

Role of microRNA and Long Non-Coding RNA in Hepatocellular Carcinoma



Meenakshi Gupta¹, Kumari Chandan¹ and Maryam Sarwat^{1,*}

¹Amity Institute of Pharmacy, Amity University, Noida-201313, Uttar Pradesh, India

Abstract: Hepatocellular carcinoma (HCC) accounts for about 80-90% of all liver cancers and is found to be the third most common cause of cancer mortality in the Asia-Pacific region. Risk factors include hepatitis B and C virus, cirrhosis, aflatoxin-contaminated food, alcohol, and diabetes. Surgically removing the tumor tissue seems effective but a high chance of recurrence has led to an urgent need to develop novel molecules for the treatment of HCC. Clinical management with sorafenib is found to be effective but it is only able to prolong survival for a few months. Various side effects like gastrointestinal and abdominal pain, hypertension, and hemorrhage are also associated with sorafenib, which calls for the unmet need of effective therapies against HCC. Similarly, the genetic mechanisms behind the occurrence of HCC are still unknown and need to be expounded further for developing newer candidates. Since unearthing the concept of these variants, transcriptomics has revealed the role of non-coding RNAs (ncRNAs) in many cellular, physiological and pathobiological processes. They are also found to be widely associated and abundantly expressed in a variety of cancer. Aberrant expression and mutations are closely related to tumorigenesis and metastasis and hence are classified as novel biomarkers and therapeutic targets for the treatment of cancer, including HCC. Herein, this review summarises the relationship between ncRNAs and hepatocellular carcinoma.

ARTICLE HISTORY

Received: October 12, 2019
Accepted: December 04, 2019

DOI:

10.2174/1381612826666200115093835



CrossMark

Keywords: microRNA (miR), long non-coding RNA (LncRNA), hepatocellular carcinoma, liver cancer, hepatotumorigenesis, hepatitis B and C virus.

1. INTRODUCTION

Of all the liver cancers, hepatocellular carcinoma (HCC) contributes to about 70-80% of its share and is found to be the leading cause of cancer mortality in the Asia-Pacific region during the past decade. Risk factors that contribute directly or indirectly in hepatotumorigenesis include alcoholism, aflatoxin B1, diabetes, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, iron accumulation, non-alcoholic fatty liver disease (NAFLD), and obesity [1], as represented in Fig. (1). Management protocols for the treatment of the HCC include radiotherapy, surgical resection, embolization, ablation, and chemotherapy. Clinical therapy with sorafenib is found to be effective but it is only able to prolong survival for a few months [2]. The use of current therapy is limited because of poor prognosis, recurrence, various side effects and complexities associated with them. Similarly, the genetic mechanisms behind the occurrence of HCC are still unknown and need to be expounded further for developing newer candidates for the management of HCC and improving the existing ones.

Non-coding RNAs (ncRNAs) are the RNAs that do not encode any protein. They account for about 90% of human RNAs and are reported to be principal players in multiple cellular processes, such as immune response, cell proliferation and migration, angiogenesis and apoptosis [3]. Particularly, microRNAs (miRs) are small RNAs comprising of 19-25 base pairs which regulate the gene expression by either degrading the targeted messenger RNA (mRNA) or by its translational inhibition (Fig. 2) [4, 5]. Long non coding RNAs (lncRNAs) are >200 base pairs long and depending upon their genomic location between neighboring transcripts, they are categorized into five subclasses: anti-sense, bidirectional, intronic,

intergenic, and sense overlapping (Fig. 3A-E). Based on their functions, they are classified as signaling, decoy, guide, and scaffold lncRNAs [6-8].

Since unearthing the concept of these variants, transcriptomics has revealed the role of ncRNAs in many cellular, physiological and pathobiological processes. They are also found to be widely associated and abundantly expressed in a variety of cancer. Anomalous expression and mutations are linked closely to tumorigenesis and metastasis and hence, are classified as innovative biomarkers and therapeutic targets for the management of cancer, including HCC. Herein, the review particularly focuses on the role of ncRNAs in HCC. The authors summarise the therapeutic potential of miRs and lncRNAs based on the emerging evidence of their contributory role in the pathogenesis and progression of HCC. Additionally, how these deregulated ncRNAs may have their utility in the prognosis or diagnosis of HCC are explained.

2. EPIGENETICS AND HCC

Epigenesis is an inherited gene alteration without modifying the sequence of DNA. Epigenetic mechanisms include modifications in genomic DNA, chemical alterations in histone tails and regulation of non-coding miRNA. In order to maintain the cellular memory, these modifications are inherited from parent cells to daughter cells [9]. DNA methyltransferases (DNMTs) enzyme catalyzes the reaction of addition of methyl group to 5' cytosine nucleotides in DNA. Mechanistically, methylation of the DNA is responsible for silencing of transcriptional gene. This silencing occurs either by methylation on CpG site (hindering the binding of transcription factors to its promoter site) or by direct binding of methylated DNA to methyl CpG binding domain (MBD). Genetic analysis of many cancers reveals gene silencing, facilitated by DNA methylation [10, 11]. Recent literature supports the fact that liver cancer initiation and progression is associated with epigenetic changes [12]. Each epigenetic modifier can be differentiated on the basis of interaction

*Address correspondence to this author at the Amity Institute of Pharmacy, Amity University, Noida-201313, Uttar Pradesh, India;
Tel: +91-9990373875; E-mail: msarwat@amity.edu

