PLK4 levels in HepG2 cells, which in turn inactivates YAP. As a

tumor suppressor, talazoparib-induced lncRNA PLK4 could offer therapeutic advantages for the treatment of HCC, according to this mechanism [113]. Long non-coding RNA ASMTL-AS1 was reported to be especially found in HCC tissues as well as upregulated in tumors following inadequate radiofrequency ablation (RFA). By inducing NLK expression and activating YAP signaling via miR-342-3p sequestration, ASMTL-AS1 increases HCC cell malignancy. Exosomal ASMTL-AS1 suggests an entirely novel approach to stop HCC recurrence or metastases following insufficient RFA [114]. HCC tissues and cells overexpress the long non-coding RNA muskelin-1 antisense RNA (MKLN1-AS), which decreases prognosis. In vitro and in vivo, MKLN1-AS increases YAP1 mRNA stability and expression, which boosts HCC cell proliferation, migration, and invasion. These data imply that MKLN1-AS may be an HCC biomarker and therapeutic target [115].

2.2.2.2 Modulating LATS1/2: Key Roles in Tumor Suppression

A study conducted by Ni et al. discovered that lncRNA uc.134 can hinder the advancement of HCC by avoiding the ubiquitination of LATS1 which is mediated by CUL4A [116]. There was a correlation between UC.134's downregulation and a bad prognosis in invasive HCC cell lines and samples from patients. In contrast to knockdown, overexpression of UC.134 decreased invasion, metastasis, and cell proliferation in HCC. UC.134 interacts with CUL4A, which suppresses *YAP* target gene expression by increasing phosphorylation of YAPS127 and preventing ubiquitination of LATS1. Based on these findings, UC.134 may be a potential target for therapy for HCC. Through epigenetically inhibiting the tumor suppressor genes CELF2 and LATS2, the long noncoding RNA CRNDE has been shown to enhance the growth of HCC. Overexpression of CRNDE in HCC tissues was associated with poor patient outcomes. The chemotherapy resistance, migration, and proliferation of HCC cells were all decreased after CRNDE was knocked down. On a molecular level, CRNDE bound to EZH2, SUV39H1, and SUZ12 which inhibited CELF2 and LATS2. The carcinogenic effects of CRNDE were counteracted by overexpressing LATS2, suggesting that CRNDE could be a therapeutic target for HCC [117]. Additionally, researchers have discovered that the LOC107985656 long non-coding RNA activates the Hippo pathway, which in turn decreases the development of HCC cells. The downregulation of LOC107985656 in HCC tissues reduces cell proliferation by regulating LATS1 via sponging miR-106b-5p and suppressing the production of YAP and TAZ proteins. This points to LOC107985656 as a possible target for HCC diagnostics and treatment [118].

According to recent research, HCC tissues and cells show elevated expression of the long noncoding RNA HOXA11-AS. By binding to EZH2, HOXA11-AS enhances HCC cell proliferation, suppresses apoptosis, and retards the progression of the cell cycle by reducing the levels of large tumor suppressor kinase 1 (LATS1). Relationships among HOXA11-AS, PRC2, and LATS1 point to novel therapeutic targets for HCC [119].

2.2.2.3 Interacting with Other Components: Expanding the Regulatory Network

In hepatoblastoma (HB), LINC01314 was found to be a tumor suppressor. By boosting MST1 expression and LATS1/YAP phosphorylation and blocking YAP nuclear translocation, LINC01314 overexpression reduced HB cell proliferation and migration. This points to LINC01314 as a possible biomarker and HB treatment target [120].

HCC is associated with an increase in the long non-coding RNA PVT1, which correlates negatively with the expression of DLC1. There is evidence that the Hippo signaling system influences the course of HCC and that high PVT1 expression is linked to negative clinical characteristics. When it comes to diagnosing HCC, both PVT1 and DLC1 are very effective [121].

As mentioned above, lncRNAs have an important role in regulating the Hippo signaling pathway in HCC. By regulating essential signaling components, they impact cell migration, invasion, tumorigenicity, and proliferation. It's possible that focusing on lncRNAs and how they interact with the Hippo pathway could lead to a new way to diagnose and treat HCC. This could lead to better patient outcomes. Finally, these results show that lncRNAs regulate components of the Hippo pathway, which is a key player in the genesis and progression of liver cancer. This suggests that lncRNAs could be therapeutic targets.

2.2.3 CircRNAs: Pivotal Influencers of the Hippo Pathway in Liver Cancer

The exact process that regulates circRNAs in HCC has been increasingly elucidated by ongoing studies. Circular RNA exerts regulatory functions either transcriptionally or post-transcriptionally. Biological roles can be categorized into three main groups: sponging miRNAs, modulators of proteins, and protein coding. Concurrently, m6A regulates the biological actions of certain circRNAs [19,122].

Through its interaction with 14-3-3ζ, CircPAK1 modulates YAP nucleus location, which in turn promotes the growth of HCC. By blocking the Hippo signaling pathway, CircPAK1—which is abundant in HCC tissues—increases migration of cells, invasion, and multiplication. This suppression happens because CircPAK1 is competing with 14-3-3Ό, which decreases 14-3-3ζ's ability to stabilize YAP in the cytoplasm and promotes the nucleus localization of YAP. Furthermore, exosomal CircPAK1 could be a therapeutic target because it causes HCC cells to become resistant to Lenvatinib [123]. CircACTN4 has been recognized as a crucial regulator in liver malignancies, encompassing intrahepatic cholangiocarcinoma (ICC) and HCC. CircACTN4 enhances YAP1 expression by sequestering miR-424-5p. CircACTN4 also recruits YBX1 to stimulate FZD7 transcription, thereby connecting it to the Hippo and Wnt/-catenin pathways. CircACTN4 is a pivotal element in facilitating tumor proliferation and metastasis, rendering it a prospective therapeutic target [124]. Furthermore, Researchers discovered that the

circular RNA hsa_circ_0098181 activates the Hippo signaling pathway through its association with eEF2, thereby inhibiting migration in liver carcinoma. An analysis has linked decreased expression of hsa_circ_0098181 in HCC tissues to a poor prognosis. The exogenous expression of hsa_circ_0098181 inhibited HCC progression by inhibiting F-actin production and activating the Hippo pathway through eEF2 sequestering. Based on this mechanism, hsa_circ_0098181 may be a promising treatment target for HCC [125].

