

# Non-Coding RNAs in Hepatocellular Carcinoma

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**Abstract:** Liver cancer ranks as the fourth leading cause of cancer-related deaths. Despite extensive research efforts aiming to evaluate the biological mechanisms underlying hepatocellular carcinoma (HCC) development, little has been translated towards new diagnostic and treatment options for HCC patients. Historically, the focus has been centered on coding RNAs and their respective proteins. However, significant advances in sequencing and RNA detection technologies have shifted the research focus towards non-coding RNAs (ncRNA), as well as their impact on HCC development and progression. A number of studies reported complex post-transcriptional interactions between various ncRNA and coding RNA molecules. These interactions offer insights into the role of ncRNAs in both the known pathways leading to oncogenesis, such as dysregulation of p53, and lesser-known mechanisms, such as small nucleolar RNA methylation. Studies investigating these mechanisms have identified prevalent ncRNA changes in microRNAs, snoRNAs, and long non-coding RNAs that can both pre- and post-translationally regulate key factors in HCC progression. In this review, we present relevant publications describing ncRNAs to summarize the impact of different ncRNA species on liver cancer development and progression and to evaluate recent attempts at clinical translation.

**Keywords:** non-coding RNAs; liver cancer; snoRNA; lncRNA; hepatocellular carcinoma; microRNA; HCC



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## 1. Introduction

Liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause for cancer death, with hepatocellular carcinoma (HCC) accounting for 80–90% of all cases [1,2]. HCC development is attributed to the complex interaction between predisposing factors, which include genetic alterations and exposure to environmental stimuli, such as carcinogens and viruses [2–5]. HCC is frequently associated with the development of chronic liver disease, manifesting as liver cirrhosis, which is characterized by the alteration of the normal anatomical structure and aberrant changes in liver function. Chronic alcohol abuse, obesity, and viral hepatitis infections represent the most prevalent environmental risk factors for the development of HCC [4,6,7].

Although the prognosis of early-stage tumors is favorable, with survival rates exceeding 70%, the median survival of intermediate- and late-stage patients is significantly lower, at 12–24 months. Due to the lack of specific symptoms and, therefore, delayed diagnoses, the majority of patients present in the intermediate and late stages. The poor prognosis of intermediate- and late-stage HCC can be attributed to the lack of specific clinical treatment regimens outside of systemic chemotherapy for patients that do not qualify for surgery, ablative techniques, or intra-arterial therapies [8–12].

Non-coding RNAs (ncRNAs) have recently received greater attention from the liver cancer research community. Increasing evidence associates ncRNAs with carcinogenesis and progression of HCC, and ncRNAs have been shown to be possible prognostic indicators in HCC patients [13–15]. A multitude of recent studies have revealed large populations of non-coding transcripts that are dysregulated in HCC and play significant

roles in carcinogenesis [13–16]. Further, ncRNAs have been shown to affect the expression of both oncogenes and tumor suppressors and regulate pathways such as MAPK/ERK, which suggests that a number of ncRNAs could be developed as new biomarkers and therapeutic targets for HCC. While this review evaluates the impact of non-coding RNAs on the development and progression of HCC, it does not represent an exhaustive list of all ncRNAs associated with HCC. Instead, it contains a selection of well-described and evaluated ncRNAs and underscores parts of the complex, evolving mechanisms associated with HCC development and progression.

## 2. microRNAs

MicroRNAs (miRNAs) are small ncRNAs, approximately 21–25 nucleotides in length, that act as post-transcriptional regulators of gene expression by complementary base pairing within the 3'-untranslated region (UTR) of target mRNAs [17]. An update from the miRTarBase in 2018 highlighted over 4000 known miRNAs with more than 420,000 miRNA-target interactions that are known to affect around 23,000 target genes [18]. Further, miRNA binding to its target mRNA has been shown to block translation or trigger degradation of that mRNA through the RISC complex [17], and miRNAs are involved in the regulation of numerous biological processes and are tightly regulated in healthy cells [19]. However, when miRNAs are dysregulated in cancer cells, they contribute to tumor development and progression through the aberrant induction of oncogenes and silencing of tumor suppressor genes, therefore acting as both oncogenes and tumor suppressors [20]. Aberrant miRNA expression results in changes to cell differentiation, tumor cell proliferation, invasion, metastases, cell cycle progression, DNA repair, and apoptosis [20,21]. Additionally, recent studies have shown that aberrant miRNA expression is associated with reduced survival, treatment failure, and tumor recurrence [20]. A number of miRNAs are aberrantly expressed in hepatocellular carcinoma (HCC) cells when compared to healthy hepatic cells [22].

### 2.1. Tumor Suppressor microRNAs

Downregulated miRNAs in HCC, compared to adjacent non-tumor liver tissue, tend to act as tumor suppressors when upregulated in HCC cell lines, HCC mouse models, or sampled from patients with HCC. Some of these tumor suppressor miRNAs include miR-122, miR-199a, miR-214, miR-124, miR-195, miR-622, miR-342-3p, and miR-587 (Table 1). These miRNAs affect HCC progression through either regulation of the cell cycle, apoptosis, migration, invasion, or a combination of such.

**Table 1.** Summary of key PDAC-related non-coding RNAs. Table listing all lncRNAs discussed in this review including their expression in HCC as noted by the aforementioned studies, including both in vitro and in vivo studies, as well as studies conducted on tumor samples. As well, the relevant signaling pathways and/or targets that are involved in the cancer phenotypes are noted based on the increase or decrease in each ncRNA's expression level, which contributes to the overall HCC profile.

TYPE OF ncRNA	NAME	EXPRESSION IN HCC	AFFECTED CANCER PHENOTYPE	SIGNALING PATHWAYS AFFECTED	REF
Tumor suppressor miRNAs	miR-122	↓	Invasion and Metastasis	TP53-MDM2, Wnt, Notch, TGFβ	[23–34]
	miR-199a	↓	Invasion and Metastasis	Raf/MEK/ERK	[35,36]
	miR-214	↓	Cell Cycle Regulation	G1/S Transition, UPR	[37,38]
	miR-124	↓	Cell Cycle Regulation	PI3K/AKT, G1/S Transition	[39,40]
	miR-195	↓	Cell Cycle Regulation and Apoptosis	NFκB, G1/S Transition	[41–44]
	miR-622	↓	Apoptosis and Colony Formation	MAPK, NFκB, JNK	[45]
	miR-342-3p	↓	Apoptosis	Lactate Transport	[46]
	miR-587	↓	Invasion and Metastasis	RPSA (Target)	[47]

Table 1. Cont.

TYPE OF ncRNA	NAME	EXPRESSION IN HCC	AFFECTED CANCER PHENOTYPE	SIGNALING PATHWAYS AFFECTED	REF
<i>OncomiRs</i>	miR-21	↑	Proliferation and Migration, Cell Cycle Regulation, EMT, Cell Death, Proliferation	P53, PI3K/AKT, ERK, TET/PTEN	[48–56]
	miR-151(-5p)	↑	Migration and Invasion	Rho Signaling Pathway	[57–59]
	miR-221	↑	Invasion and Metastasis, Cellular Proliferation, Apoptosis	DNA Repair (MGMT), RB1	[35,60–66]
	miR-222	↑	Invasion and Metastasis, Cellular Proliferation, Apoptosis	TEN/PTEN, AKT	[52,66,67]
	miR-224	↑	Cellular Proliferation, Metastasis and Apoptosis	AKT, MAPK	[68–70]
	miR-93-5p	↑	Cell Cycle Regulation, Colony Formation, Metastasis, Invasion and Migration, Cellular Proliferation	MAPK, JNK	[71–73]
<i>Other miRNAs</i>	miR-96	↑	Cancer Stem Cell Proliferation	Ephrin Signaling	[74,75]
	miR-182	↑	Cancer Stem Cell Proliferation	Ephrin Signaling	[76]
<i>C/D Box snoRNAs</i>	SNORD126	↑	Tumor Growth and Proliferation	PI3K/AKT	[41,77,78]
	SNORD78	↑	Cellular Proliferation, Migration and Invasion, Cell Cycle Regulation	Unknown	[79,80]
	SNORD76	↑	Cell Cycle Regulation, Cellular Proliferation, EMT, Migration and Invasion	Wnt	[13]
	SNORD17	↑	Tumor Progression, Cellular Proliferation	P53	[81]
	SNORD113-1	↓	Tumorigenesis, Apoptosis and Cellular Growth	TGFβ, MAPK, ERK	[82,83]
<i>H/ACA Box snoRNAs</i>	SNORA18L5	↑	Proliferation and Migration, Apoptosis, Cell Cycle Regulation	P53-MDM2	[84]
	SNORA47	↑	Cellular Proliferation, Migration, Invasion and Metastasis	Unknown	[85,86]
<i>SCARNA</i>	ACA11	↑	Oncogenesis, Migration, Invasion and Metastasis, Cellular Proliferation	PI3K, AKT	[41,87]
<i>LncRNAs</i>	Lnc-ELF209	↓	EMT	Epithelial and Mesenchymal Markers (Targets)	[88,89]
	GATA3-AS	↑	Invasion and Metastasis, Migration, Apoptosis, Cellular Proliferation	GATA3 (Target)	[90]
	PURPL	↑	Tumor Size and Growth, Cancer Phenotype Differentiation, Cell Cycle Regulation, Apoptosis	P53-MDM2	[91]
	HAND2-AS1	↑	Self-Renewal of Liver Cancer Stem Cells, Tumor Growth	BMP Signaling	[92]
	BCYRN1	↑	Invasion and Metastasis, Migration	BATF (Target)	[93]
	Hbx-LINE1	↑	Tumor Development and Progression	Wnt	[94]
	Linc-p21	↓	Proliferation and Migration, Invasion and Metastasis, EMT, Apoptosis	P53, Notch	[95–100]
	Linc01419	↑	EMT, Proliferation and Migration, Invasion and Metastasis	LSM4 (Target)	[101]
	Linc01194	↑	Proliferation and Migration, Tumor Progression	miR-655-3p/SMAD5 Axis (Target)	[102]
	XIST	↓	Proliferation and Migration, Apoptosis, Tumor Growth	MGMT (Target)	[64]

In the healthy liver, miRNA-122 (miR-122) accounts for 52% of the total hepatic miRNA. This miRNA plays a significant role in liver development, differentiation, homeostasis, and function [103]. This is due, in part, to the regulation of miR-122 by liver-enriched transcription factors (LETFs) during liver development. This precise balance between miR-122 and LETFs expression is suggested to play a central role in cell proliferation and differentiation in the hepatocyte lineage, which is fundamental to its major role among hepatic miRNAs [104–106]. Increasing evidence has shown that miR-122 expression is reduced in up to 70% of HCC patients [23,107]. This reduction results in the overexpression of target genes, such as Mdm2 (mouse double minute 2 homolog) [24] and cyclin G1, that serve as negative regulators of the tumor suppressor p53 [25,26]. Further, miR-122 has been demonstrated to act as a tumor suppressor by hindering p53 degradation and supporting p53 stability through the reduction of Mdm2 expression [26]. Additionally, miR-122 is involved in the direct post-transcriptional regulation of pyruvate kinase isoform M2 (PKM2) [23], Wnt family member 1 (WNT1) [27], and parentally expressed gene 10 (PEG10) [28]. Through these target genes, miR-122 regulates the metabolic switch from oxidative phosphorylation to glycolysis, in addition to regulating Wnt and TGF $\beta$  pathway activation [23,27,29–32]. Decreased expression of miR-122 is, furthermore, associated with venous migration of HCC cells via increases in ADAM10 and ADAM17 expression [33,34]. This leads to increased metastatic capacity and poor prognosis [15,108]. However, miR-122 is only one of many miRNAs that have been implicated in the regulation of invasion and metastasis of HCC cells.