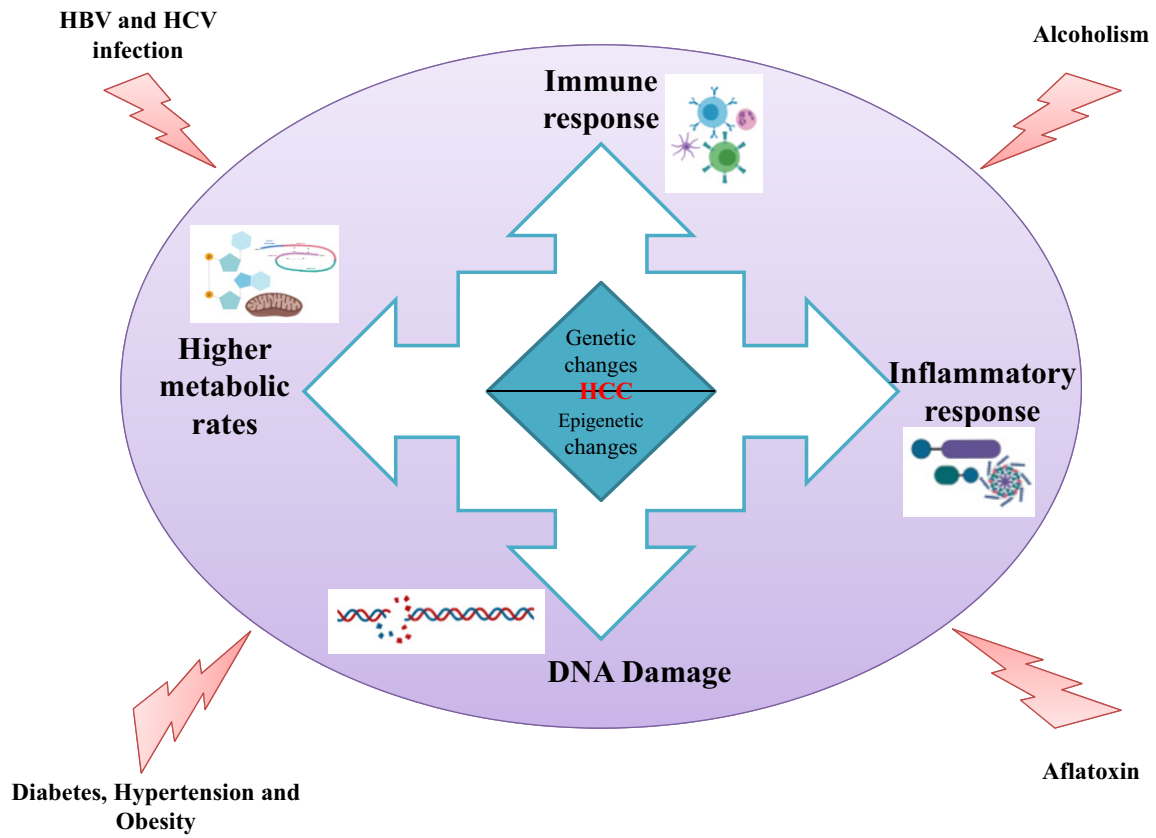


Fig. (1). Genetic and Epigenetic events contributing in the initiation and development of HCC.

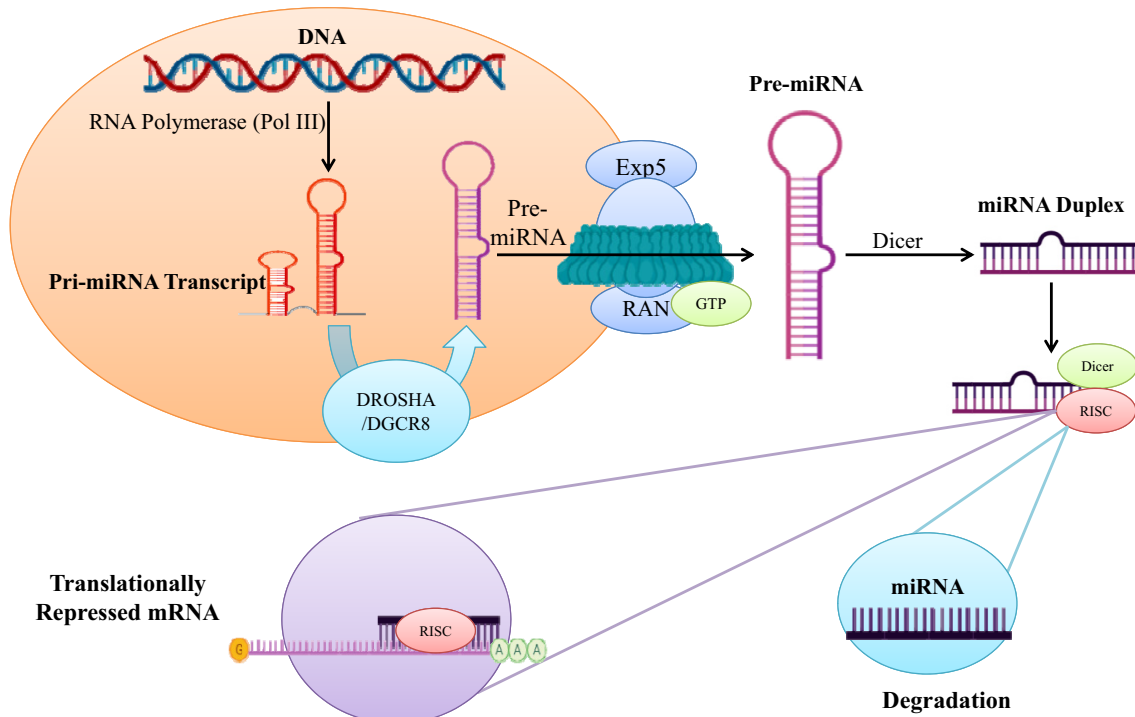


Fig. (2). Biogenesis of microRNA. miRs are generally transcribed by RNA Polymerase III from non-coding part of gene into primary miRNAs (pri-miRNAs) and processed into precursor miRNAs (pre-miRNAs) by the microprocessor complex. This complex is exported to cytoplasm and is cleaved by Dicer-1. This triggers the association of RNA-induced silencing complex (RISC). At this stage, double stranded miRNA splits into two strands: The passenger strands (removed and degraded) and the guide strand -bound to RISC (binds to target and translationally inhibits it).