CircRNA_104075 is also crucial in the progression of HCC. It functions as a ceRNA for miR-582-3p, enhancing YAP expression. The m6A mutation in the 3'UTR of YAP is essential for its interaction with miR-582-3p. CircRNA_104075 exhibits exceptional diagnostic efficacy, characterized by remarkable sensitivity and specificity, highlighting its potential as both a biomarker and a therapeutic target [126]. Huang et al. discovered that circUHRF1 enhances the spread of HCC by enhancing the long-term persistence of G9a and UHRF1 mRNAs[127]. This occurs when eukaryotic translation initiation factor 4A3 (EIF4A3) is involved. The study showed that circUHRF1, G9a, and UHRF1 exhibit increased expression, whereas PDLIM1 shows decreased expression in HCC tissues and cells. CircUHRF1 promotes HCC cell growth, spread, movement, and transformation by interacting with G9a to suppress PDLIM1 transcription. The results show how important the circUHRF1-G9a-UHRF1-EIF4A3-PDLIM1 network is in the development of HCC and suggest new ways to treat it. Additionally, studies have demonstrated that CircHIPK3 facilitates the metastasis and migration of HCC cells through the miR-381-3p-YAP axis. CircHIPK3 stimulates the Hippo-YAP signaling pathway by sponging miR-381-3p, hence promoting tumor growth. This approach identifies CircHIPK3 as an additional critical therapeutic target in HCC [128].

A key finding in hepatocellular carcinoma is the activation of YAP1 by circCPSF6, which has been N6-methyladenosine (m6A) altered. A worse outlook for the patient is linked to higher CircCPSF6, which is managed by ALKBH5-mediated demethylation and YTHDF2-mediated destabilization in HCC. According to functional studies, circCPSF6 stabilizes YAP1 mRNA through competitive interaction with PCBP2, which in turn enhances cell proliferation, mobility, tumor development, and metastasis. Because of its role in HCC advancement and the circCPSF6-YAP1 axis, circCPSF6 has therapeutic potential [129].

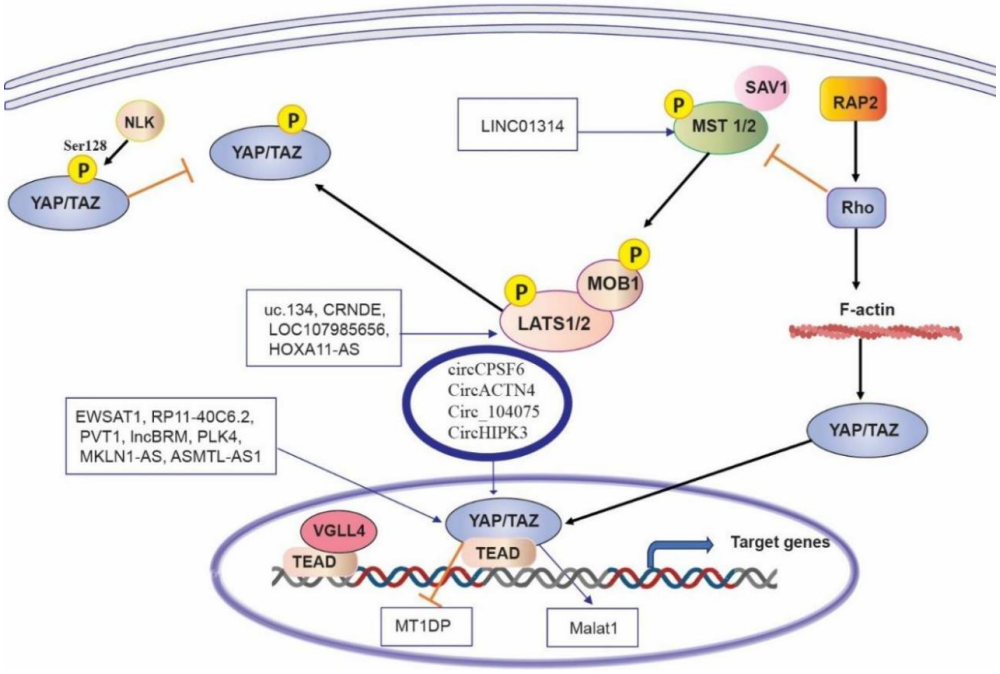

Figure 2. Role of lncRNAs and circRNAs in Hippo Signaling Pathway in HCC

By controlling the Hippo signaling system and impacting tumor growth, circRNAs collectively have a substantial impact on HCC. Through their interactions with key molecules like eEF2 and 14-3-3ζ, circRNAs can control how cells divide, move, and metastasize. CircACTN4, CircRNA_104075, and CircHIPK3 further underscore the various mechanisms of circRNA-mediated regulating in HCC. These results demonstrate the potential of circRNAs as biomarkers and therapeutic targets in HCC, opening up new possibilities for disease diagnosis and treatment. In the end, these studies show that circRNAs have the potential to disrupt the Hippo pathway, which in turn affects the spread and progression of liver cancer. Additionally, they provide potential targets for new and improved treatments (Figure 2).

3. Role of ncRNAs in Tumor-Associated Macrophages and the Tumor Microenvironment of HCC

The tumor microenvironment (TME) is crucial in the advancement and treatment resistance of HCC [130]. Tumor cells, immune cells, stromal components, and

signaling molecules form a complex ecosystem that interacts in a continuously changing network that encourages tumor invasion, growth, and immune evasion [131]. Among the key players in the tumor microenvironment (TME) are tumor-associated macrophages (TAMs), which demonstrate exceptional flexibility, transitioning between the M1 phenotype, known for its anti-tumor effects, and the M2 phenotype, which supports tumor growth and progression [132]. Cytokines, chemokines, and non-coding RNAs (ncRNAs), a new group of regulators, send signals from the tumor microenvironment (TME) and the tumor itself that change the balance of different states [133].

The importance of ncRNAs in regulating the interaction between TAMs and HCC cells has recently been demonstrated [134]. By mediating cellular communication, these ncRNAs play a critical role in controlling tumor biology and macrophage polarization. Some ncRNAs generated from macrophages, like miR-125a/b and miR-142-3p, limit glycolysis, invasion, and proliferation of cancer cells; they are thus tumor suppressors [135,136]. To enhance their anti-tumor actions, these ncRNAs boost macrophage M1 polarization. On the other hand, carcinogenic ncRNAs, such as miR-15b, that originate from macrophages promote M2 polarization and tumor growth via pathways like TGF-β signaling and inhibition of the Hippo pathway [137,138]. Notably, due to their dual role, ncRNAs play a pivotal role in determining the TME immunological landscape.

Conversely, ncRNAs produced by tumors exacerbate the TME's pro-tumor dynamics. HCC cells release exosomal ncRNAs, such as circASAP1 and lncRNA H19, which macrophages then pick up, skewing them towards the M2 phenotype [139,140]. This facilitates immune suppression, angiogenesis, and metastasis, establishing a detrimental loop of tumor advancement. Researchers have demonstrated that tumor-derived miR-23a-3p enhances PD-L1 expression in macrophages, thereby facilitating immune evasion and further polarizing macrophages towards an M2 phenotype [141]. These findings demonstrate the ability of tumor-derived non-coding RNAs to manipulate macrophage plasticity for their survival and propagation.

The consequences of these discoveries for HCC treatment are significant. Strategies aimed at ncRNA pathways possess significant potential for reconfiguring the tumor microenvironment to inhibit tumor growth. Restoring the expression of tumor-suppressive non-coding RNAs, such as miR-26a and miR-148b, may restrict macrophage invasion and bias their polarization toward the M1 phenotype [142,143]. Conversely, silencing oncogenic ncRNAs, such as lncRNA MALAT1 or circASAP1, may disrupt the tumor-promoting signals within the TME [144]. Advanced technologies, including miRNA mimics, antisense oligonucleotides, and CRISPR-Cas9, are being explored to achieve these therapeutic goals, offering new avenues to combat HCC [141].