The invasive and metastatic properties of HCC cells have been associated with the inhibition of miR-199a-3p (miR-199a) [20,35]. Indeed, miR-199a negatively regulates the oncogene c-Met [35,36], which is overexpressed in 40–70% of HCC patients [109,110]. Furthermore, the growth of HCC cells has been shown to be suppressed by an increase in miR-199a/b-3p expression through the inhibition of p21-activated kinase 4 (PAK4), an activator of the Raf/MEK/ERK pathway [111]. Another kinase affected by miR-199a is mTOR [36], whose overexpression is associated with poor prognosis, invasion, and metastasis [112]. Further, miR-199a has been demonstrated to cluster with miR-214, forming miR-199/214, which is downregulated in the majority of HCC patients and clinically associated with shorter survival time [35,37], and miR-199a and miR-214 are transcribed from the antisense strand, located within an intron of Dynamin on chromosome 1, as a single intron-less transcript [38]. In response to activation of the unfolded protein response (UPR), the protein complex nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) inhibits the expression of miR-199/214 [38]. Downregulated in HCC as well, miR-214 contributes to tumor growth in HCC in vivo and in vitro [37]. Further, miR-214 post-transcriptionally regulates the translation of the cell cycle, promoting genes transcription factor E2F2 (E2F2), cyclin-dependent kinase 3, or cell division protein kinase 3 (CDK3), and cyclin-dependent kinase 6 or cell division protein kinase 6 (CDK6), and controls proliferation by inhibition of the G1/S transition in the cell cycle progression [37]. The transcription factor X-box binding protein 1 (XBP1), a key effector of UPR and ER stress, has also been shown to be a direct target of miR-214 and supports tumor cell survival and growth in HCC in vivo and in vitro without miR-214-mediated suppression [48]. Overexpression of miR-214 has been reported to reverse the impact on cell proliferation and induced apoptosis in HepG2 and SMMC-7721 HCC cell lines [38].

Further, miRNA-124 (miR-124) is another miRNA affecting mTOR and protein kinase B (AKT), key components of the PI3K/AKT signaling pathway, that enhances tumor cell proliferation. This pathway has been shown to play an important role in diverse cellular processes, such as cell proliferation, cell cycle progression, differentiation, cell survival, and apoptosis [39]. In the PI3K/AKT signaling pathway, PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2), generating phosphatidylinositol 3,4,5-bisphosphate (PIP3), thereby activating the signal transduction pathway, leading to activation of AKT. PIP3 acts as a second messenger that facilitates the activation of AKT, which subsequently activates mTOR. The activation of the PI3K/AKT signaling pathway can be suppressed by the tumor

suppressor phosphatase and tensin homolog (PTEN), which reverses the phosphorylation status of PIP3 to PIP2 [113]. When present, miR-124 directly targets the 3'UTR of phosphoinositide 3-kinase catalytic subunit alpha (PIK3CA), another mediator of this pathway, resulting in suppression of the PI3K/AKT pathway. However, miR-124 has been shown to be downregulated in HCC. Furthermore, overexpression of miR-124 suppresses tumor cell proliferation in HepG2 cell lines by inducing a G1-phase cell cycle arrest. While an effect of the downregulation of PIK3CA is a significant downregulation of mTOR and AKT, overexpression of PIK3CA restores mTOR and AKT expression and enhanced cancer cell proliferation by mediating the G1/S-phase cell cycle transition. These findings could be confirmed in xenograft mouse models where miR-124 overexpression reduced tumor growth [40].

Similarly, miRNA-195 (miR-195) is frequently downregulated in HCC [114]. In non-cancerous cells, miR-195 promotes apoptosis by suppressing B-cell lymphoma 2 (BCL2) and Bcl-2-like protein 2 (BCL-w) expression [42,115]. Downregulation in HCC results in increased cancer cell proliferation due to abnormal cell cycle progression through the increase in expression of cyclin-dependent kinase 6 (CDK6), cyclin E1 (CCNE1), CDC25A, G1 cell cycle regulator cyclin D1, cyclin-dependent kinase 4 (CDK4), and E2F transcription factor 3 (E2F3) [15,81,116]. Dysregulation of these factors results in overwriting the G1/S-cell cycle checkpoint [15,35,43,116]. Further, miR-195 reduces tumor growth and size, cancer cell proliferation, migration, and metastasis by interacting with fibroblast growth factor 2 (FGF2), vascular endothelial growth factor A (VEGFA), I $\kappa$ B (inhibitor of nuclear factor kappa B) kinase alpha (IKK $\alpha$ ), TGF- $\beta$  activated kinase 1/MAP3K7 binding protein 3 (TAB3), and nuclear factor kappaB (NF-kB) [43,44]. Overexpression of miR-195 reduced migration and invasion in the HCC cell line BEL-7402 [58]. Further, miR-195 directly targets FGF2, VEGFA, TAB3, and IKK $\alpha$  via post-transcriptional regulation, thus inhibiting the NF-kB signaling pathway [43,44].

The tumor suppressor miRNA-622 (miR-622) likewise indirectly targets the NF-kB signaling pathway, as well as the JNK signaling pathway via targeting mitogen-activated protein kinase kinase kinase kinase 4 (MAP4K4). Both signaling pathways are associated with cell proliferation, invasion, and reduced apoptosis in cancer. Analysis of fresh HCC and adjacent non-cancerous liver tissue revealed that miR-622 is significantly downregulated, which has also been shown in other malignancies, such as glioma, gastric, colorectal, and pancreatic cancer. Downregulation of miR-622 is associated with increased proliferation, colony formation, tumor survival, overall poor prognosis, and aggressive tumor properties. Overexpression in miR-622 low HCC cell lines (MHHC-97H, Hep3B) and HCC xenograft models significantly inhibited tumor growth and induced apoptosis in HCC cell lines. Bioinformatic analysis revealed MAP4K4 mRNA as a direct target of miR-622 with a binding site in the 3'-UTR, and the expression levels of both genes could be shown to be significantly inversely correlated. By targeting MAP4K4, the NF-kB signaling pathway and the JNK signaling pathway are indirectly affected, mediating the anticancer effects of miR-622. Overexpression of MAP4K4 could partially reverse the proliferation and colony formation suppressing effects of miR-622, as well as reduce apoptosis in the HCC cell lines [45].

Suppression of miRNA-342-3p (miR-342-3p) *in vitro* and *in vivo* is also associated with increased cell proliferation, tumor growth, migration, and colony formation in HCC. The monocarboxylic acid transporter 1 (MCT1) could be identified as a direct target of miR-342-3p with inversely correlated expression in human HCC. Normal or increased miR-342-3p expression is suggested to impair the bidirectional lactate transport, with increased extracellular lactate, decreased intracellular lactate, and decreased glucose uptake in HCC. The 3'UTR of MCT1 could be confirmed as a direct binding site for miR-342-3p, resulting in a decreased MCT1 protein level in non-tumor liver tissue. Injection of therapeutic miR-342-3p in HRAS-driven transgenic HCC mouse models decreased tumor proliferation and increased apoptosis, resulting in reduced tumor progression and improved overall survival [46].

Another miRNA that has recently been shown to be associated with tumor progression in HCC is miRNA-587 (miR-587). Aberrant expression profiles of miR-587 have been reported in colorectal cancer, melanoma, and glioma. Initial database analysis and qRT-PCR analysis of 86 paired clinical tissues showed significant downregulation of miR-587 in HCC tissue. Further studies investigating cellular functions in the HCC cell line SMMC-7721 showed that increased expression of miR-587 resulted in reduction of proliferation, G1- to S-phase cell cycle progression, migration, and invasion. Among 13 differentially expressed target genes of miR-587, the ribosomal protein SA (RPSA) has been reported to display higher transcript levels in response to miR-587 overexpression and to be involved in cancer progression in different malignancies [47]. RPSA is a laminin receptor 1 that interacts with the extracellular matrix glycoprotein laminin and could be associated with cancer cell proliferation, migration, and invasion in melanoma, breast, and esophageal cancer, and colorectal carcinoma [47,117–119]. The 3'-UTR of RPSA is a direct target of miR-587, showing inverse expression and cellular functions of these two genes in HCC [47].

Taken together, downregulation of tumor suppressor miRNAs affects diverse cellular mechanisms, which contributes to HCC progression. Downregulation of some miRNAs leads to proliferation and tumor growth through a lack of regulation in cell cycle progression and thus the overwriting of cell cycle checkpoints. Such miRNAs include: miR-214, miR-195, miR-124, and miR-587 (Table 1). Additionally, some miRNAs are associated with apoptosis regulation, resulting in suppressed apoptosis initiation in HCC, such as miR-195, miR-342-3p, and miR-622. The absence of other miRNAs facilitates invasion and/or metastasis, such as miR-122, miR-199a, and miR-587, or enhances colony formation, such as miR-622.