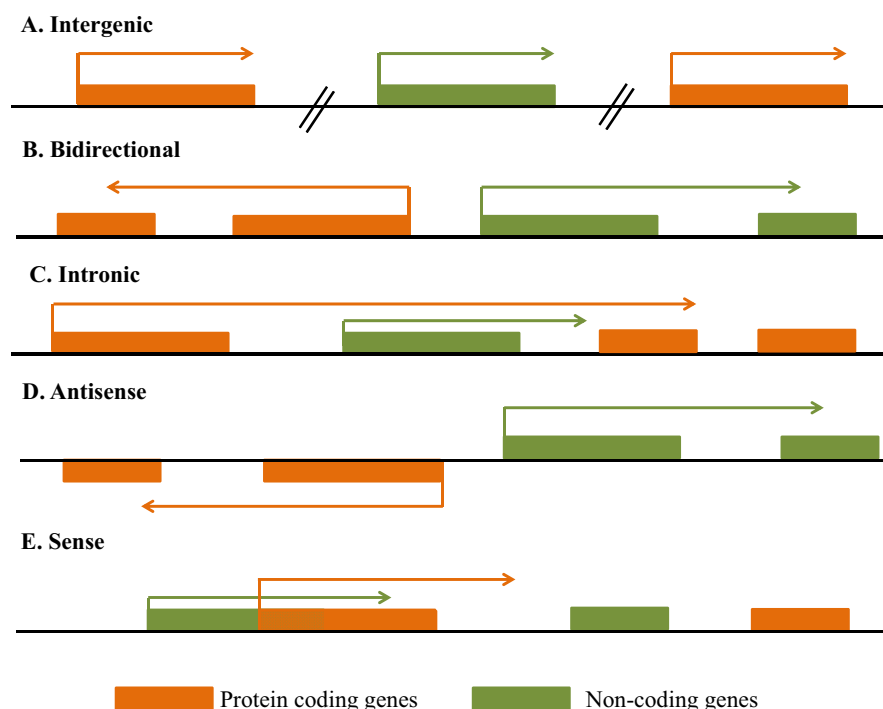


Fig. (3). Overview of five broad categories of lncRNAs: (A.) Intergenic (B.) Bidirectional (C.) Intronic (D.) Antisense (E.) Sense.

between the risk factor and host DNA as well as epigenetic components at different stages of HCC, which is explained further.

3. LNCRNAs AND HCC

3.1. lncRNAs and its Role in Initiation, Progression, and Metastasis of HCC

lncRNAs are significant players in controlling genomic circuitry and their dysregulation is found to be related to various malignancies. Abnormal expression of lncRNA directly affects its targeted genes which in turn, are involved in the onset of various diseases, including cancer (Fig. 4) [13]. HCC is one of the most widespread forms of cancer in the Asia-Pacific region. However, the underlying mechanism of its development is less implicit. lncRNAs, lately, have been publicized to have a high stake in HCC, and the examples are ANRIL, HULC, HOTAIR, HOTTIP, MALAT1, CCAT1, *etc.* as briefed in Table 1 [14-25] and represented in Fig. (5). In this review, we have discussed the involvement of lncRNAs in HCC development, progression and metastasis, and their diagnostic benefits in HCC.

3.1.1. HULC (Highly Upregulated in Liver Cancer)

HULC is a 482 bp single spliced, oncogenic, canonically polyadenylated ncRNA, transcribed from chromosome 6p24.3. It localizes in the cytoplasm and co-purifies with the ribosomes of cancer cells [5, 13, 25]. It is present in the primates, although the genome of mouse and rat do not possess the HULC homolog. HULC was firstly identified as novel transcript associated with the molecular pathogenesis of HCC [25]. It is reported to be linked to anomalous lipid metabolism in HCC cells. HULC is upregulated in tumors and plasma of patients suffering from HCC and is a potential biomarker of HCC [13]. Downregulation of miR-372 is mediated by HULC because of its activity as an endogenous sponge. This downmodulation represses the translational inhibition of miR-372 gene. The transcriptional activity of HULC is highly dependent upon a cAMP response element-binding (CREB) site in the promoter region [6, 8, 14-16].

Long-term infection with hepatitis B virus (HBV) is one of the major contributors in HCC development. HBx, a protein produced

by HBV, is found to be raised in the liver cells of patients suffering from HCC. This protein is found to be associated with genes regulating cellular growth [26, 27]. Du and collaborators reported the positive association between expression levels of HBV and HULC. Knockdown or overexpression of HBx is directly linked to a decrease or increase in the expression profile of HULC respectively [28].