Besides their therapeutic potential, ncRNAs present considerable promise as biomarkers for HCC. Encapsulated in exosomes, ncRNAs such as miR-21 and lncRNA CCAT1 demonstrate extraordinary stability in physiological fluids like blood and saliva, making them great candidates for non-invasive diagnostic and prognostic tools [141]. Monitoring circulating ncRNAs may yield real-time insights into tumor processes, facilitating early detection and assessment of therapy response. These findings highlight the necessity for additional research on ncRNA-mediated interactions within the TME. Understanding the complicated networks that control how macrophages and tumors interact could lead to new ways to treat HCC. By targeting ncRNAs that modulate these interactions, we may not only impede tumor growth but also augment the effectiveness of current therapies. The future of HCC treatment lies in understanding the complexity of the TME, where ncRNAs hold the key to undermining the tumor’s protective niche and restoring the balance of immune surveillance.

4. Future Perspectives

Researchers are increasingly recognizing the dysregulation of non-coding RNAs, including microRNAs, long non-coding RNAs, and circular RNAs, as an important tool for the early detection and monitoring of HCC [64]. A notable accomplishment in recent research is the finding of distinct ncRNA patterns in HCC tumors and bodily fluids, facilitating the creation of non-invasive biomarkers. For example, miRNAs like miR-21 [92] and miR-132 [77] have surfaced as potential candidates for early diagnosis owing to their unique expression patterns in malignant compared to normal tissues. Moreover, the stability of miRNAs in circulation enhances their utility in monitoring disease development and therapy response. In addition to miRNAs, lncRNAs function as crucial regulatory molecules in the Hippo signaling pathway and have demonstrated potential as biomarkers for prognosis and diagnosis. By interacting with SRSF1, lncRNA-MALAT1 enhances YAP signaling and promotes tumor growth, suggesting its potential as a biomarker for early identification and disease progression [107]. Likewise, it promotes HCC cell motility and invasion by decreasing miR-186-5p and regulating YAP1, establishing it as a potential target for diagnostic and prognostic purposes [110]. CircRNAs demonstrate considerable potential owing to their stable, circular configuration and varied regulatory functions in cancer advancement. CircPAK1 influences YAP location within the nucleus via its interaction with 14-3-3ζ, hence enhancing HCC cell proliferation and invasion [123]. These attributes render circRNAs appealing candidates for disease surveillance and evaluating treatment responses. Future research should concentrate on developing complete ncRNA panels designed for early identification, prognosis, and real-time monitoring of HCC. The incorporation of ncRNA-based diagnostics with current molecular diagnostic methods could significantly enhance patient outcomes, providing more individualized and accurate therapy strategies. Further investigation into the molecular functions of ncRNAs in signaling pathways such as Hippo will provide novel

targeted therapeutics, potentially revolutionizing HCC medical treatment.

5. Conclusions

In summary, some noncoding RNAs (ncRNAs), like miRNAs, lncRNAs, and circRNAs, play key roles in managing the Hippo signaling pathway, which has a big effect on how liver cancer grows and spreads. These non-coding RNAs regulate important elements of the Hippo pathway, impacting biological functions like cell growth, programmed cell death, and the spread of cancer cells. Understanding the complicated relationship between ncRNAs and the Hippo pathway is important for understanding the underlying causes of liver cancer and finding potential therapeutic targets. Next research should focus on creating diagnostic tools and medicines based on non-coding RNA (ncRNA), which could improve how quickly people with liver cancer are diagnosed and how well they do after treatment. The encouraging findings from research on ncRNAs highlight their potential for developing liver cancer therapies and personalized medicine.

Abbreviation List

circRNAs (Circular RNAs), VP (Verteporfin), CK1 (Casein Kinase 1), SAV1 (Salvador Homolog 1), PTEN (Phosphatase and Tensin Homolog), MOB1 (MOB Kinase Activator 1), miRNAs (MicroRNAs), ncRNAs (Noncoding RNAs), RhoA (Ras Homology Family Member A), TEAD (TEA Domain Transcription Factors), MST1/2 (Mammalian Ste20-like Kinases 1/2), lncRNAs (Long Noncoding RNAs), PP2 (Protein Phosphatase 2), YAP (Yes-Associated Protein), EMT (Epithelial-Mesenchymal Transition), AMPK (AMP-Activated Protein Kinase), HCC (Hepatocellular Carcinoma), FLC (Fibrolamellar Carcinoma), PKC (Protein Kinase C), SRSF1 (Serine/Arginine-Rich Splicing Factor 1), LOC107985656 (Long Noncoding RNA 107985656), MAP4K (Mitogen-Activated Protein Kinase Kinase Kinase), SUZ12 (Suppressor of Zeste 12), KLF2 (Kruppel-Like Factor 2), APC (Adenomatous Polyposis Coli), PKA (Protein Kinase A), NF2 (Neurofibromin 2), CRNDE (Colorectal Neoplasia Differentially Expressed), SCF-β-TRCP (Skp, Cullin, F-box containing complex-β-Transducin Repeat-Containing Protein), TAZ (Transcriptional Co-Activator with PDZ-Binding Motif), LATS2 (Large Tumor Suppressor 2), TAOK1-3 (Tao Kinases 1-3), PDLIM1 (PDZ and LIM Domain Protein 1), HOXA11-AS (HOXA11 Antisense RNA), PLK4 (Polo-Like Kinase 4), DNMT3B (DNA Methyltransferase 3 Beta), UHRF1 (Ubiquitin-Like with PHD and Ring Finger Domains 1), GREM2 (Gremlin 2), ASMTL-AS1 (ASMTL Antisense RNA 1), TALAZOPARIB (PARP1/2 Inhibitor), MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1), eEF2 (Eukaryotic Elongation Factor 2), AFP (Alpha-Fetoprotein), MKLN1-AS (Muskelin 1 Antisense RNA), EIF4A3 (Eukaryotic Translation Initiation Factor 4A3), YTHDF2 (YTH N6-Methyladenosine RNA Binding Protein 2), RASSF1A (Ras Association Domain Family Member 1A), N6-Methyladenosine (m6A).

Competing Interests

The authors declare no competing interests

Authors' Contributions

F.S. and Z. R. contributed to the conceptualization, writing the original draft, review, and editing. All authors read and approved the final manuscript.

References

[1] Shi L, Shang X, Nie K, Lin Z, Zheng M, et al. Identification of potential crucial genes associated with the pathogenesis and prognosis of liver hepatocellular carcinoma. Journal of Clinical Pathology. 2021, 74(8), 504-512.

[2] Fu XT, Qie JB, Chen JF, Gao Z, Li XG, et al. Inhibition of SIRT1 relieves hepatocarcinogenesis via alleviating autophagy and inflammation. International Journal of Biological Macromolecules. 2024, 278(Pt 1), 134120.