## 2.2. Tumor Suppressor microRNAs in Non-Parenchymal Hepatic Cells

The liver consists of parenchymal and non-parenchymal cells. Parenchymal cells perform the majority of liver functions and constitute the predominant cell type in the liver [120]. Non-parenchymal cells include hepatic stellate cells (HSCs), Kupffer cells (hepatic resistant macrophages), and hepatic sinusoidal endothelial cells (HSECs), which contribute to the liver microenvironment and have been shown to influence the tumor microenvironment in HCC [120,121]. Kupffer cells play an important role in the liver immune response by producing a variety of proinflammatory regulators, the processing and presentation of antigens, and phagocytosis. However, Kupffer cells can adapt to exogenous signals by polarizing between two different activation states, M1 and M2, and display opposite responses in different microenvironments. M1 is the classical activation stage, in which Kupffer cells can produce large amounts of pro-inflammatory cytokines, whereas M2-polarization (alternative activation) is defined by the production of anti-inflammatory mediators [122]. M2-polarization has been shown to contribute to HCC development in AKT/Ras mice by depleting cytotoxic T-cells (CTLs) and impairing miRNA-206 (miR-206) biogenesis. Further, miR-206 targets the Kruppel-like factor 4 (Klf4), which drives M1-polarization in Kupffer cells, including enhanced production of M1 marker C-C motif chemokine ligand 2 (CCL2). CCL2 facilitates the recruitment of CTLs via the C-C chemokine receptor type 2 (CCR2) and has been shown to prevent tumor formation entirely in AKT/Ras mice. Any disruption of this Klf4/CCL2/CCR2 axis impaired the miR-206-mediated M1-polarization of Kupffer cells and the recruitment of CTLs [123].

Another Kupffer-cell-associated tumor suppressor miRNA is miRNA-22 (miR-22), which has been shown to act as a tumor suppressor via the post-transcriptional regulation of galectin-9 expression in HCC cell lines [121,124,125]. Galectin-9 is an interferon- $\gamma$  (INF- $\gamma$ )-induced immunosuppressor that is produced in Kupffer cells. Tumor-infiltrating T-cells provide INF- $\gamma$  and increase the galectin-9 expression in Kupffer cells in the HCC microenvironment, which drives precancerous lesion formation and HCC development and progression [121]. This is further supported by enhancer of zeste homolog 2 (EZH2), a known suppressor of miRNA tumor suppressors, including miR-22 [121,126]. Specifically, EZH2 writes the histone 3 lysine 27 tri-methylation (H3K27me3) at the miR-22 promoter

and inhibits the expression of miR-22. Under forced miR-22 expression, galectin-9 levels are decreased, which suppresses HCC cell growth, migration, and invasion in HCC cell lines. Decreased cell viability and induced apoptosis in vitro were driven by repression of BCL2 and elevated levels of cleaved-caspase 3 and BAX. This was supported by HCC xenograft mouse models that presented suppressed HCC tumor growth, metastasis, and angiogenesis. Interestingly, restored expression of galectin-9 in miR-22 overexpression models enhanced the tumor suppressive effect of miR-22 [121].

HCC tumor endothelial cells (TECs) are malignant HSECs that have been shown to contribute to HCC progression. The miRNA-3178 (miR-3178) acts as a tumor suppressor and is downregulated in HCC TECs compared to healthy HSECs. Further, miR-3178 mimics significantly reduced cell proliferation, metastasis, and angiogenesis in vitro by inducing G1-phase cell cycle arrest and apoptosis [127]. This effect is driven by miR-3178-mediated inhibition of the early growth responsive gene 3 (EGR3), a key activator of the VEGF signaling pathway, which affects mRNA and protein level of EGR3 [127,128].

Taken together, non-parenchymal hepatic cells have been shown to play an important role in the regulation of the HCC tumor microenvironment. Shown to act as both tumor suppressors as well as drivers of oncogenesis, Kupffer cells influence the biogenesis of tumor suppressor miRNA miR-206 based on their polarization state. On the other hand, it has been shown that the expression of galectin-9, a target of miR-22, enhances HCC development and progression. Malignant hepatic endothelial cells have been shown to suppress miR-3178, leading to EGR3-mediated VEGF signaling pathway activation and HCC TECs proliferation, migration, invasion, and angiogenesis.

### 2.3. Oncogenic microRNAs (OncomiRs)

In addition to miRNAs acting as tumor suppressors, several miRNAs with oncogenic characteristics, called oncomiRs, have been identified in liver cancer [20]. These oncomiRs have been shown to be frequently overexpressed in liver cancer when compared to adjacent normal liver tissue. This overexpression facilitates HCC development, progression, and increased tumor cell survival [129]. A sample of liver-cancer-associated oncomiRs are miRNA-21, miRNA-222, miRNA-221, and miRNA-224 (Table 1). All of these oncomiRs are consistently increased in HCC.

Further, miRNA-21 (miR-21) has been classified as a key regulator of tumor initiation, development, progression, and cell survival in HCC cells [130] because of its role in the regulation of multiple cellular pathways. Additionally, miR-21 interferes with the p53/Srebp1c pathway by targeting HMG-box transcription factor 1 (HBP1), a regulator of G1/S cell cycle transition, thereby modulating hepatic steatosis and cancer progression (Figure 1A) [48]. The presence of HBP1 has shown to significantly enhance the expression of p53, which is believed to be indirect, including the interaction with other transcription factors to elevate p53 expression since there is no known binding site for HBP1 on the promoter region of p53 [48]. Inhibition of the tumor suppressor PTEN expression, an important regulator of the G1/S and G2/M cell cycle checkpoints and major antagonist of the PI3K/AKT signaling pathway, by miR-21 results in increased proliferation and metastatic potential [49–51]. Further, miR-21 directly binds to the 3'UTR of PTEN mRNA to suppress translation [49]. Similarly, suppression of PTEN and human sulfatase-1 (hSulf-1) promotes cell proliferation and migration through the activation of the AKT/ERK pathway. In addition, aberrant miR-21 expression has been shown to induce the epithelial-to-mesenchymal transition (EMT) [52] by increasing  $\beta$ -catenin and cyclin D1 expression, resulting in activation of the canonical Wnt/ $\beta$ -catenin signaling pathway [53]. Ras homolog family member B (RHOB) is another tumor suppressor targeted by miR-21 [131]. It binds directly to RHOBs 3'-UTR, leading to mRNA degradation, which is associated with more aggressive tumors, changes in cell shape, migration, and adhesion. This occurs not only in HCC cell lines Huh-7 and HepG2 but also in the metastatic breast cancer cell line MDA-MB-231 [131]. In vitro, miR-21 has been described to reduce protein expression of programmed cell death 4 (PDCD4) by creating a miR-21-PDCD4-AP-1 feedback loop,

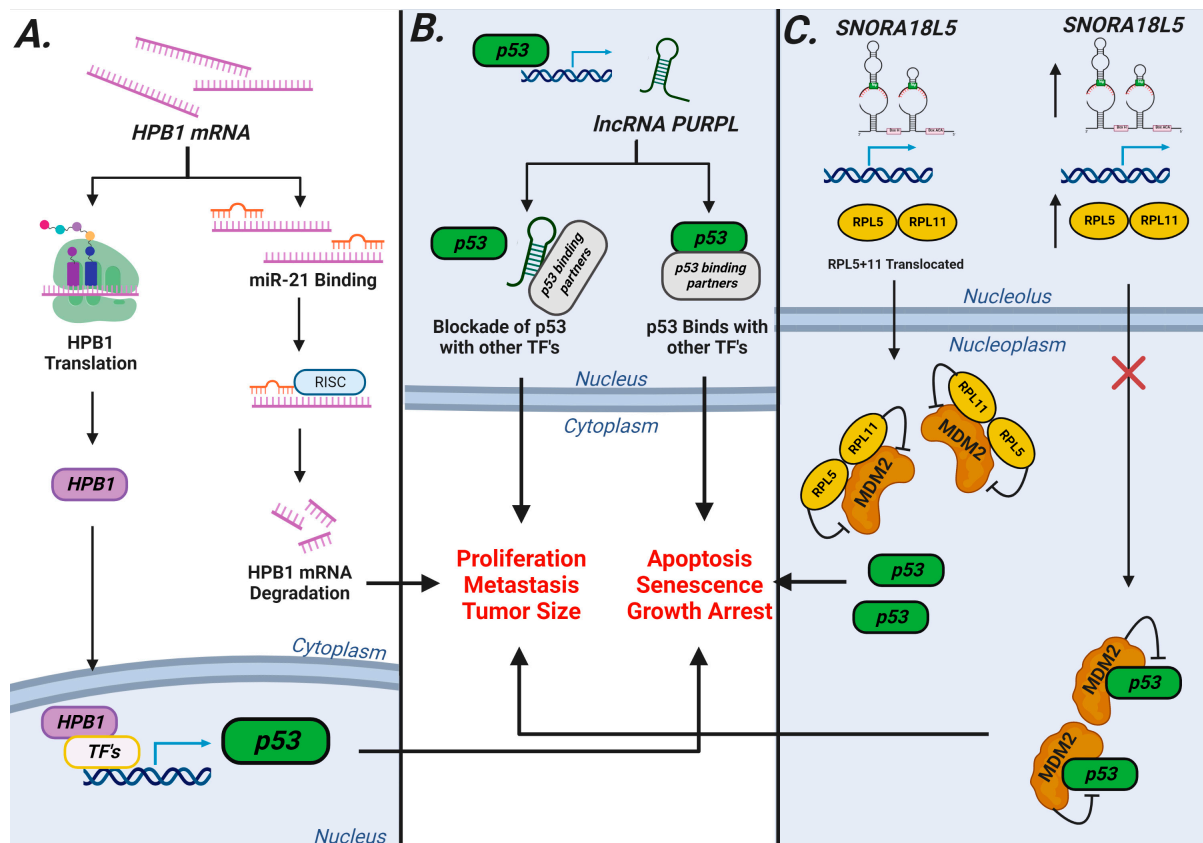
promoting migration and invasion of the HCC cell line HepG2 [54]. High mobility group box 1 (HMGB1) is secreted by immune cells during inflammatory reactions and stimulates miR-21 expression in the inflammatory microenvironment of liver tumors [55]. This results in post-transcriptional suppression of tissue inhibitor of metalloproteinase (TIMP3) and reversion, inducing cysteine rich protein with kazal motifs (RECK), which are inhibitors of the matrix metalloproteinases (MMPs) [55]. Members of the MMP family, namely matrix metalloproteinase-2 and -9 (MMP-2 and MMP-9), are associated with cell migration and invasion of cancer cells through degradation of the extracellular matrix [49,55]. Therefore, the overexpression of miR-21 due to HMGB1 secretion results in lack of inhibition of TIMP3 and RECK, which, under normal conditions, serve to inhibit MMPs that are associated with malignant cancer phenotypes [55]. Another direct target of miR-21 was found in the mitogen-activated protein kinase kinase 3 (MAP2K3), which is significantly repressed in HCC and inversely correlated with miR-21 expression. Downregulated MAP2K3 leads to increased tumor cell proliferation and a disrupted MAPK signaling pathway, which was previously reported to support tumor progression in various types of cancer, including HCC [56]. Surprisingly, a recent study suggested that miR-21 could not only be a potent oncomiR in HCC but also have a bidirectional role in HCC, supporting tumor development and progression in vivo. Lack of miR-21 in genetically engineered mice seemed to enhance carcinogen-induced (diethylnitrosamine or PTEN deficiency) tumor development and progression by increased expression of the cell cycle regulating oncogene *Cdc25a* and deregulation of signaling pathways MAPK, Hippo, PI3K/AKT, and STAT3 [132]. Notably, miR-21 was shown to act as a tumor suppressor in other malignancies, such as colon and breast cancer, partially by repressing the expression of CDC25A [133,134]. Furthermore, an enhanced inflammatory microenvironment and decreased immune anti-tumoral responses were observed, creating an overall pro-tumoral microenvironment and enhancing tumorigenesis and HCC progression over time in these mice [132].