Various other studies have also revealed the role of HULC in HCC development. Downregulation of p18 (a tumor suppressor gene, positioned near HULC) by HULC has led to the proliferation of hepatoma cells. HBx downregulates the expression of P18, which is overturned by HULC knockdown, incriminating a mechanism in which downregulation of p18 by HBx-mediated downregulation of HULC might lead to the proliferation of cancer cells [5, 8, 15, 25, 29]. HULC has been reported to upregulate the levels of SPHK1 (Sphingosine kinase 1), an enzyme that contributes to the survival, growth, differentiation, and proliferation of cells, and angiogenesis. HULC regulates a cascade of pathway leading to the upregulation of E2F1, a transcription factor that binds to SPHK1 promoter. MiR-107, a regulator of E2F, is sequestered by HULC leading to a series of events and eventually, tumor angiogenesis [25]. The metastasis and recurrence of HCC are regulated by epithelial-mesenchymal transition (EMT), which acts on ZEB1 and miR-200a-3p. HULC sequesters miR-200a-3p, corresponding to amplified levels of ZEB1, leading to the stabilization of ZEB1 [25]. Together, these studies reflect novel mechanisms by which HULC contributes to the pathophysiology of HCC.

3.1.2. HOTAIR (Homeobox [HOX] Transcript Antisense RNA)

HOTAIR is a 2158 nucleotide long antisense lncRNA, which is transcribed near the HOXC loci on chromosome 12q13.13 [5, 13, 16]. It is a polycomb group protein that represses the transcription of thousands of genes involved in stem cell pluripotency and various differentiation pathways during development [26]. Initially, it was identified to be upregulated in the breast epithelial tumors, inducing the metastasis of breast cancer [16]. It is reported to be a therapeutic biomarker of oesophageal squamous cell carcinoma. These lncRNAs have been reported to interact with two major

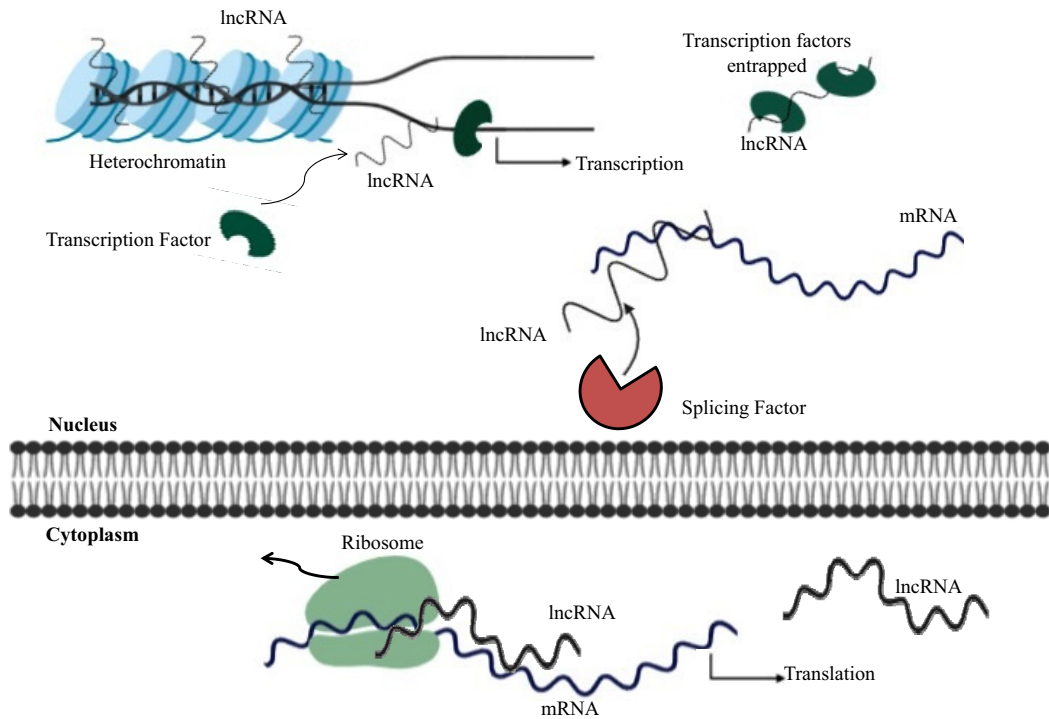


Fig. (4). Mechanism of action of lncRNAs. lncRNAs can regulate the gene expression *via* regulating chromatin condensation , altering DNA transcription, determining the stability of mRNA and affecting its splicing or modifying the pattern of mRNA translation into protein. This regulation may lead to origination of various cancer hallmarks.