[3] Anwanwan D, Singh SK, Singh S, Saikam V, Singh R. Challenges in liver cancer and possible treatment approaches. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2020, 1873(1), 188314.

[4] Carroll HK, Duffy AG, O'Farrelly C. Liver immunology, immunotherapy, and liver cancers: Time for a rethink? Seminars in Liver Disease. 2022, 42(2), 212-224.

[5] Luo J, Huang Z, Wang M, Li T, Huang J. Prognostic role of multiparameter MRI and radiomics in progression of advanced unresectable hepatocellular carcinoma following combined transcatheter arterial chemoembolization and lenvatinib therapy. BMC Gastroenterology. 2022, 22(1), 108.

[6] Liu Y, Yang H, Li T, Zhang N. Immunotherapy in liver cancer: overcoming the tolerogenic liver microenvironment. Frontiers in Immunology. 2024, 15, 1460282.

[7] Wang J, Peng Y, Jing S, Han L, Li T, et al. A deep-learning approach for segmentation of liver tumors in magnetic resonance imaging using UNet+. BMC Cancer. 2023, 23(1), 1060.

[8] Torres-Hernandez A, Wang W, Nikiforov Y, Tejada K, Torres L, et al. Targeting SYK signaling in myeloid cells protects against liver fibrosis and hepatocarcinogenesis. Oncogene. 2019, 38(23), 4512-4526.

[9] Dey A, Varelas X, Guan KL. Targeting the Hippo pathway in cancer, fibrosis, wound healing and regenerative medicine. Nature Reviews Drug Discovery. 2020, 19(7), 480-494.

[10] Driskill JH, Pan D. The Hippo pathway in liver homeostasis and pathophysiology. Annual Review of Pathology. 2021, 16(1), 299-322.

[11] Su Q, Hua F, Xiao W, Liu B, Wang D, et al. Investigation of Hippo pathway-related prognostic lncRNAs and molecular subtypes in liver hepatocellular carcinoma. Scientific Reports. 2023, 13(1), 4521.

[12] Hombach S, Kretz M. Non-coding RNAs: classification, biology and functioning. Advances in Experimental Medicine and Biology. 2016, 937, 3-17.

[13] Ghidini M, Braconi C. Non-coding RNAs in primary liver cancer. Frontiers in Medicine. 2015, 2, 36.

[14] Beermann J, Piccoli MT, Viereck J, Thum T. Non-coding RNAs in development and disease: background, mechanisms, and therapeutic approaches. Physiological Reviews. 2016, 96(4), 1297-1325.

[15] Hosseini SF, Javanshir-giv S, Soleimani H, Mollaei H, Sadri F, et al. The importance of hsa-miR-28 in human

malignancies. Biomedicine & Pharmacotherapy. 2023, 161, 114453.
[16] Chamani E, Sargolzaei J, Tavakoli T, Rezaei Z. microRNAs: Novel Markers in Diagnostics and Therapeutics of Celiac Disease. DNA and Cell Biology. 2019, 38(7), 708-717.
[17] Bian EB, Xiong ZG, Li J. New advances of lncRNAs in liver fibrosis, with specific focus on lncRNA–miRNA interactions. Journal of Cellular Physiology. 2019, 234(3), 2194-2203.
[18] Zhao Y, Wu J, Liangpunsakul S, Wang L. Long non-coding RNA in liver metabolism and disease: Current status. Liver Research. 2017, 1(3), 163-167.
[19] Wang P, Zhang Y, Deng L, Qu Z, Guo P, et al. The function and regulation network mechanism of circRNA in liver diseases. Cancer Cell International. 2022, 22(1), 141.
[20] Chien Y, Tsai PH, Lai YH, Lu KH, Liu CY, et al. CircularRNA as novel biomarkers in liver diseases. Journal of the Chinese Medical Association. 2020, 83(1), 15-17.
[21] Wang Y, Zhang J, Yang Y, Liu Z, Sun S, et al. Circular RNAs in human diseases. MedComm. 2024, 5(9), e699.
[22] Zeng X, Yuan X, Cai Q, Tang C, Gao J. Circular RNA as an epigenetic regulator in chronic liver diseases. Cells. 2021, 10(8), 1945.
[23] Yao T, Chen Q, Fu L, Guo J. Circular RNAs: biogenesis, properties, roles, and their relationships with liver diseases. Hepatology Research. 2017, 47(6), 497-504.
[24] Chen L, Shan G. CircRNA in cancer: fundamental mechanism and clinical potential. Cancer Letters. 2021, 505, 49-57.
[25] Jiang X, Lu Y, Xie S, Chen Y, Liu X, et al. miR-624 accelerates the growth of liver cancer cells by inhibiting EMC3. Noncoding RNA Research. 2023, 8(4), 641-644.
[26] Zhang R, Zhan Y, Lang Z, Li Y, Zhang W, et al. LncRNA-SNHG5 mediates activation of hepatic stellate cells by regulating NF2 and Hippo pathway. Communications Biology. 2024, 7(1), 266.
[27] Louis C, Coulouarn C. One stone, two birds: circACTN4, a nexus for a coordinated activation of Hippo and Wnt/β-catenin pathways in cholangiocarcinoma. Journal of Hepatology. 2022, 76(1), 8-10.
[28] Li J, Xue J, Ling M, Sun J, Xiao T, et al. MicroRNA-15b in extracellular vesicles from arsenite-treated macrophages promotes the progression of hepatocellular carcinomas by blocking the LATS1-mediated Hippo pathway. Cancer Letters. 2021, 497, 137-153.