An miRNA mainly associated with migration and invasion in HCC in vitro and in vivo is miRNA-151 (miR-151) [57]. This miRNA is located in intron 22 of the focal adhesion kinase gene (FAK, also known as PTK2). FAK and miR-151 are often expressed together, and FAK is associated with cell mobility [58]. Specifically, miR-151-5p and not miR-151-3p appears to exert the metastatic property of this miRNA by targeting the 3'-UTR of RhoGDI A, which downregulates its mRNA and protein level. RhoGDI A is a negative regulator of Rho GTPases, such as Rac1, Cdc42, and Rho, and is suggested to function as a metastasis suppressor in HCC. FAK, on the other hand, is a Rho GTPase activator, which plays a central role in all types of cell migration [57,59]. FAK and miR-151 were found to act synergistically to enhance HCC motility and metastasis [57].

Other frequently overexpressed miRNAs, miRNA-221 (miR-221) and miRNA-222 (miR-222), form the miR-221/222 cluster and have been implicated in liver cancer occurrence, development, metastasis, and survival [15,35]. Further, miR-221 has been shown to promote tumor capsular infiltration, which affects invasion, metastasis, and cell proliferation by suppressing the cell cycle arrest at the G1/S-phase checkpoint [135], and miR-221 targets retinoblastoma protein (RB1), a key G1/S cell cycle checkpoint protein, and cyclin-dependent kinase inhibitor 1C (CDKN1C/p57), which suggests that miR-221 overexpression results in the overwrite of the cell cycle checkpoint [35,60]. A number of studies have shown that miR-221 overexpression promotes survival by decreasing the expression of pro-apoptotic members of the Bcl-2 family Bcl-2 and BID, thus protecting the cancer cells from anoikis, a specific form of apoptosis caused by the detachment of anchorage-dependent cells from their surrounding extracellular matrix [61–63]. Additionally, miR-221-3p has been shown to repress its downstream target O6-methylguanine-DNA methyltransferase (MGMT) by binding to its 3'-UTR. MGMT is weakly expressed in HCC with high levels of miR-221, which was shown in HCC cell lines (SNU-182 and Hep3B) and HCC tumor specimens compared to non-tumor specimens. While overexpression of MGMT repressed proliferation and migration, as well as enhanced apoptosis, this effect was abolished when miR-221-3p was simultaneously overexpressed [64]. Moreover, miR-



222 overexpression promotes HCC progression by targeting and decreasing Bcl-2 binding component 3 (BBC3) [21], as well as by inhibiting PTEN [65] and TIMP3 expression [66]. Additionally, the overexpression of miR-222 promotes cancer progression by activating the AKT pathway [52,67] and MMPs, which are known to enhance cellular migration [66]. Cyclin-dependent kinase (Cdk) inhibitor p27 (p27Kip1) and DNA damage-inducible transcription 4 (DDIT4) expression were found to be targeted and decreased by the miR-221/222 cluster, as well as to promote growth of hepatic cancer progenitor cells [136].



**Figure 1.** ncRNA's impact on hepatocellular carcinoma. While the mechanisms of action of various classes of ncRNAs in the development and progression of HCC vary, they can have overlapping functions on important regulators of oncogenesis. This, in effect, leads to a complexity of interactions that are poorly understood. (A) miR21 is highly upregulated in HCC and acts on its target RNA, HPB1. HPB1 mRNA, when not marked for degradation by miR21, is translated in HPB1, which acts in concert with other transcription factors to increase production of p53. In the presence of miR21, HPB1 mRNA is degraded, leading to a lack of p53 production and, therefore, an increase in proliferation, metastasis, and tumor size. (B) lncRNA PURPL is also upregulated in HCC and acts in a similar manner to miR24 by binding components necessary for p53 regulation. In the presence of lncRNA PURPL, which is positively regulated by p53, p53 is unable to bind to its partners for downstream gene expression, leading to further oncogenesis. (C) SNORA18L5, an H/ACA box snoRNA that is upregulated in HCC, acts to increase transcription of rRNA RPL5 and RPL11. However, instead of these rRNAs translocating to the nucleoplasm and inhibiting MDM2-mediated degradation of p53, they are sequestered to the nucleolus, allowing for p53 degradation and, like other oncogenic ncRNAs, leading to further oncogenesis. Reprinted with permission from BioRender.com. Copyright 2022 BioRender.

Several other miRNAs have been shown to target the same cellular RNAs, suggesting a tight regulation of protein expression in healthy cells. Further, miR-224-mediated activation of AKT signaling promotes HCC progression, similar to the miR-221/-222 cluster [68].

The downregulation of the mothers against decapentaplegic homolog (SMAD) family member 4 (SMAD4) by miR-224 enhances cell proliferation and has been correlated with poor prognosis in patients with HCC [137]. A lack of intracellular autophagy has been suggested to be a source for miR-224 accumulation, resulting in reduced SMAD4 expression and promotion of tumor development and metastatic progression [69]. Additional target genes of miR-224, which are downregulated on mRNA and protein level, include the cell division control protein 42 homolog (CDC42), the cell–cell adhesion tumor suppressor cadherin-1 (CDH1), the apoptosis inducing serine/threonine-protein kinase PAK 2 (PAK2), and the transcription factor homeobox D10 (HOXD10) [70,138]. The downregulation of HOXD10 promotes the expression of the tumor-invasion-associated proteins p-PAK4 and MMP-9 [96]. These genes, which are downregulated by miR-224, are strongly associated with metastasis of HCC [70,138]. Apoptosis suppressing BCL-2 and the signal transducing mitogen-activated protein kinase 1 (MAPK1), which are important factors for cell survival and proliferation in HCC, are significantly upregulated and associated with miR-224 upregulation in hepatic cancer [70].

Additionally, miRNA-93-5p (miR-93-5p) is another oncomiR that influences the MAPK pathway and contributes to HCC progression. Increased expression of miR-93-5p could be verified in 73 HCC patient samples and several HCC cell lines, suggesting that this is a frequently event in HCC. Further, miR-93-5p directly targets the 3'-UTR of mitogen-activated protein kinase kinase kinase 2 (MAP3K2) and thereby stabilizes MAP3K2 mRNA, leading to increased protein levels [71]. MAP3K2 acts as a signal transducer, as well as phosphorylates downstream proteins, thereby activating MAPK kinases (MKKs). MKKs, in turn, phosphorylate and activate other mitogen-activated protein kinases (MAPKs), including p38 and c-Jun N-terminal kinase (JNK), which then activate/phosphorylate substrates, such as c-Jun and activating transcription factor 2 (ATF2) [139]. Further investigation confirmed that miR-93-5p does affect the phosphorylation level of MAP3K2 downstream targets through MAP3K2 kinase function, while the total protein levels of MKK4, p38, JNK, c-Jun, and ATF2 did not change. Additionally, miR-93-5p regulates the mRNA and protein level of the tumor suppressor p21 indirectly via c-Jun, which targets p21, and directly since miR-93-5p binds to the 3'-UTR of p21 mRNA, which promotes its degradation [72,73]. Without the p21-induced cell cycle arrest, the G1/S-phase cell cycle transition is overwritten, leading to increased tumor cell proliferation *in vitro* and *in vivo*. This most likely is further enhanced by the JNK pathway, which is reported to facilitate G1-to S-phase cell cycle transition by reducing p53 and inducing cyclin D1 [140,141]. Further *in vitro* miR-93-5p knockdown experiments also revealed decreased cell growth, colony formation capability, wound healing, and increased G1- to S-phase cell cycle block. These findings indicate that miR-93-5p also enhances metastatic properties in HCC. Moreover, c-Jun was found to directly activate miR-93-5p transcription through direct interaction with the promoter region, establishing a miR-93-5p/MAP3K2/c-Jun positive feedback loop [71]. Taken together, miR-93-5p enhances HCC progression via MAP3K2/p38-JNK/p21 signaling pathway regulation, resulting in increased proliferation, migration, and invasion.

#### 2.4. Other microRNAs

Unlike other oncomiRs, miRNA-96 (miR-96) and miRNA-182 (miR-182) do not seem to affect the MAPK/JNK or the AKT pathway but instead regulate the expression of ephrinA5, an ephrin ligand. Ephrin ligands bind to erythropoietin-producing human hepatocellular receptors (Eph receptors), which triggers diverse processes during embryonic development, as well as diverse maintenance processes in adults [74,75]. Ephrins and Eph receptors were also found to be associated with the regulation of stem cell proliferation and cancer in terms of promotion and suppression [142]. Additionally, miR-96 and miR-182, which are upregulated in HCC, were found to be inversely associated with ephrinA5 protein levels. Both miRNAs can directly bind to the 3'-UTR of ephrinA5 mRNA, reducing the protein translation and enhancing HCC proliferation and migration. However, the details

about the mechanism behind the relationship between HCC tumor growth, ephrinA5, and miR-96/miR-182 are not fully elucidated [76].