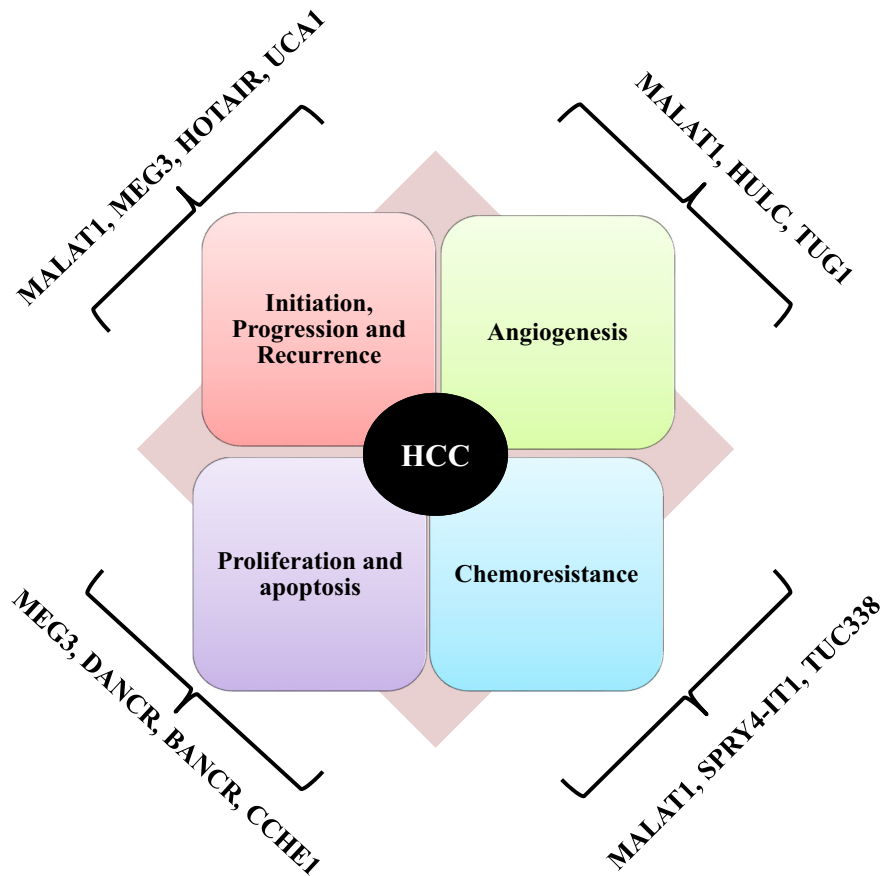


Fig. (5). lncRNAs as regulators of cell proliferation, migration, apoptosis, invasion, tumorigenicity, cell cycle, and metastasis.

Table 1. Some important long noncoding RNAs in hepatocellular carcinoma.

S. No.	Name	Gene Locus	Size (bp)	Classification	Cancer Type	Deregulation in HCC	Potential Role in HCC	Site of Detection	Upstream Regulators	Downstream Targets	Refs.
1.	HULC	6p24.3	1638	LincRNA	Hepatocellular, pancreatic	Upregulated	Associated with HBV infection and tumor growth	Plasma	CREB, HBx	miR-372, p18	[5, 14]
2.	H19	11p15.5	2660	LincRNA	Bladder, Brain, gastric, renal, lung, ovarian, colorectal, pancreatic	Upregulated	Suppresses progression and metastasis. Promotes cell proliferation	-	-	-	[5,14, 15]
3.	MALAT1	11q13.1	8708	LincRNA	Lung, prostate, breast, colorectal, liver, gastric, leukemia, brain, renal	Upregulated	Associated with tumor metastasis and recurrence	-	TGF-beta	Caspase-3, Caspase-8, BAX, BCL-2, BCL-XL	[16-18]
4.	HOTAIR	12q13.13	12649	Antisense	Breast, hepatocellular, colorectal, pancreatic, lung, ovarian	Upregulated	Associated with invasion and metastasis. Increases chemosensitivity	Tumor	Suz-Twelve	PRC2, LSD1	[5, 13, 16]
5.	HOTTIP	7p15.2	6839	Bidirectional	Prostate, liver, pancreatic	Upregulated	Associated with tumor progression and disease outcome. Chemoresistance	-	-	-	[14, 19]
6.	HEIH	5q35.3	1665	LincRNA	Hepatocellular	Upregulated	Associated with HBV-HCC. HCC recurrence	Plasma	-	EZH2, PRC2	[5, 14]
7.	MEG3 (GTL2)	14q32.3	34919	LincRNA	Renal, gastric, ovarian, liver, lung, brain, bladder	Downregulated	Associated with methylation. Predictive biomarker for monitoring epigenetic therapy	-	cAMP	P53, MDM2, GDF15	[20]

Table 1 contd....

S. No.	Name	Gene Locus	Size (bp)	Classification	Cancer Type	Deregulation in HCC	Potential Role in HCC	Site of Detection	Upstream Regulators	Downstream Targets	Refs.
8.	Linc00974	17q21.31	4890	-	Hepatocellular	Upregulated	Predicts tumor growth and metastasis	-	-	-	[21]
9.	UCA1	19p13.12	7375	Intronic	Bladder, leukemia, ovarian, breast	Upregulated	Involved in chemotherapeutic resistance. Associate with metastasis and postoperative survival	-	-	-	[22-24]
10.	CCAT1	8q24.21	11887	-	Colorectal, leukemia, gastric, Lung, esophageal squamous cell carcinoma	Upregulated	Promotes HCC progression	-	-	-	[25]

gene-silencing factors: PRC2 (a multiprotein complex) and LSD1 (lysine-specific demethylase 1) [17]. HOTAIR, along with PRC2, silences several metastasis suppressor genes, which lead to breast epithelial cell cancer [16].

The upregulation of HOTAIR is also observed in the HCC tissues and is reported to be directly interrelated with recurrence and poor survival rate in cancer patients receiving liver transplants. The downregulation of HOTAIR also inhibits the tumor invasion in liver cancer cell lines. Reduction in the levels of matrix metalloproteinase-9 and vascular endothelial growth factor (VEGF) protein (necessary for motility and metastasis of cells) is observed upon reduction in the expression of HOTAIR [25]. Overexpression of HOTAIR in HBx-positive human liver tumors is reported to be regulated by Wnt signaling genes like Sox2, Oct4, Nanog and EpCAM [13, 25, 27].

3.1.3. MALAT1 (Metastasis Associated Lung Adenocarcinoma Transcript)/ NEAT2 (Nuclear Rich Abundant Transcript 2)

It is a 7.5kb long lncRNA, originally expressed in primary non-small cell lung cancers. It is conserved in mammals and is expressed in many tissues [16-18]. The expression of this lncRNA is found to be dependent on the cell cycle and necessary for G1/S and mitotic progression. The literature reflects that Hippo/yes associated protein (YAP) and Wnt/TCF/ β -catenin signaling pathway, generally, acts on MALAT1. Also, it is negatively controlled by serine and arginine rich splicing factor 1 (SRSF1). SRSF1 acts by either promoting the degradation of MALAT1 or by binding to YAP. This binding prevents the transcription of YAP and hence the activity of YAP on the promoter site of MALAT1 is inhibited [30]. Post-transcriptional changes in MALAT1 produce short, cytoplasmic RNA and a long transcript, localized in the nucleus. This influences the level of phosphorylated splicing-associated serine arginine (SR) proteins [31, 32].