[29] Oka T, Mazack V, Sudol M. Mst2 and Lats kinases regulate apoptotic function of Yes kinase-associated protein (YAP). Journal of Biological Chemistry. 2008, 283(41), 27534-27546.
[30] Zhang H, Liu CY, Zha ZY, Zhao B, Yao J, et al. TEAD transcription factors mediate the function of TAZ in cell growth and epithelial-mesenchymal transition. Journal of Biological Chemistry. 2009, 284(20), 13355-13362.
[31] Sadri F, Hosseini SF, Rezaei Z, Fereidouni M. Hippo-YAP/TAZ signaling in breast cancer: Reciprocal regulation of microRNAs and implications in precision medicine. Genes & Diseases. 2024, 11(2), 760-771.
[32] Zhao B, Wei X, Li W, Udan RS, Yang Q, et al. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes & Development. 2007, 21(21), 2747-2761.
[33] Zhao B, Li L, Tumaneng K, Wang CY, Guan KL. A coordinated phosphorylation by Lats and CK1 regulates YAP stability through SCFβ-TRCP. Genes & Development. 2010, 24(1), 72-85.
[34] Moon YA, Shah NA, Mohapatra S, Warrington JA, Horton JD. Identification of a mammalian long chain fatty acyl elongase regulated by sterol regulatory element-binding proteins. Journal of Biological Chemistry. 2001, 276(48), 45358-45366.
[35] Li P, Silvis MR, Honaker Y, Lien WH, Arron ST, et al. αE-catenin inhibits a Src–YAP1 oncogenic module that couples tyrosine kinases and the effector of Hippo signaling pathway. Genes & Development. 2016, 30(7), 798-811.
[36] Nguyen-Lefebvre AT, Selzner N, Wrana JL, Bhat M. The hippo pathway: A master regulator of liver metabolism, regeneration, and disease. The FASEB Journal. 2021, 35(5), e21570.
[37] Zheng Y, Pan D. The Hippo signaling pathway in development and disease. Developmental Cell. 2019, 50(3), 264-282.
[38] Liu CY, Zha ZY, Zhou X, Zhang H, Huang W, et al. The hippo tumor pathway promotes TAZ degradation by phosphorylating a phosphodegron and recruiting the SCFβ-TrCP E3 ligase. Journal of Biological Chemistry. 2010, 285(48), 37159-37169.
[39] Zender L, Spector MS, Xue W, Flemming P, Cordon-Cardo C, et al. Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. Cell. 2006, 125(7), 1253-1267.
[40] Dong J, Feldmann G, Huang J, Wu S, Zhang N, et al. Elucidation of a universal size-control mechanism in Drosophila and mammals. Cell. 2007, 130(6), 1120-1133.
[41] Hagenbeek TJ, Webster JD, Kljavin NM, Chang MT, Pham T, et al. The Hippo pathway effector TAZ induces TEAD-dependent liver inflammation and tumors. Science Signaling. 2018, 11(547), eaaj1757.
[42] Yimlamai D, Fowl BH, Camargo FD. Emerging evidence on the role of the Hippo/YAP pathway in liver physiology and cancer. Journal of Hepatology. 2015, 63(6), 1491-1501.
[43] Tao J, Calvisi DF, Ranganathan S, Cigliano A, Zhou L, et al. Activation of β-catenin and Yap1 in human hepatoblastoma and induction of hepatocarcinogenesis in mice. Gastroenterology. 2014, 147(3), 690-701.
[44] Zhang J, Liu P, Tao J, Wang P, Zhang Y, et al. TEA domain transcription factor 4 is the major mediator of Yes-associated protein oncogenic activity in mouse and human hepatoblastoma. The American Journal of Pathology. 2019, 189(5), 1077-1090.
[45] Smith JL, Rodríguez TC, Mou H, Kwan SY, Pratt H, et al. YAP1 withdrawal in hepatoblastoma drives therapeutic differentiation of tumor cells to functional hepatocyte-like cells. Hepatology (Baltimore, Md.). 2021, 73(3), 1011-1027.
[46] Tomlinson GE, Kappler R. Genetics and epigenetics of hepatoblastoma. Pediatric Blood & Cancer. 2012, 59(5), 785-792.
[47] Cai J, Maitra A, Anders RA, Taketo MM, Pan D. β-Catenin destruction complex-independent regulation of Hippo–YAP signaling by APC in intestinal tumorigenesis. Genes & Development. 2015, 29(14), 1493-1506.
[48] Tanas MR, Sboner A, Oliveira AM, Erickson-Johnson MR, Hespelt J, et al. Identification of a disease-defining gene fusion in epithelioid hemangioendothelioma. Science Translational Medicine. 2011, 3(98), 98ra82.
[49] Tanas MR, Ma S, Jadaan FO, Ng CKY, Weigelt B, et al. Mechanism of action of a WWTR1 (TAZ)-CAMTA1 fusion oncoprotein. Oncogene. 2016, 35(7), 929-938.
[50] Yuan WC, Pepe-Mooney B, Galli GG, Dill MT, Huang HT, et al. NUAK2 is a critical YAP target in liver cancer. Nature Communications. 2018, 9(1), 4834.
[51] Zhao YL, Yang XL. The H ippo pathway in chemotherapeutic drug resistance. International Journal of Cancer. 2015, 137(12), 2767-2773.