OncomiRs have also been shown to be secreted from different cells at the tumor site in extracellular vesicles and influence the tumor microenvironment towards a pro-progressive and pro-metastatic environment. Besides HCC cells, hepatic stellate cells (HSCs) were shown to release miRNAs and are considered key interstitial cells for a pro-metastatic environment, especially when HSCs were activated [143,144]. Among 21 miRNAs that were found to be significantly upregulated in HCC, three miRNAs: miR-21, miR-221, and miR151 were selected in order to investigate the role of secreted miRNAs in the crosstalk between HCC cells and HSCs. It was found that these miRNAs contribute to the recruitment and activation of HSCs, transforming them into cancer-associated HSCs (caHSCs) by HCC cells. These caHSCs, in turn, secrete miRNAs that promote HCC cell proliferation, EMT, invasion, and migration. This group of secreted oncomiRs results in suppressed PTEN, RhoGDI, and E-cadherin, which enhances  $\alpha$ -SMA and vimentin. This also enhances activation of the AKT/ERK signaling pathway in HCC and caHSCs. These enhanced pathways reveal a communication pathway between cancer cells and stellate cells through extracellular vesicles in the tumor microenvironment [144].

Many oncomiRs have been shown to frequently affect either the MAPK/JNK or the AKT signaling pathway, further supporting the importance of these pathways for the development and progression of HCC. Many oncogenic miRNAs (miR-21, miR-221/222, miR-224, and miR-93-5p) influence tumor initiation and progression via increased proliferation, cell survival, and enhancement of metastatic properties in HCC by activating these pathways (Table 1). Unlike these oncomiRs, miR-96 and miR-182 affect ephrinA5, which induces HCC proliferation and migration (Table 1). Finally, miR-151 targets RhoGDI and is mainly associated with HCC cell mobility and metastasis (Table 1).

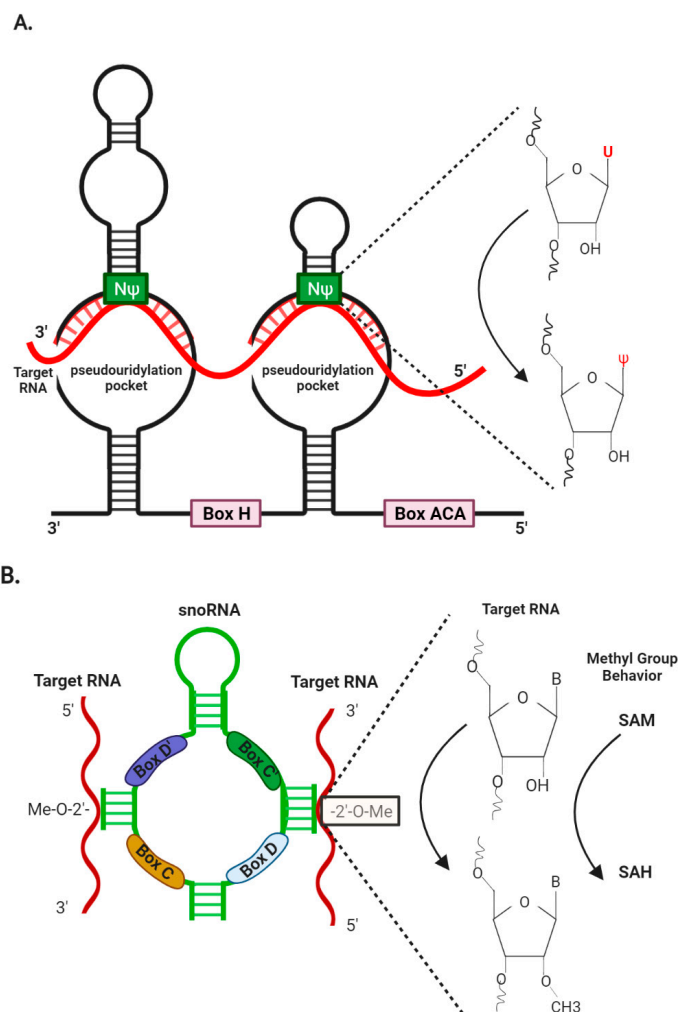
Dysregulated miRNAs have been shown to generally affect a variety of important cellular signaling pathways. The MAPK/JNK pathway has been shown to be affected by tumor suppressor miRNAs miR-622 and oncomiRs miR-21 and miR-93-5p. The PI3K/AKT/ERK signaling pathway is being regulated by tumor suppressor miRNAs miR-124, miR-199a, and the oncomiRs miR-21 and miR-222. Other regulated pathways are Wnt/ $\beta$ -catenin (tumor suppressor miR-122/ oncomiRs miR-21), TGF- $\beta$  (tumor suppressor miR-122), and NF- $\kappa$ B (tumor suppressor miR-195 and miR-622). Additionally, oncomiR miR-21 also affects the p53/Srebp1c, HIPPO, and STAT3 signaling pathways. Numerous pathways and targets are shared between the above-mentioned miRNAs, highlighting the complexity of their mechanisms.

In addition to cellular miRNAs, which have been reported to impact HCC development and progression, hepatitis B virus (HBV) transcripts have been shown to contain binding sites for miR-122 and miR-199a. Although some studies suggest that HBV escapes the direct miRNA-mediated repression [145,146], the mechanisms underlying this evasion remain elusive [147].

### 3. Small Nucleolar RNAs

Small nucleolar RNAs (snoRNAs) belong to a group of non-coding RNAs with regulatory functions. SnoRNAs are involved in the regulation of post-transcriptional modifications of other non-coding RNAs, such as small nuclear RNAs (snRNAs) and ribosomal RNAs (rRNAs) [148]. SnoRNAs are typically 60–300 nucleotides in length and have been shown to modify, mature, and stabilize rRNA [149]. SnoRNAs have been reported to contribute to cancer progression through processes such as invasion and metastasis, cell proliferation, cell cycle progression, apoptosis, and cell survival [148,150]. This is due, in part, to participation in rRNA cleavage, methylation, and pseudouridylation [148]. This makes snoRNAs responsible for a variety of nucleoside modifications in a series of processing steps towards the mature rRNA [151]. Recent studies suggest that snoRNAs impact small nuclear RNAs (snRNAs) [148,152,153] and messenger RNAs (mRNAs) by regulating alternative splicing mechanisms [148,154,155].

Interestingly, snoRNA expression profiles vary among different tissues, indicating tissue-specific functions through alternative splicing and editing of pre-mRNA, as well as exerting an miRNA-like influence on mRNA translation [148,156–158]. Based on their structure and function, snoRNAs are divided into two major families: C/D box (Figure 2A) snoRNAs (SNORD), and H/ACA box (Figure 2B) snoRNAs (SNORA). It is widely accepted that C/D box snoRNAs mainly operate via methylations on target RNAs and H/ACA box snoRNAs modulate the nucleoside uridine [159,160].



**Figure 2.** snoRNA modulation of RNAs. snoRNAs contribute to HCC progression through interactions with target RNAs. (A) H/ACA box snoRNAs modify target RNAs by converting the nucleoside uridine into pseudouridine. The conserved motives H box (ANANNA; N for any nucleotide) and ACA box (ACA trinucleotide) form the characteristic “hairpin–hinge–hairpin–tail” structure with two pseudouridylation pockets, where the target RNA is isomerized. The pseudouridylation pockets contain 9–13 nucleotides complementary to the target RNA that flank the uridylation side. The H box motive is positioned in the hinge region and the ACA box motive close to the 3′-terminal region. (B) C/D box small nucleolar RNAs (snoRNAs) modulate target RNAs by transferring a methyl group, termed a 2′-O′-ribose-methylation. S-adenosylmethionine (SAM) serves as methyl group donor to S-adenosylhomocysteine (SAH). C/D box snoRNAs contain conserved box C (PuUGAUGA) and box D (CUGA) motives and less conserved C′ box and D′box motives. The molecule forms a “kink–turn” (stem–bulge–stem) structure that brings the C box and the D box motives in proximity that is essential for the snoRNA function. The enzyme Nop1p (fibrillarin) catalyzes the shift of the methyl group to the complementary target RNA, bound to the snoRNA. Reprinted with permission from BioRender.com. Copyright 2022 BioRender.

### 3.1. C/D Box snoRNAs

Upregulated SNORD126, a C/D box snoRNA, in HCC activates the PI3K/AKT pathway, thereby stimulating cell growth and proliferation [41]. SNORD126 is located on chromosome 14q11.2, within the intron of cyclin B1-interacting protein 1 (CCNB1IP1), which is also overexpressed in HCC [161]. Using Huh-7 cells, aberrant expression of SNORD126 has been linked to increased cellular growth and proliferation through the upregulation of fibroblast growth factor receptor 2 (FGFR2), an upstream regulator of the PI3K/AKT signaling pathway [77,78]. The regulation of the PI3K/AKT signaling pathway, partly by SNORD126, and its effects on cellular processes are key to HCC progression [77]. However, the increased prevalence of SNORD126 has not been associated with metastatic properties of Huh-7 cells, nor has it been found to regulate its host gene expression (CCNB1IP1) [77]. While some studies have shown an increase in SNORD126 in HCC progression, one study noted a downregulation of SNORD126 in HCC. However, this study was not able to elucidate any possible impacts on processes in carcinogenic liver cells [162].

SNORD78 is another upregulated snoRNA found in HCC that is located on chromosome 1q25.1 and is aberrantly co-transcribed with its host gene growth arrest specific 5 (GAS5) [150,163]. Aberrant expression of SNORD78 promotes cell proliferation, migration, and invasion [79,80]. Conversely, knockdown of SNORD78 induces cell cycle arrest at the G0/G1 phase, resulting in increased apoptosis, decreased proliferation, migration, and invasion, with no significant effect on the host gene expression. Thus far, the cellular mechanism behind the effects of SNORD78 remains elusive [79]. SNORD76, which is located within the third intron of the same host gene, impacts the Wnt/ $\beta$ -catenin pathway contributing to HCC development and progression [13,164]. Increased SNORD76 expression is correlated with an increased level of  $\beta$ -catenin and, thus, both c-Myc and cyclin D1, thus affecting cell cycle progression and, subsequently, cell proliferation in HCC [13]. Further in vitro studies using SK-Hep1 and Huh-7 cells identified significantly increased cell proliferation in response to overexpressed SNORD76 and cell cycle arrest at the G0/G1 checkpoint in response to knockdown of SNORD76 [13]. In vivo experiments supported these findings, with noted reductions in tumor growth in response to SNORD76 suppression [13]. Moreover, aberrant SNORD76 expression results in EMT progression through the reduction in claudin-1 and E-cadherin, with concomitant increases in the expression of FN1, N-cadherin, and vimetin [13]. Taken together, these changes support migration and invasion of HCC cells [13]. Further evidence of the involvement of SNORD76 showed a mitigation of these properties following its knockdown [13].