MALAT1 is found to be overexpressed in various cancers including breast cancer, liver cancer, ovarian cancer, and bladder carcinoma and is a potential therapeutic target. The upregulation of

MALAT1 is seen in neoplastic samples obtained from patients suffering from liver cancer. A high level of MALAT1 in patients has been observed as a signature of tumor recurrence after liver transplantation. This relativity implies that this lncRNA may show important clinical implications in the treatment of hepatocellular cancer [30]. Further, reduced expression of MALAT1 inhibits the motility and migration of cells and increases apoptosis in liver carcinoma and bladder cancer [7, 30].

For malignant cells to become invasive, epithelial-mesenchymal transition (EMT) is necessary. Downregulation of MALAT1 alters the expression profile of various genes like ZEB1, ZEB2, E-cadherin, Slug, which are associated with EMT. An increase in the levels of E-cadherin and a decrease in the levels of Slug, ZEB1, and ZEB2 have been widely reported [30, 33].

3.1.4. HEIH (High Expression in HCC)

HEIH is a 1.7-kb SP1-regulated long lncRNAs, located in the 5q34.3 locus. It is differentially expressed in HCC and closely associated with HCC recurrence. It is considered as a prognostic factor for HCC [5, 14, 15]. HEIH networks with enhancer of zeste homolog 2 (EZH2) and regulates EZH2 target genes including cell-cycle-regulatory genes p15, p16, p21, and p57. HEIH knockdown leads to reduction in the proliferation of cells and suppression of tumor growth. In short, HCC recurrence has a close association with HEIH and HBV infection [2, 8, 13, 18, 26, 33, 34]. Hence, the role of this dyad is worth reading further to detect the possibility of HCC recurrence.

3.1.5. HOTTIP (HOXA transcript at the distal tip)

It is a 7.9kb sized lncRNA, located at 7p15.2 and originated from the distal tip of the HOXA13 gene [14, 19]. It is the most upregulated variant in human HCC, even at an early stage. The oncogenic effect of HOTTIP is conferred by upregulation of several HOXA genes *via* interaction of WD repeat-containing protein 5 (WDR5) [an adapter protein with mixed-lineage leukemia (MLL) complexes]. This complex along with HOTTIP, mediates the

trimethylation of H3K4 and HOXA, facilitating gene transcription [26, 15]. In the HOX cluster, chromatin interactions are chiefly regulated by HOTTIP. As observed in an orthotopic implantation nude murine model, knocking down HOTTIP abrogates lung metastasis by significantly inhibiting the cell proliferation and migration. HOTTIP also regulates chemoresistance by activation of β -catenin signaling. The knockdown of HOTTIP is able to suppress chemoresistance and mesenchymal characteristics [35].

3.1.6. H19

H19 is a 2.3kb long ncRNA located at 11p15.5 and is solely expressed from the maternal allele. The upregulation of H19 is widely seen in HBV-associated HCC. Its involvement is highly recorded in genomic imprinting during growth and development [5, 14]. Authors have reported the role of two imprinted genes located on the same gene locus: Insulin-like growth factor 2 (IGF2) and H19. Biallelic expression of H19 and IGF2 are the critical players in the epigenetic mechanism employed behind the development and progression of tumors [13, 15]. The expression of this lncRNA is mediated by c-Myc. It binds to E-boxes, positioned near the imprinting control region, facilitating acetylation of histone and translationally initiating H19 gene in HCC cells [15, 34]. In *in vivo* models of HCC, knockdown of H19 significantly abolishes anchorage-independent growth after hypoxia recovery. The possible mechanism behind the same is the diminished expression of p57kip2 [36]. Furthermore, the expression of P-glycoprotein and multidrug resistance 1 (MDR1)-allied drug resistance in HCC cells has a direct association with the expression of the *H-19* gene [8]. H19 also activates miR-200 by linking with the protein complex hnRNP U/PCAF/RNAPol II, and subsequently, suppressing the progression and metastasis of HCC [37].

3.1.7. MEG3 (Maternally Expressed gene 3)

MEG3 is a paternally imprinted single-copy gene which comprises of 10 exons [33]. 12 isoforms of *MEG3* have been detected and each of them can be distinguished by their differential blend of 4-7 exons in the transcript. The original isoform of *MEG3* is a 1.6kb chromatin-associated polyadenylated transcript, located in the nucleus [16, 38].

MEG3 lncRNA is 34919bp sized, paternally imprinted and transcribed from chromosome 14q32.2 [5, 13]. It is normally expressed in human tissues but has its highest expression in the brain and pituitary gland. It has been revealed that ectopic expression inhibits the proliferation of a variety of cancer cell lines by majorly acting on tumor suppressor, p53. *MEG3* is found to be involved in the accumulation of tumor suppressor p53 and regulation of TGF- β pathway genes involved in cell invasion, immune regulation, etc. It also interacts with PRC2 to repress murine double minute 2 homolog (MDM2), which contributes to p53 accumulation [13]. It has been observed that the activation of p53 depends upon the secondary structure of the *MEG3* RNA, instead of its primary sequence. A study designed by Zhang and team provided proof for the preservation of the original secondary structure. They reported that replacement in some particular regions of *MEG3* with unrelated sequence does not affect p53 activation [38]. From this, a conclusion can be drawn that in the absence of sequence conservation, the potential of these unique RNA species will still be preserved.