[52] Sohn BH, Shim JJ, Kim SB, Jang KY, Kim SM, et al. Inactivation of Hippo pathway is significantly associated with poor prognosis in hepatocellular carcinoma. Clinical Cancer Research. 2016, 22(5), 1256-1264.
[53] Xu MZ, Yao TJ, Lee NP, Ng IO, Chan YT, et al. Yes-associated protein is an independent prognostic marker in hepatocellular carcinoma. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2009, 115(19), 4576-4585.
[54] Sia D, Hoshida Y, Villanueva A, S. Roayaie, J. Ferrer, et al. Integrative molecular analysis of intrahepatic cholangiocarcinoma reveals 2 classes that have different outcomes. Gastroenterology. 2013, 144(4), 829-840.
[55] Zhou D, Conrad C, Xia F, Park JS, Payer B, et al. Mst1 and Mst2 maintain hepatocyte quiescence and suppress hepatocellular carcinoma development through inactivation of the Yap1 oncogene. Cancer Cell. 2009, 16(5), 425-438.
[56] Zhang N, Zhao Z, Long J, Li H, Zhang B, et al. Molecular alterations of the NF2 gene in hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Oncology Reports. 2017, 38(6), 3650-3658.
[57] Chang L, Azzolin L, Di Biagio D, Zanconato F, Battilana G, et al. The SWI/SNF complex is a mechanoregulated inhibitor of YAP and TAZ. Nature. 2018, 563(7730), 265-269.
[58] Hill MA, Alexander WB, Guo B, Kato Y, Patra K, et al. Kras and Tp53 mutations cause cholangiocyte-and hepatocyte-derived cholangiocarcinoma. Cancer Research. 2018, 78(16), 4445-4451.
[59] Ziosi M, Baena-López LA, Grifoni D, Froldi F, Pession A, et al. dMyc functions downstream of Yorkie to promote the supercompetitive behavior of hippo pathway mutant cells. PLoS Genetics. 2010, 6(9), e1001140.
[60] Neto-Silva PM, De Beco S, Johnston LA. Evidence for a growth-stabilizing regulatory feedback mechanism between Myc and Yorkie, the Drosophila homolog of Yap. Developmental Cell. 2010, 19(4), 507-520.
[61] Szymanski M, Barciszewska MZ, Zywicki M, Barciszewski J. Noncoding RNA transcripts. Journal of Applied Genetics. 2003, 44(1), 1-20.
[62] Iaconetti C, Gareri C, Polimeni A, Indolfi C. Non-coding RNAs: the “dark matter” of cardiovascular pathophysiology. International Journal of Molecular Sciences. 2013, 14(10), 19987-20018.
[63] Liu C, Wu Y, Ma J. Interaction of non-coding RNAs and Hippo signaling: Implications for tumorigenesis. Cancer Letters. 2020, 493, 207-216.
[64] Wong CM, Tsang FHC, Ng IOL. Non-coding RNAs in hepatocellular carcinoma: molecular functions and pathological implications. Nature Reviews Gastroenterology & Hepatology. 2018, 15(3), 137-151.
[65] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011, 144(5), 646-674.
[66] Lin S, Gregory RI. MicroRNA biogenesis pathways in cancer. Nature Reviews Cancer. 2015, 15(6), 321-333.
[67] Giordano S, Columbano A. MicroRNAs: new tools for diagnosis, prognosis, and therapy in hepatocellular carcinoma? Hepatology (Baltimore, Md.). 2013, 57(2), 840-847.
[68] Liu AM, Poon RT, Luk JM. MicroRNA-375 targets Hippo-signaling effector YAP in liver cancer and inhibits tumor properties. Biochemical and Biophysical Research Communications. 2010, 394(3), 623-7.
[69] Perra A, Kowalik MK, Ghiso E, Ledda-Columbano GM, Di Tommaso L, et al. YAP activation is an early event and a potential therapeutic target in liver cancer development. Journal of Hepatology. 2014, 61(5), 1088-96.
[70] Dinh TA, Jewell ML, Kanke M, Francisco A, Sritharan R, et al. MicroRNA-375 Suppresses the Growth and Invasion of Fibrolamellar Carcinoma. Cellular and Molecular Gastroenterology and Hepatology. 2019, 7(4), 803-817.
[71] Yu K, Li H, Jiang Z, Hsu HJ, Hsu HC, et al. miR-375/Yes-associated protein axis regulates IL-6 and TGF-β expression, which is involved in the cisplatin-induced resistance of liver cancer cells. Oncology Reports. 2021, 46(2), 162.
[72] Ren K, Li T, Zhang W, Ren J, Li Z, et al. miR-199a-3p inhibits cell proliferation and induces apoptosis by targeting YAP1, suppressing Jagged1-Notch signaling in human hepatocellular carcinoma. Journal of Biomedical Science. 2016, 23(1), 79.
[73] Tumaneng K, Schlegelmilch K, Russell RC, Yimlamai D, Basnet H, et al. YAP mediates crosstalk between the Hippo and PI(3)K–TOR pathways by suppressing PTEN via miR-29. Nature Cell Biology. 2012, 14(12), 1322-9.
[74] Ruan T, He X, Yu J, Hang Z. MicroRNA-186 targets Yes-associated protein 1 to inhibit Hippo signaling and tumorigenesis in hepatocellular carcinoma. Oncology Letters. 2016, 11(4), 2941-2945.
[75] Chen M, Wu L, Tu J, Zhao Z, Fan X, et al. miR-590-5p suppresses hepatocellular carcinoma chemoresistance by targeting YAP1 expression. EBioMedicine. 2018, 35, 142-154.
[76] Wang Y, Cui M, Sun BD, Liu FB, Zhang XD, et al. MiR-506 suppresses proliferation of hepatoma cells through targeting YAP mRNA 3'UTR. Acta Pharmacologica Sinica. 2014, 35(9), 1207-14.
[77] Lei CJ, Li L, Gao X, Zhang J, Pan QY, et al. Hsa-miR-132 inhibits proliferation of hepatic carcinoma cells by targeting YAP. Cell Biochemistry and Function. 2015, 33(5), 326-33.
[78] Jung KH, McCarthy RL, Zhou C, Uprety N, Barton MC, et al. MicroRNA Regulates Hepatocytic Differentiation of Progenitor Cells by Targeting YAP1. Stem Cells (Dayton, Ohio). 2016, 34(5), 1284-96.
[79] Hong Y, Ye M, Wang F, Fang J, Wang C, et al. MiR-21-3p Promotes Hepatocellular Carcinoma Progression via SMAD7/YAP1 Regulation. Frontiers in Oncology. 2021, 11, 642030.
[80] Zhang H, Liu H, Bi H. MicroRNA-345 inhibits hepatocellular carcinoma metastasis by inhibiting YAP1. Oncology Reports. 2017, 38(2), 843-849.
[81] Higashi T, Hayashi H, Ishimoto T, Takeyama H, Kaida T, et al. miR-9-3p plays a tumour-suppressor role by targeting TAZ (WWTR1) in hepatocellular carcinoma cells. British Journal of Cancer. 2015, 113(2), 252-8.
[82] Liu P, Zhang H, Liang X, Ma H, Luan F, et al. HBV preS2 promotes the expression of TAZ via miRNA-338-3p to enhance the tumorigenesis of hepatocellular carcinoma. Oncotarget. 2015, 6(30), 29048-59.
[83] Li J, Fang L, Yu W, Wang Y. MicroRNA-125b suppresses the migration and invasion of hepatocellular carcinoma cells by targeting transcriptional coactivator with PDZ-binding motif. Oncology Letters. 2015, 9(4), 1971-1975.
[84] Han LL, Yin XR, Zhang SQ. miR-103 promotes the metastasis and EMT of hepatocellular carcinoma by directly inhibiting LATS2. International Journal of Oncology. 2018, 53(6), 2433-2444.
[85] Wu H, Zhang W, Wu Z, Liu Y, Shi Y, et al. miR-29c-3p regulates DNMT3B and LATS1 methylation to inhibit tumor progression in hepatocellular carcinoma. Cell Death & Disease. 2019, 10(2), 48.
[86] Guan L, Li T, Ai N, Wang W, He B, et al. MEIS2C and MEIS2D promote tumor progression via Wnt/β-catenin and hippo/YAP signaling in hepatocellular carcinoma. Journal of Experimental & Clinical Cancer Research: CR. 2019, 38(1), 417.