SNORD17 was also found to be upregulated in HCC and to promote tumor progression through the p53 signaling pathways. Knockdown of SNORD17 in the HCC cell lines HepG2 and SK-Hep1 showed enhanced p53 protein level and increased p53-mediated cell cycle arrest and apoptosis. Western blot analysis revealed the downregulation of cell cycle progressor proteins cyclin D1 and CDK4 and the upregulation of cell cycle inhibitors p21 and p27 during SNORD17 knockdown. Conversely, overexpression of SNORD17 decreased the p53 protein level, which also suppressed mRNA expression of downstream effector p53 upregulated modulator of apoptosis (Puma). Nucleophosmin (NPM1) and Myb-binding protein 1A (MYBBP1A) were found to be the mediators of SNORD17 p53 regulation. SNORD17 colocalizes with NPM1 and MYBBP1A in the nucleolus, hindering their translocation into the nucleoplasm, which enhances p53 proteasomal degradation [56]. Mouse double minute 2 homolog (MDM2), which is a well-recognized E3 ubiquitin ligase, is known to be antagonistic to p53 and affects p53 stability by ubiquitination and subsequent degradation. NPM1 is associated with disrupting MDM2 effects on p53 [165]. Under SNORD17 knockdown, NPM1 increases MDM2-mediated p53 stability and half-life, while MYBBP1A enhances p53 transcriptional activity. MYBBP1A was reported to acetylate p53, a crucial modification for p53 activation [166]. Additionally, p300 was found to be an important part of the MYBBP1A/p53/p300 complex, which mediates p53 activation. Under p300 knockdown, p53 acetylation was decreased even in SNORD17 knockdown

cell lines. SNORD17 and p53 are linked through a positive feedback loop, where p53 knockdown increases SNORD17 expression while p53 upregulation decreases SNORD17 expression. Initial *in vivo* experiments suggest that SNORD17 promotes tumorigenesis and metastasis in mice [81]. Upregulated snoRNAs contribute to HCC progression through various pathways (Table 1). SNORD126 induces cell proliferation through activation of the PI3K/AKT signaling pathway, but increased metastatic properties could not be demonstrated. SNORD78 and SNORD76 are localized on the same host gene and, while the cellular mechanisms of SNORD78 remain unknown, it is known that SNORD76 activates the Wnt/ $\beta$ -catenin signaling pathway. Both snoRNAs induce proliferation by overwriting the G0/G1 cell cycle checkpoint and, furthermore, induce cell migration and invasion. SNORD17 affects the p53 signaling pathway and induces proliferation, migration, and invasion through indirect regulation of wildtype p53 mediated by interception of NPM1 and MYBBP1A.

A few studies have associated snoRNA downregulation with HCC progression [82,148,150]. Specifically, downregulation of SNORD114-1, SNORD114-17, SNORD113-6, and SNORD113-1 has been observed in HCC patients [82]. However, only the mechanism of SNORD113-1 downregulation has been elucidated to date [82,150].

The expression of SNORD113-1, a snoRNA located on chromosome 14q32, has been shown to be downregulated in HCC due to hypermethylation of its putative promoter region [82,83]. The reduced expression of SNORD113-1 is associated with increased tumorigenesis in HCC. Rescue studies *in vitro*, in HepG2 and Huh-7, and *in vivo* showed reduced cell growth and cell cycle arrest [82]. An effect on tumor cell migration and invasion was not observed [82]. In addition, SNORD113-1 has been demonstrated to affect two pathways: the TGF- $\beta$  and the MAPK/ERK signaling pathways. Overexpression of SNORD113-1 significantly decreased the phosphorylation of the MAPK/ERK downstream proteins MEK and ERK1/2 without affecting protein expression or stability. Similarly, overexpression of SNORD113-1 resulted in decreased phosphorylation of the TGF- $\beta$  pathway proteins SMAD2/3. Considering the impact of both pathways on gene expression regulation and cellular progression, including cell growth, proliferation, and apoptosis, these results indicate an involvement of both pathways in SNORD113-1-induced tumor suppression [82] (Table 1).

### 3.2. H/ACA Box snoRNAs

While the sections above discussed C/D box snoRNAs specifically, H/ACA box snoRNAs also contribute to HCC. One of these elements that is prevalent in HCC is SNORA18L5. SNORA18L5 is located on chromosome 11q21 and has been shown to be overexpressed in HCC. SNORA18L5 increases MDM2-mediated degradation of p53 by preventing ribosomal protein L5 (RPL5) and L11 (RPL11) from binding to MDM2 (Figure 1C). In HCC cell lines HepG2 and SMMC-7721, SNORA18L5 induced proliferation and inhibited p53-dependent cell cycle arrest and apoptosis. *In vivo*, SNORA18L5 contributed to increased tumor growth. Knockdown of SNORA18L5 reduced cell proliferation *in vitro* and tumor growth *in vivo* [84].

SNORA47 has a similar prevalence in HCC cells and is located on chromosome 5q13.3. Overexpression of SNORA47 has been identified in several HCC samples and has been shown to impact cell proliferation, migration, and invasion in HCCLM9 and SK-Hep1 cells [85]. The knockdown of SNORA47 resulted in diminished cell proliferation and an increased number of early apoptotic cells [85]. Subsequently, knockdown of SNORA47 resulted in the downregulation of the mesenchymal markers FN1, N-cadherin, vimentin, and the transcription factor zinc finger E-box binding homeobox 1 (ZEB1), which is known to repress epithelial (E)-cadherin [85,86]. Concomitantly, the epithelial marker E-cadherin was upregulated, supporting the suggestion that SNORA47 might induce the expression of these EMT markers, which affect tumorigenesis by inducing EMT [85].

The snoRNAs SNORA18L5 and SNORA47 are both upregulated in HCC. SNORA18L5 induces proliferation and tumor growth, as well as reduces cell cycle arrest and apoptosis

through MDM2-mediated p53 degradation. The cellular mechanisms of SNORA47 remain elusive, but this snoRNA has shown to induce proliferation, invasion, migration, and EMT (Table 1).

### 3.3. Small Cajal Body-Specific RNAs (SCARNAs)

While most snoRNAs fall into either C/D box or H/ACA classes, some small Cajal body-specific RNAs (SCARNAs) are a class of snoRNAs that are composites of C/D and H/ACA box elements [153]. These snoRNAs can induce 2'-O-methylation and pseudouridylation on snRNAs [152,153].

ACA11 (SCARNA22) is a known SCARNA in HCC. Upregulated ACA11, similar to SNORD126, activates the PI3K/AKT pathway, stimulating oncogenesis in HCC [41]. ACA11 is encoded on 4q16.3, an area known to be amplified in cancer, namely HCC [167,168]. Besides the evidence of ACA11 activating the PI3K/AKT pathway by influencing the phosphorylation status of PI3K and AKT, further *in vitro* studies revealed specific factors upregulated during ACA11-mediated PI3K/AKT activation [77,87]. Two of these factors, cyclin D1 and EMT markers, are components of PI3K/AKT and are involved in proliferation, migration, and invasion of tumor cells [41]. *In vitro* knockdown studies using the HCC cell lines HCCLM9 and SK-Hep1, which contain endogenously high expression of ACA11, resulted in increased expression of epithelial markers, such as claudin-1. However, cyclin D1 and mesenchymal markers, including fibronectin (FN1), neural (N)-cadherin, and vimentin, were decreased, resulting in reduced cell proliferation, migration, and invasion [87]. Reinstatement of elevated cyclin D1 and EMT mesenchymal marker expression levels resulted in increased proliferation, migration, and invasion, and have been observed when ACA11 levels were returned to high endogenous expression in HCCLM9 and SK-Hep1 cells [87]. Overexpression of ACA11 in Huh-7 cells, which normally feature low endogenous ACA11 expression, led to increased cell proliferation, migration, and invasion [87]. These findings were supported by *in vivo* studies where upregulated ACA11 resulted in higher tumor weight, while downregulation resulted in reduced tumor and weight [87] (Table 1).

The association of snoRNAs with HCC development and progression could be predominantly linked with snoRNA overexpression, leading to evolving oncogenic abilities. Only one snoRNA, SNORD113-1, has been shown so far to exhibit anti-tumor effects when restored to a physiologically normal level [82]. This regulation might be elucidated with future research for other downregulated snoRNAs in HCC. Aberrant snoRNA expression in HCC might also result from oncogenic processes accompanied by changes in transcriptional activity that target snoRNA host-genes rather than the snoRNA itself [157]. Abnormal snoRNA expression may contribute to tumor progression indirectly due to its function on other RNAs [169]. Yet, snoRNAs are correlated with metastatic potential, tumor cell proliferation, and invasion, which have a considerable impact on carcinogenesis, and, thus, they should be treated as oncogenes when their expression is altered from its "normal" physiological level [170].

## 4. Long Non-Coding RNAs

Long non-coding RNAs (lncRNAs) are distinguished from small non-coding RNAs by their size, which is over 200 nucleotides in length [171]. Even though lncRNAs in general are reported not to encode proteins, many of them show structural similarities to mRNAs, such as a 5' cap, splicing, and 3' polyadenylation [172,173]. lncRNAs are classified as non-coding and are considered a subclass of functional ncRNAs with a diverse impact on cellular processes, including regulation of gene expression and a variety of molecular functions through interaction with DNA, RNA, and proteins [174–177]. Many lncRNAs have differential regulatory roles in specific tissues through exhibiting cell type- and developmental-stage-specific expression patterns [178]. lncRNAs, which are present in the nucleus and the cytoplasm, affect the expression of target genes, as well as the stability and operation of their downstream targets at epigenetic, transcriptional, and

post-transcriptional levels [179]. Because lncRNAs represent a relatively new field, little consensus exists in terms of their definitive functions and mechanisms, partially due to variations in study design and interpretation of each study's findings [173,178]. To date, 74 lncRNAs have been identified to be dysregulated in HCC, and 52 of these lncRNAs were reported to be upregulated and associated with hallmarks of cancer. Conversely, 22 of these lncRNAs were associated with tumor suppressive properties and were reported to be downregulated in HCC [180]. Since the publication of this comprehensive review, a number of additional lncRNAs have been reported to be dysregulated in HCC.