3.1.8. DANCR (Differentiation Antagonizing Non-protein Coding RNA)

The stemness feature of the liver cancer cells has been greatly amplified in the presence of *DANCR* lncRNA. These lncRNAs are reported responsible for an increased intra- and extra-hepatic tumor development. It primarily interacts with cadherin-associated protein catenin beta 1, CTNBN1 mRNA at its 30 untranslated regions (UTRs). This leads to the blockage of the binding site of many miRs (miR-214, miR-320a, and miR-199a) competitively. This also allowed this gene to upregulate, resulting in the activation of the Wnt pathway. This further results in increased spheroid forma-

tion and stem cell like-feature of the affected cells. On the other hand, knockdown of *DANCR* *in vivo* improves the survival rate in mice by decreasing tumor cell survival and increasing tumor shrinkage [26, 30, 39].

3.1.9. UCA1 (Urothelial Carcinoma-Associated 1)

The lncRNA urothelial carcinoma-associated 1 (UCA1) is 7375bp in size and located on chromosome 19p13.12. It was originally duplicated from the human bladder cell line and is overexpressed in embryonic tissues, bladder cancers, liver cancers, and other cancers [22-24]. Studies have shown that UCA1 acts as an endogenous sponge that attaches to miR-216b and downregulates its expression. This mitigates the repression of FGFR in the cancer cells, increasing its level in the HCC cells. Downregulation of UCA1 suppresses ERK $\frac{1}{2}$ and p-ERK $\frac{1}{2}$, inhibiting the cell proliferation in both *in vitro* and *in vivo* models of HCC. This argument suggests the positive correlation of UCA1 and HCC initiation and progression through the regulation of FGFR1/ERK signaling pathways [40]. Also, researchers have reported that UCA1 activates NF- κ B/STAT3 signaling in cancer cells. It is observed in an experimental mouse model that the transformation of hepatocyte-like-stem cells is induced by UCA1 [41]. The proliferation of HCC cells is also linked to the expression of UCA1 *via* CDKN1B regulation [42]. Drug resistance is also a major factor associated with the expression of UCA1 [43].

3.1.10. Linc00974

Linc00974 is another lncRNA that is 4890bp in size and is located on chromosome 17q21.31. It is significantly upregulated in HCC [25]. A strong linkage between *Linc00974* and KRT19 (biomarkers of HCC) and HCC development has been reported by Tang and coworkers. Hypomethylation of the promoter of *Linc00974* upregulates this lncRNA. *Linc00974* acts as an endogenous sponge, repressing the levels of KRT19. Deletion of *Linc00974* increases apoptosis and arrests cell cycle in HCC cell lines. This further inhibits cell multiplication and invasion. Suppression of lncRNA, mediated by miR, amplifies the levels of KRT19. Recent literature reflects a strong connection between KRT19, NOTCH and TGF cascades [21]. Therefore, it can be deduced that *Linc00974* and KRT19 may be innovative manifestations for the prediction of tumor initiation and metastasis. *Linc00974* may also be utilized in the management of HCC in the future.

3.1.11. ZFAS1 (ZNF1 Antisense RNA 1)

ZFAS1 (ZNF1 antisense RNA 1) is a spliced and polyadenylated lncRNA transcribed from the end of *ZNF1*. It is derived from chromosome 20q13.13 and is implicated in different types of cancer including gastric cancer, colorectal cancer, and hepatocellular cancer, among others [13]. It has been reported to interact with CDK1 and cyclin B to control p53-dependent cell-cycle regulation [44]. In addition, it promotes cell proliferation by employing EZH2 and LSD1/ CoREST to the promoters of genes including KLF2 (Kruppel like factor 2) and NKD2 (naked cuticle 2) to regulate their expression [45]. It also acts as a sponge for tumor suppressor miR-150. The knockdown of *ZFAS1* represses cell proliferation, migration, and colony formation [15]. Similarly, *ZNF1* sequesters miR-150, which directly targets the EMT regulator, ZEB1. Levels of ZEB1 are affected by the expression of *ZEB1-AS1* lncRNA. This lncRNA has a bidirectional promoter and shares it with ZEB1. It is a positive regulator of ZEB1 expression and EMT [33].

3.1.12. SIRT1 (Sirtuin/Silent Mating type Information Regulation 2 Homolog 1)

SIRT1 gene has been found to play an imperative role in cell proliferation and apoptosis. Overexpression of *SIRT1* has been witnessed in various HCC samples. *SIRT1*-antisense RNA (*SIRT1-AS*) lncRNA shows its action by covering the binding site of miR-29c on 31-UTR *via* repression in the translational inhibition of *SIRT1* mRNA. Binding of *SIRT1-AS* to 31-UTR region of *SIRT1* prevents the binding of miR-29c and hence, stabilization *SIRT1*

mRNA is observed. This increased the level of SIRT1, subsequently increasing cell survival. This complete process is possible because of the 622C mutation in SIRT1-AS. In fact, increased expression of this mutant suppresses the proliferation of HCC cells [35]. This may offer a newer target for gene therapy.

3.1.13. DILC (*Downregulated in Liver Cancer*)

DILC is a tumor suppressor whose reduced expression was detected in all HCC cell lines and was so entitled as lncRNA downregulated in liver cancer (DILC) [13]. Its expression is inversely related to those of EpCAM (epithelial cell adhesion molecule), CD24, and CD90 in hepatoma spheroids. This lncRNA is found to interfere with the NF- κ B pathway mediated IL6 expression, exerting a negative effect on STAT3 signalling, and in this manner, suppressing tumor [26, 46].