[87] Han LL, Yin XR, Zhang SQ. miR-650 Promotes the Metastasis and Epithelial-Mesenchymal Transition of Hepatocellular Carcinoma by Directly Inhibiting LATS2 Expression. Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology. 2018, 51(3), 1179-1192.
[88] Ma G, Chen J, Wei T, Wang J, Chen W. Inhibiting roles of FOXA2 in liver cancer cell migration and invasion by transcriptionally suppressing microRNA-103a-3p and activating the GREM2/LATS2/YAP axis. Cytotechnology. 2021, 73(4), 523-537.
[89] Yang X, Yu J, Yin J, Xiang Q, Tang H, et al. MiR-195 regulates cell apoptosis of human hepatocellular carcinoma cells by targeting LATS2. Die Pharmazie. 2012, 67(7), 645-51.
[90] Xin Y, Yang X, Xiao J, Zhao W, Li Y, et al. MiR-135b promotes HCC tumorigenesis through a positive-feedback loop. Biochemical and Biophysical Research Communications. 2020, 530(1), 259-265.
[91] Cheng L, Wang H, Han S. MiR-3910 Promotes the Growth and Migration of Cancer Cells in the Progression of Hepatocellular Carcinoma. Digestive Disease and Sciences. 2017, 62(10), 2812-2820.
[92] Kim Y, Kim W, Song Y, Kim JR, Cho K, et al. Deubiquitinase YOD1 potentiates YAP/TAZ activities through enhancing ITCH stability. Proceedings of the National Academy of Sciences of the United States of America. 2017, 114(18), 4691-4696.
[93] Pu J, Xu Z, Nian J, Fang Q, Yang M, et al. M2 macrophage-derived extracellular vesicles facilitate CD8+T cell exhaustion in hepatocellular carcinoma via the miR-21-5p/YOD1/YAP/β-catenin pathway. Cell Death Discovery. 2021, 7(1), 182.
[94] Lu X, Yang C, Hu Y, Xu J, Shi C, et al. Upregulation of miR-1254 promotes Hepatocellular Carcinoma Cell Proliferation, Migration, and Invasion via Inactivation of the Hippo-YAP signaling pathway by decreasing PAX5. Journal of Cancer. 2021, 12(3), 771-789.
[95] Lin H, Peng J, Zhu T, Xiong M, Zhang R, et al. Exosomal miR-4800-3p Aggravates the Progression of Hepatocellular Carcinoma via Regulating the Hippo Signaling Pathway by Targeting STK25. Frontiers in Oncology. 2022, 12, 759864.
[96] Shen S, Lin Y, Yuan X, Shen L, Chen J, et al. Biomarker MicroRNAs for Diagnosis, Prognosis and Treatment of Hepatocellular Carcinoma: A Functional Survey and Comparison. Scientific Reports. 2016, 6, 38311.
[97] Neuberger J, Cain O. The need for alternatives to liver biopsies: non-invasive analytics and diagnostics. Hepatic Medicine: Evidence and Research. 2021, 13, 59-69.
[98] Cheng G. Circulating miRNAs: roles in cancer diagnosis, prognosis and therapy. Advanced Drug Delivery Reviews. 2015, 81, 75-93.
[99] Lee NH, Kim SJ, Hyun J. MicroRNAs Regulating Hippo-YAP Signaling in Liver Cancer. Biomedicines. 2021, 9(4), 347.
[100] Chen X, Ba Y, Ma L, Cai X, Yin Y, et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Research. 2008, 18(10), 997-1006.
[101] Kosaka N, Iguchi H, Ochiya Y. Circulating microRNA in body fluid: a new potential biomarker for cancer diagnosis and prognosis. Cancer Science. 2010, 101(10), 2087-92.
[102] Bie B, Sun J, Li J, Guo Y, Jiang W, et al. Baicalein, a Natural Anti-Cancer Compound, Alters MicroRNA Expression Profiles in Bel-7402 Human Hepatocellular Carcinoma Cells. Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology. 2017, 41(4), 1519-1531.
[103] Wang C, Zhu X, Feng W, Yu Y, Jeong K, et al. Verteporfin inhibits YAP function through up-regulating 14-3-3σ sequestering YAP in the cytoplasm. American Journal of Cancer Research. 2016, 6(1), 27-37.
[104] O'Neill CP, Dwyer RM. Nanoparticle-Based Delivery of Tumor Suppressor microRNA for Cancer Therapy. Cells. 2020, 9(2), 521.
[105] Hong DS, Kang YK, Borad M, Sachdev J, Ejadi S, et al. Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours. British Journal of Cancer. 2020, 122(11), 1630-1637.
[106] Jin L, He Y, Tang S, Huang S. LncRNA GHET1 predicts poor prognosis in hepatocellular carcinoma and promotes cell proliferation by silencing KLF2. Journal of Cellular Physiology. 2018, 233(6), 4726-4734.
[107] Wang J, Wang H, Zhang Y, Zhen N, Zhang L, et al. Mutual inhibition between YAP and SRSF1 maintains long non-coding RNA, Malat1-induced tumourigenesis in liver cancer. Cell Signal. 2014, 26(5), 1048-59.
[108] He X, Chen J, Zhou J, Mao A, Xu W, et al. LncRNA-EWSAT1 promotes hepatocellular carcinoma metastasis via activation of the Src-YAP signaling axis. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2022, 36(12), e22663.
[109] Zhu P, Wang Y, Wu J, Huang G, Liu B, et al. LncBRM initiates YAP1 signalling activation to drive self-renewal of liver cancer stem cells. Nature Communications. 2016, 7, 13608.
[110] Lan T, Yan X, Li Z, Xu X, Mao Q, et al. Long non-coding RNA PVT1 serves as a competing endogenous RNA for miR-186-5p to promote the tumorigenesis and metastasis of hepatocellular carcinoma. Tumour Biology: the Journal of the International Society for Oncodevelopmental Biology and Medicine. 2017, 39(6), 1010428317705338.
[111] Yu W, Qiao Y, Tang X, Ma L, Wang Y, et al. Tumor suppressor long non-coding RNA, MT1DP is negatively regulated by YAP and Runx2 to inhibit FoxA1 in liver cancer cells. Cell Signal. 2014, 26(12), 2961-8.
[112] Wang CZ, Yan GX, Dong DS, Xin H, Liu ZY. LncRNA-ATB promotes autophagy by activating Yes-associated protein and inducing autophagy-related protein 5 expression in hepatocellular carcinoma. World Journal of Gastroenterology. 2019, 25(35), 5310-5322.
[113] Jia Y, Jin H, Gao L, Yang X, Wang F, et al. A novel lncRNA PLK4 up-regulated by talazoparib represses hepatocellular carcinoma progression by promoting YAP-mediated cell senescence. Journal of Cellular and Molecular Medicine. 2020, 24(9), 5304-5316.
[114] Ma D, Gao X, Liu Z, Lu X, Ju H, et al. Exosome-transferred long non-coding RNA ASMTL-AS1 contributes to malignant phenotypes in residual hepatocellular carcinoma after insufficient radiofrequency ablation. Cell Proliferation. 2020, 53(9), e12795.
[115] Guo C, Zhou S, Yi W, Yang P, Li O, et al. Long non-coding RNA muskelin 1 antisense RNA (MKLN1-AS) is a potential diagnostic and prognostic biomarker and therapeutic target for hepatocellular carcinoma. Experimental and Molecular Pathology. 2021, 120, 104638.
[116] Ni W, Zhang Y, Zhan Z, Ye F, Liang Y, et al. A novel lncRNA uc.134 represses hepatocellular carcinoma progression by inhibiting CUL4A-mediated ubiquitination of LATS1. Journal of Hematology & Oncology. 2017, 10(1), 91.
[117] Xie SC, Zhang JQ, Jiang XL, Hua XY, Xie SW, et al. LncRNA CRNDE facilitates epigenetic suppression of CELF2 and LATS2 to promote proliferation, migration and chemoresistance in hepatocellular carcinoma. Cell Death & Disease. 2020, 11(8), 676.