A recent study reported the dysregulation of a previously uncharacterized lncRNA, lnc-ELF209, which acts as a tumor suppressor in HCC [88]. Located on the reverse strand of human chromosome 4q31.1, lnc-ELF209 is suggested to be an isoform of the human ELF2 gene, which encodes for 13 protein-coding variants [88]. Heterogeneous nuclear ribonucleoprotein AB (HNRNPAB) negatively regulates the transcription of lnc-ELF209 by binding directly to the promoter region [88]. HNRNPAB is a member of the heterogeneous nuclear ribonucleoproteins (hnRNPs), which are known to affect tumor progression and metastasis in different cancer types, including HCC [89]. lnc-ELF209 expression levels are inversely correlated with those of HNRNPAB. Lower expression of lnc-ELF209 was noted in HCC cell lines MHCC97H and HCCLM3, with high metastatic potential. In probes of nonrecurrent HCC patients, higher lnc-ELF209 expression levels were correlated with lower levels of HNRNPAB [88]. A knockdown of lnc-ELF209 in a low metastatic HCC cell line, PLC/PRF/5, resulted in the upregulation of three mesenchymal markers: N-cadherin, vimentin, and snail, and the downregulation of two epithelial markers: E-cadherin and Zonula occludens-1 (ZO-1), which increased metastatic potential [88]. Conversely, overexpression of lnc-ELF209 in HCCLM3 cells led to a reduction in mesenchymal markers and an upregulation of the epithelial markers, reducing the migration potential [88]. Further experiments *in vivo* on an orthotopic HCC mouse model supported these findings [88].

lnc-ELF209 knockdown has been shown to increase the expression of cancer stem cell (CSC) markers, such as sex determining region Y-box 2 (SOX2), MYC proto-oncogene (MYC), and cluster of differentiation 24 (CD24), which suggests an involvement of lnc-ELF209 in the maintenance of a differentiated phenotype [88]. Enriched in the cytoplasm, lnc-ELF209 has been suggested to function at the post-transcriptional level on RNAs or proteins [88]. Further evidence indicates an association between lnc-ELF209 and triosephosphate isomerase (TPI), heat shock protein 90-beta (HSP90AB1), and vimentin [88]. Knockdown and overexpression of lnc-ELF209 resulted in reduced and increased TPI protein level, respectively, with unaffected TPI mRNA expression, assuming a stabilizing impact of lnc-ELF209 on TPI [88]. Aside from the functional impact of lnc-ELF209 on EMT, TPI may be important for the tumor suppressive function of lnc-ELF209 as knockdown of TPI enhances the migration and invasion ability of HCC [88].

The lncRNA ELF209 is downregulated in HCC and associated with tumor progression and metastasis (Table 1). Negatively regulated by HNRNPAB, an increase in EMT markers and reduction in tumor suppressor proteins could be observed *in vitro* and *in vivo*, which enhances metastatic properties. Furthermore, CSC markers have been shown to increase during ELF209 knockdown, allowing the suggestion that ELF209 might play a role in evolving tumor stem cells. Further investigations are necessary to elucidate these assumptions.

Unlike lnc-ELF209, lncRNA GATA3-antisense (AS) inhibits the tumor suppressor protein GATA binding protein 3 (GATA3) in HCC [90]. GATA3-AS guided KIAA1492-mediated degradation of GATA3 is associated with HCC cell proliferation, apoptosis resistance, invasion, and migration [90]. Located on chromosome 10p14 on the antisense stand of GATA3, GATA3-AS participates in the preferential recognition of GATA3 pre-mRNA by KIAA1492 (Vir-like m6A methyltransferase associated (VIRMA or KIAA1492)), connecting GATA3-AS to the epigenetic regulation of multiple target genes [90]. Depletion of GATA3-AS resulted in reduced KIAA1492-mediated m6A-modulation of GATA3 pre-mRNA and, thus, elevated levels of GATA3 pre-mRNA, RNA, and protein [90]. GATA3-AS was found to interact preferentially with KIAA1492 and GATA3, further supporting the hypothesis of GATA3-AS



as a guide lncRNA that facilitates KIAA1429-dependent GATA3 pre-mRNA modulation and degradation [90]. Reduction of either GATA3-AS or KIAA1429 *in vivo* and *in vitro* resulted in an improved HCC phenotype, while simultaneous silencing of GATA3 in the same experimental approaches reversed its positive impact on cell proliferation, apoptosis resistance, invasion, and migration, and, thus, *in vivo* on tumor weight, volume, and metastasis [90]. As a result, GATA3 is highly suggested to be the mediator of the oncogenic functions driven by KIAA1429 and GATA3-AS [90].

The intergenic lncRNA p53 upregulated regulator of P53 levels (PURPL) has recently been shown to be significantly upregulated in liver cancer and some cancer cell lines (HepG2 and Huh-7) and is associated with poor tumor cell differentiation and increased tumor size [91]. In addition to enhancing cancer cell proliferation and cell cycle progression, PURPL inhibits apoptosis through p53 degradation (Figure 1B) [91]. When silenced, the carcinogenic impact of PURPL on cell proliferation, cell cycle progression, and inhibited apoptosis can be reversed through induction of the G1 cell cycle checkpoint [91].

The lncRNA HAND2-AS1 has been shown to be overexpressed in HCC and has been implicated in liver CSCs (LCSCs) self-renewal and thus contributes to HCC development through the initiation of tumor growth [92]. Located on chromosome 4q34.1, HAND2-AS1 is associated with the recruitment of the chromatin-remodeling complex INO80 to the promoter of bone morphogenetic protein receptor type IA (BMPRI1A) [92]. Subsequently, the expression of BMPRI1A activates bone morphogenetic protein (BMP) signaling for the maintenance LCSC properties [92]. *In vivo*, a knockdown of lncHand2 (the mouse ortholog to human HAND2-AS1) resulted in significantly decreased tumor formation and volumes of HCC tumor foci, while knockdown in a patient-derived xenograft decreased tumor growth [92]. HAND2-AS1 functions through interaction with the INO80 chromatin-remodeling complex by binding to the subunits INO80 and RuvB-like 2 (RUVBL2), both of which are overexpressed in HCC and LCSCs [92]. HAND2-AS1 promotes LCSC self-renewal by interacting with the INO80, promoting the expression of BMPRI1A and activating BMP signaling [92].

The lncRNA cytoplasmic RNA 1 (BCYRN1) is another lncRNA found to be extensively expressed in HCC patient tissues compared to non-malignant tissue. BCYRN1 enhances tumor proliferation, migration, and invasion by recruiting the basic leucine zipper transcription factor (BATF) to the transmembrane 4 L6 family member 1 (TM4SF1) promoter [93]. TM4SF1 has previously been reported to enhance HCC cell invasion [181]. Knockdown of either BATF or TM4SF1 reversed the BCYRN1-mediated enhancement of HCC migration and invasion, which confirmed the BATF/TM4SF1-mediated effect of BCYRN1 on HCC. Notably, TM4SF1 knockdown does not affect BATF expression, but the level of BATF and BCYRN1 expression directly influences the level of TM4SF1 expression. Thus, it is suggested that the BCYRN1-mediated HCC malignancy is at least partly dependent on the recruitment of BATF to the TM4SF1 promoter and subsequent TM4SF1 expression. These results could be verified *in vivo* [93].

Upregulated lncRNAs in HCC promote tumor progression or are associated with LCSC maintenance and self-renewal (Table 1). GATA3-AS promotes GATA3 degradation, which results in increased proliferation, migration, and invasion, as well as repressed apoptosis *in vitro* and *in vivo*. PURPL could be associated with proliferation through cell cycle checkpoint overwrite, increased tumor size, and inhibition of apoptosis through p53 degradation. BCYRN1 induces proliferation, migration, and invasion by recruiting the transcription factor BATF to the promoter region of TM4SF1 and increasing TM4SF1 expression. HAND2-AS1 binds to the INO80 chromatin remodeling complex and is suggested to support LCSC maintenance and self-renewal, which leads to increased tumor formation and size.

HBV infection is associated with an increased risk of HCC [182]. The HBV key gene Hbx (hepatitis B viral protein) has been shown to dysregulate the expression of lncRNAs that positively affect the progression of liver cancer [183,184]. The fusion transcript lncRNA Hbx-LINE1 activates the canonical Wnt signaling pathway and promotes HCC devel-

opment and progression (Table 1) [94]. Another lncRNA associated with HBV-infected patients is lincRNA-p21 [100]. This lncRNA is located on chromosome 6, about 15 kilo base pairs upstream of the p21 gene, and is also called cyclin-dependent kinase inhibitor 1A (Cdkn1a). This lncRNA is transcribed from the opposite orientation of the p21 gene [99]. Decreased levels of lincRNA-p21 were linked to later stages of liver fibrosis in HBV patients, increased cell proliferation, migration, and invasion [97,98,100]. One target of lincRNA-p21 is miR-9 expression, which is negatively regulated by lincRNA-p21 [97]. Further, miR-9 is overexpressed in HCC and contributes to HCC migration and invasion *in vitro* by directly targeting the mRNA of the EMT-related, tumor invasion suppressive protein E-cadherin, inhibiting its translation (Table 1) [185]. Furthermore, studies have shown that lincRNA-p21 overexpression inhibits the Notch signaling pathway and thus EMT in HCC [185]. Being a major target of p53 activity, lincRNA-p21 was shown to interact with heterogeneous nuclear ribonucleoprotein K (hnRNP-K) and participate in p53-mediated apoptosis [99]. Further, lincRNA-p21 has also been demonstrated to be induced by p53, but its role in p53-mediated tumor suppressive effects needs further investigation [95].

Other lncRNAs that exert their effect on HCC malignancy via miRNAs are LINC01419, LINC01194, and X-inactive specific transcript (XIST). LINC01419 and LINC01194 are up-regulated in HCC and promote tumor progression, while XIST is downregulated and acts as a tumor suppressor (Table 1) [64,101,102].

LINC01419 was localized in the cytoplasm of HCC cells and sponges the miRNA miR-485-5p. Further, miR-485-5p was found to negatively regulate LSM4 mRNA and protein level. LSM4 is a member of the LSM protein family, which is involved in pre-mRNA splicing and mRNA degradation. This protein is highly expressed in HCC and is associated with growth, invasion, and migration in HCC. Downregulation of LSM4 in HCC cell lines Huh7 and Hep3B decreased the malignant behavior in these cell lines, accompanied by elevated expression of E-cadherin and decreased expression of N-cadherin and vimentin. Expression levels of miR-485-5p and LSM4 are inversely correlated in HCC, and miR-485-5p regulates proliferation, migration, and invasion in HCC through LSM4. Through LINC01419 targeting miR-485-5p, the expression level of LSM4 is regulated, which enhances HCC progression *in vitro* and *in vivo* [101].

Similar to LINC01419, the lncRNA LINC01194 is upregulated in HCC and negatively regulates the miRNA miR-655-3p. The direct correlation between the expression levels of both ncRNAs and the malignant behavior of HCC cells was verified with a LINC01194 knockdown, which resulted in decreased HCC progression and increased apoptosis in Huh-7 cell lines. This was accompanied by significantly downregulated cyclin D1 and MMP9. However, this effect could be reversed with a simultaneous knockdown of miR-655-3p. It is suggested that the regulation of proliferation and migration in HCC through LINC01194 is exerted through the miR-655-3p/SMAD5 axis. SMAD5 is a direct target of miR-655-3p, affecting mRNA and protein level [102]. SMAD5 has also been previously reported to promote tumor progression in other cancer entities, such as bladder cancer and esophageal cancer [186,187]. It is downregulated during LINC01194 knockdown, but mRNA and protein level increase when miR-655-3p is downregulated simultaneously [102].

XIST is an upstream regulator of miR-221-3p and weakly expressed in HCC cells and tumor samples. High expression of miR-221-3p paired with weak XIST expression is associated with tumor cell proliferation, migration, and blocked apoptosis *in vitro*, as well as induced tumor growth *in vivo*. Knockout of XIST further enhanced this malignant phenotype *in vitro* and *in vivo*, while XIST upregulation suppressed these malignant properties in HCC cell lines and retarded tumor growth *in vivo*. This effect could be partially reversed when miR-221-3p was overexpressed simultaneously with XIST. As discussed in the miRNA section, miR-221-3p directly targets and represses MGMT, which leads to enhanced tumor progression. Taken together, this indicates that the decelerated HCC development is carried out through an XIST-mediated depletion of miR-221-3p and the regulation of MGMT [64].

The lncRNAs LINC01419 and LINC01194 are both upregulated in HCC and are associated with increased tumor proliferation and migration. They both exert their function through negative regulation of the miRNAs miR-485-5p and miR-655-3p, respectively. XIST acts as a tumor suppressor and is an upstream regulator of the oncomiR miR-221-3p. When downregulated in HCC, it is associated with tumor proliferation, migration, invasion, and increased tumor size in vitro and in vivo through the miR-221-3p-mediated negative regulation of MGMT.

## 5. Biomarkers in HCC

With a late onset of symptoms and, thus, late-stage diagnosis, there is an urgent need for effective non-invasive diagnostic and prognostic biomarkers for HCC [188]. Even though current diagnostic approaches using ultrasound and serum  $\alpha$ -fetoprotein (AFP) level show early-stage HCC detection rates of 60–70%, this screening is mainly conducted for patients with chronic liver diseases, such as cirrhosis, that have a significantly elevated risk of developing HCC [189]. Meanwhile, detection of AFP level alone only shows success rates of 30–50% for early-stage HCC diagnosis [188,190]. However, elevated AFP level is not a definitive indicator for HCC and can also be detected in patients with non-malignant chronic liver diseases, such as cirrhosis or chronic hepatitis infection [191]. Thus, circulating ncRNAs seem to represent promising diagnostic and predictive biomarkers to evaluate HCC, including HCC patients with low AFP [192]. Further, ncRNAs can be found in the bloodstream in exosomes, in apoptotic bodies, or bound to serum proteins or lipids [193]. In the network of ncRNAs, the focus has been especially centered on miRNAs and lncRNAs as potential biomarkers. Recent reviews, RNA-sequencing, and database studies discussed extensive lists of miRNAs and lncRNAs as diagnostic, prognostic, and specific therapy-resistant markers in HCC and HCC-promoting liver diseases [17,194–196]. Several differentially expressed miRNAs discussed in this review are implicated to play a role in drug-resistant HCC, such as miR-21, miR-221, and miR-122, which were reported to promote sorafenib resistance. Further, miR-199a-3p has been shown to be involved in adriamycin resistance, and miR-195 promotes resistance against 5-FU [194]. Additionally, miR-122 and exosomal miR-21 were described as potential biomarkers for diagnosis and poor prognosis in HCC patients [17,197].

## 6. Clinical Relevance

Recently, ncRNAs have come into focus as potential biomarkers and targets for therapeutic intervention due to their involvement in all aspects of HCC. The malign participation of ncRNAs in HCC development, maintenance, and progression is well-known, yet treatment options addressing these oncogenic ncRNAs remain limited [198]. Besides possible off-target effects and toxicities that have to be overcome when using an ncRNA antagonist as a putative drug, the difficulty of delivering this compound in effective concentrations to the appropriate location in the body is a large obstacle [198–200]. RNA degradation, instability of delivered nucleic acids, and low transfection efficiencies demand more advanced delivery strategies when considering ncRNAs as targets in cancer therapy [200,201]. Several clinical trials utilizing precision medicine to fight ncRNA-related carcinogenesis are ongoing, yet there are, to date, no approved drugs in general clinical use [198]. Specifically, new therapeutic strategies involving miRNA inhibition, miRNA replacement, and manipulation of aberrant miRNA levels are attracting increased attention as promising therapeutic tools [35]. Thus far, three major mediators have been suggested to address oncogenic ncRNAs: locked nucleic acids (LNAs), morpholino oligonucleotides (MO), and single-stranded antisense oligonucleotides (ASOs) [202–206]. With varying characteristics, these approaches utilize complementary binding to the target RNA and RNase H-mediated degradation [203,205–207]. Unfortunately, even promising approaches must be considered with caution since some ncRNAs display a bidirectional role in different malignancies, acting as tumor suppressors in some and oncogenes in others [132–134]. A recent in vivo study on miR-21 in HCC suggested that, sometimes, even both directions play into the com-

plex mechanisms of tumor development and progression in the same cancer entity [132], vastly exacerbating the approach of addressing oncogenic ncRNAs as therapeutic targets in some cases.

In HCV-derived liver diseases, an LNA, an anti-miR-122-containing drug (miravirsen or SPC3649), was examined in clinical trials and has been shown to inhibit the translation of the virus genome and viral load with no dose-limiting toxicities [208–211] (clinicaltrials.gov NCT01200420). Further, miR-122 is an important host factor for HCV and binds to its target RNA to mediate enhanced viral RNA transcription [212]. Although miR-122 acts as a tumor suppressor in HCC and is downregulated, a chronic HCV infection is known to greatly increase the risk of developing HCC [213]. Miravirsen was the first anti-miRNA oligonucleotide administered for human treatment [210]. In recent years, studies have identified other miRNAs, such as miR-21 or miR-221/miR-222, as potential therapeutic targets. Therapeutics to target these miRNAs are planned for clinical trials [198] (clinicaltrials.gov). In the case of miR-21 specifically, the clinical trial is focused on colorectal cancers and has not entered the stage of recruiting (clinicaltrials.gov NCT02466113). An alternative biomarker, capable of detecting miR-221/miR-222 expression levels, will be investigated as a therapeutic to monitor progression of HCC using a minimally invasive procedure (clinicaltrials.gov NCT02928627).

All other discussed miRNAs, snoRNAs, and lncRNAs associated with HCC are only proposed to be clinically used in the future, often first as a biomarker with the hope of advancing to an effective treatment strategy. Recent studies have shown that snoRNAs are stable and detectable in blood serum and plasma, making them suitable as diagnostic and prognostic biomarkers, as well as possible therapeutic targets [214]. SNORA71A and SNORA52, both downregulated in HCC cell lines and HCC specimens, were associated with large tumor diameter, multiple lesions, capsular invasion, bad tumor differentiation, TNM stage, lower disease-free and overall survival, as well as higher risk of post-operative tumor relapse. Thus far, these snoRNAs are potentially useful as diagnostic and prognostic markers for HCC, but the underlying cellular mechanisms remain elusive [215,216]. Although lncRNAs have been associated with all stages of tumor development and progression, the exact mechanisms often remain elusive. Therefore, despite preclinical evidence suggesting the utility of lncRNAs as biomarkers, little has translated into the clinic.

As a point of consideration, mimicking or antagonizing ncRNAs without major off-target side effects, with sufficient bioactivity and cancer-cell-specific delivery, remains difficult and stands to place a heavy burden on preclinical and clinical trials in the future [178]. Until these barriers are overcome, aiming to utilize ncRNAs as potential therapeutics outside of clinical trials is not an option in HCC treatment [178].

## 7. Discussion

Despite extensive research efforts to develop novel biomarkers and therapeutic options, the prognosis for HCC patients remains poor [21,217]. Due to the genetic heterogeneity observed in patients with HCC, individual biomarkers only describe HCC subpopulations, and a reliable diagnosis is often not made until later stages of disease progression [21].

However, recent investigations seem promising for new biomarkers to evolve, leading to earlier diagnosis and better prognosis for HCC patients. An enormous step towards better overall prognoses and relapse-free survival was made with an miR-122 targeting drug, which is already being evaluated in clinical trials. The desired results of efficient targeting combined with minimal adverse reactions and side effects were demonstrated to be potentially possible with ncRNA-targeted treatment. Nevertheless, a thorough understanding of the underlying mechanisms of ncRNAs is vital for true success in achieving new therapeutic options. The involvement of ncRNAs in all cellular processes is extensive and far from being well-understood (Table 1). However, current research advances into the underpinnings of these mechanisms demonstrate that further research might lead to the development of potent therapies not only for HCC but also for all tumor entities. While this list of ncRNAs in HCC is not exhaustive, it brings to light specific ncRNAs that

have been identified, and their effect on various pathways involved in numerous cancer phenotypes can be elucidated. The pathways most commonly affected by the presented ncRNAs were PI3K/AKT, MAPK, and Wnt. These signaling pathways are associated with tumor progression in HCC and overall poor prognosis. Future studies will continue work on these ncRNAs, and, by the time of publication, several unmentioned ncRNAs may be uncovered. However, this work chose to highlight those that are of current interest and best describe the interactions of ncRNAs in HCC to bring some clarity to a complex subject. Aside from the complexity of mechanisms of various ncRNAs (Figure 1A–C), the heterogeneity observed in HCC patients hinders the development of a universal strategy for the diagnosis, prognosis, and treatment of HCC. This limitation makes intensive research on ncRNAs, in connection with cancer development, fundamentally important. The unique nature of each type of cancer necessitates individualized diagnoses that would provide better, more personalized, and more efficient therapies. In the future, the focus on RNAs circulating in the blood may eliminate the frequent problem of late-stage diagnosis of HCC by providing easily detectable biomarkers. Additionally, an miRNA antagonist in clinical trials is on a promising path to becoming a helpful drug in the fight against liver cancer, which provides hope that, with further intensive research and many clinical trials, the use of ncRNA treatments may be feasible despite all their difficulties.

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