[118] Zeng Y, Xu Q, Xu N. Long non-coding RNA LOC107985656 represses the proliferation of hepatocellular carcinoma cells through activation of the tumor-suppressive Hippo pathway. Bioengineered. 2021, 12(1), 7964-7974.
[119] Yu J, Hong JF, Kang J, Liao LH, Li CD. Promotion of LncRNA HOXA11-AS on the proliferation of hepatocellular carcinoma by regulating the expression of LATS1. European Review for Medical and Pharmacological Sciences. 2017, 21(15), 3402-3411.
[120] Lv B, Zhang L, Miao R, Xiang X, Dong S, et al. Comprehensive analysis and experimental verification of LINC01314 as a tumor suppressor in hepatoblastoma. Biomedicine & Pharmacotherapy. 2018, 98, 783-792.
[121] Zhang Y, Dang YW, Wang X, Yang X, Zhang R, et al. Comprehensive analysis of long non-coding RNA PVT1 gene interaction regulatory network in hepatocellular carcinoma using gene microarray and bioinformatics. American Journal of Translational Research. 2017, 9(9), 3904-3917.
[122] Qu X, Zhang L, Li S, Li T, Zhao X, et al. m(6)A-Related Angiogenic Genes to Construct Prognostic Signature, Reveal Immune and Oxidative Stress Landscape, and Screen Drugs in Hepatocellular Carcinoma. Oxidative Medicine and Cellular Longevity. 2022, 2022, 8301888.
[123] Hao X, Zhang Y, Shi X, Liu H, Zheng Z, et al. CircPAK1 promotes the progression of hepatocellular carcinoma via modulation of YAP nucleus localization by interacting with 14-3-3ζ. Journal of Experimental & Clinical Cancer Research: CR. 2022, 41(1), 281.
[124] Chen Q, Wang H, Li Z, Li F, Liang L, et al. Circular RNA ACTN4 promotes intrahepatic cholangiocarcinoma progression by recruiting YBX1 to initiate FZD7 transcription. Journal of Hepatology. 2022, 76(1), 135-147.
[125] Gao P, Yang Y, Li X, Zhao Q, Liu Y, et al. Circular RNA hsa_circ_0098181 inhibits metastasis in hepatocellular carcinoma by activating the Hippo signaling pathway via interaction with eEF2. Annals of Hepatology. 2023, 28(5), 101124.
[126] Zhang X, Xu Y, Qian Z, Zheng W, Wu Q, et al. circRNA_104075 stimulates YAP-dependent tumorigenesis through the regulation of HNF4a and may serve as a diagnostic marker in hepatocellular carcinoma. Cell Death & Disease. 2018, 9(11), 1091.
[127] Huang X, Zhou LZ, Feng WJ, Liu YQ, Chen M, et al. Circ ubiquitin-like-containing plant homeodomain and RING finger domains protein 1 increases the stability of G9a and ubiquitin-like-containing plant homeodomain and RING finger domains protein 1 messenger RNA through recruiting eukaryotic translation initiation factor 4A3, transcriptionally inhibiting PDZ and homeobox protein domain protein 1, and promotes the metastasis of hepatocellular carcinoma. Journal of Gastroenterology and Hepatology. 2024, 39(3), 596-607.
[128] Liang Q, Wang J, Pei Y, Yu X, Liu Q, et al. CircRNA HIPK3 facilitates the metastasis and migration of hepatocellular carcinoma through regulation of miR-381-3p-YAP axis. arxiv. 2023.
[129] Chen Y, Ling Z, Cai X, Xu Y, Lv Z, et al. Activation of YAP1 by N6-Methyladenosine-Modified circCPSF6 Drives Malignancy in Hepatocellular Carcinoma. Cancer Research. 2022, 82(4), 599-614.
[130] Xue C, Gu X, Bao Z, Su Y, Lu, et al. The mechanism underlying the ncRNA dysregulation pattern in hepatocellular carcinoma and its tumor microenvironment. Frontiers in Immunology. 2022, 13, 847728.
[131] Huang Q, Zhong X, Li J, Hu R, Yi J, et al. Exosomal ncRNAs: Multifunctional contributors to the immunosuppressive tumor microenvironment of hepatocellular carcinoma. Biomedicine & Pharmacotherapy. 2024, 173, 116409.
[132] Zhang Y, Ding X, Zhang X, Li Y, Xu R, et al. Unveiling the contribution of tumor-associated macrophages in driving epithelial-mesenchymal transition: a review of mechanisms and therapeutic Strategies. Frontiers in Pharmacology. 2024, 15, 1404687.
[133] Lv Y, Wang Z, Yuan K, Zeng Y. Noncoding RNAs as sensors of tumor microenvironmental stress. Journal of Experimental & Clinical Cancer Research. 2022, 41(1), 224.
[134] Lv Y, Wang Z, Yuan K. Role of Noncoding RNAs in the Tumor Immune Microenvironment of Hepatocellular Carcinoma. Journal of Clinical and Translational Hepatology. 2023, 11(3), 682.
[135] Wang Y, Wang B, Xiao S, Li Y, Chen Q. miR-125a/b inhibits tumor-associated macrophages mediated in cancer stem cells of hepatocellular carcinoma by targeting CD90. Journal of Cellular Biochemistry. 2019, 120(3), 3046-3055.
[136] Hua S, Liu C, Liu L, Wu D. miR-142-3p inhibits aerobic glycolysis and cell proliferation in hepatocellular carcinoma via targeting LDHA. Biochemical and Biophysical Research Communications. 2018, 496(3), 947-954.
[137] Ji WB, Liu X, Luo Y, Zhang WZ. High expression of miR-15b predicts poor prognosis for hepatocellular carcinoma after curative hepatectomy. Oncology Reports. 2016, 36(4), 1901-8.
[138] Song S, Qiu X. LncRNA miR503HG inhibits epithelial-mesenchymal transition and angiogenesis in hepatocellular carcinoma by enhancing PDCD4 via regulation of miR-15b. Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2021, 53(1), 107-116.
[139] Ye Y, Guo J, Xiao P, Ning J, Zhang R, et al. Macrophages-induced long noncoding RNA H19 up-regulation triggers and activates the miR-193b/MAPK1 axis and promotes cell aggressiveness in hepatocellular carcinoma. Cancer Letters. 2020, 469, 310-322.
[140] Hu ZQ, Zhou SL, Li J, Zhou ZJ, Wang PC, et al. Circular RNA Sequencing Identifies CircASAP1 as a Key Regulator in Hepatocellular Carcinoma Metastasis. Hepatology (Baltimore, Md.). 2020, 72(3), 906-922.
[141] Xiang Y, Yang Y, Lin C, Wu J, Zhang X. MiR-23a-3p promoted G1/S cell cycle transition by targeting protocadherin17 in hepatocellular carcinoma. Journal of Physiology and Biochemistry. 2020, 76(1), 123-134.
[142] Chai ZT, Zhu XD, Ao JY, Wang WQ, Gao DM, et al. microRNA-26a suppresses recruitment of macrophages by down-regulating macrophage colony-stimulating factor expression through the PI3K/Akt pathway in hepatocellular carcinoma. Journal of Hematology & Oncology. 2015, 8, 1-11.
[143] Zhang JG, Shi Y, Hong DF, Song M, Huang D, et al. MiR-148b suppresses cell proliferation and invasion in hepatocellular carcinoma by targeting WNT1/β-catenin pathway. Scientific Reports. 2015, 5(1), 8087.
[144] Hou ZH, Xu XW, Fu XY, Zhou LD, Liu SP, et al. Long non-coding RNA MALAT1 promotes angiogenesis and immunosuppressive properties of HCC cells by sponging miR-140. American Journal of Physiology-Cell Physiology. 2020, 318(3), C649-C663.