Other lncRNAs implicated in liver cancer include TCF7, CD24, HANR, NR2F1-AS1, MVIH, and CCAT1. TCF7 is regulated by UCA1 *via* interaction with SWI/SNF (switch/sucrose non-fermentable) in various types of cancer [40]. CCAT1 promotes hepatocellular carcinoma progression by acting as let-7 sponge [47]. MVIH acts together with protein phosphoglycerate kinase 1 (PGK1), which further increases angiogenesis and tumor growth [48].

3.2. lncRNAs and its Diagnostic Benefits in HCC

Since HCC is an intricate disease, molecular biomarkers are essential predictive tools that can ease its management. As equated to coding protein, lncRNAs offers a better advantage as a marker because of the direct link between its expression and tumor status. Various lncRNAs are associated with HCC, as mentioned above, due to emerging technologies in the field of molecular biology as key regulators. A lot of databases (as listed in Table 2) have been established in the literature which can predict the potential of lncRNAs. Existing literature has shed light on various lncRNAs for the diagnosis and prognosis of HCC. For example, the detection of HCC can be done by measuring the expression profile of HULC in the plasma of diseased and healthy volunteers. Hence, HULC may act as a promising novel marker for detecting and diagnosing HCC [14]. Similarly, MVIH (Microvascular invasion) has been reported to be overexpressed, when a cohort study containing 215 patients was carried out. It was observed that this overexpression is linked to increased tumor growth and metastasis and hence, leading to poor patient survival [25]. Additionally, the overexpression of HOTAIR was noticed in 110 HCC samples (60 underwent liver transplantation) [30]. A positive correlation between lymph node metastasis and expression of HOTAIR was also demonstrated by various

Table 2. Long non-coding RNA online databases widely accessible.

S. No.	Name of the Database	URL	Features	References
1.	ncRNAimprint	http://rnaqueen.sysu.edu.cn/ncRNAimprint/	Contains a catalog of imprinted ncRNAs, three comprehensive collections of imprinted ncRNA-related diseases, ICRs, and imprinted regions, and deep sequencing reads.	[49]
2.	ncRNAdb	http://research.imb.uq.edu.au/rnadb/	RNAs included in the database have been demonstrated or are suspected to function without being translated into proteins and they are not constitutively expressed housekeeping transcripts.	[50]
3.	NONCODE	http://www.noncode.org/	Contains 527,336 lncRNAs from 16 different species.	[51]
4.	lncRNAdb	http://longnoncodingma.com/	Each entry contains referenced information about the RNA, including sequences, structural information, genomic context, expression, subcellular localization, conservation, functional evidence, and other relevant information.	[52]
5.	Rfam	http://rfam.sanger.ac.uk/	Allow the user to search a query sequence against a library of covariance models, and view multiple sequence alignments and family annotation.	[53]
6.	ncRNA Database	http://biobases.ibch.poznan.pl/ncRNA/	In addition to the RNAs for which regulatory activities have been documented, the database also contains sequences of ncRNAs that are known to be expressed, but their role in a cell is still unknown.	[50]
7.	NPInter	http://www.bioinfo.org.cn/NPInter/	Documents experimentally determined functional interactions between noncoding RNAs (ncRNAs) and protein related biomacromolecules (proteins, mRNAs or genomic DNAs).	[54]
8.	Functional RNAdb	http://www.ncrna.org/frnadb/	Helps in annotating non-coding transcripts acquired from publicly available databases like H-inv 2.0, NONCODE, RNAdb, RNAdb (literature curation), RNAdb (human chromosome 7 project), RNAdb.	[55]
9.	NRED	http://jsm-research.imb.uq.edu.au/nred/cgi-bin/ncrnadb.pl	Supplies ancillary information for featured ncRNAs, including evolutionary conservation, secondary structure evidence, genomic context links, and antisense relationships.	[56]

researchers, suggesting it to be a potential biomarker for the detection of lymph node metastasis [57-59]. Recent findings also suggested that silencing the activity of MALAT1 can be a potential anti-cancer therapy for preventing recurrence of tumors after orthotopic liver transplantation [31].

It has been observed that lncRNAs possess a tissue-specific expression profile. This specific nature of lncRNAs makes them appropriate candidates to be used as cancer biomarkers. Although, the existing knowledge is enough for using lncRNAs as a diagnostic and therapeutic tool, but still, a deeper understanding of the mechanism through which they channelize the cascade is needed. Alternatively, modifying the expression of lncRNA along with the administration of chemotherapeutic agents can be considered beneficial. Special molecules can be developed which can either bring about some changes in the secondary structure of lncRNA or can inactivate them by the formation of complexes. To bring such molecules into existence, more studies about the complex mechanisms need to be studied well.

4. MIR AND HCC

MicroRNAs (miRs) are small (containing ~22 nucleotides) non-coding RNAs that regulate gene expression and protein translation. These are evolutionarily conserved molecules that are involved in organ and tissue differentiation during embryogenesis. They also participate in cell proliferation and apoptosis. Coming shreds of evidence highlight that their deregulation plays an active role in the pathogenesis and progression of various types of cancer [60]. They may either act as oncogenes or onco-suppressors (Table 3). In this section, we have summarized the role of liver cancer in context to liver cancer onset and progression and the underlying mechanisms and how they may act as diagnostic and therapeutic agents.

4.1. Expression Profile of miRs in HCC

Two decades back, this small class of miRs was discovered and was found to be involved in various physiological processes. In

2006, a profiling study was conducted with 180 mature miRs and 206 pre-miR oligo probes using a miR microarray, which concluded with the result that various miRs were aberrantly expressed in HCC cells as compared to normally growing cells. It suggested that miR might have oncogenic or tumor-suppressive effects in HCC as few of them were found to be upregulated (pre-miR-18, miR-18, and miR-224) and some were found to be suppressed (miR-125a, miR-195, miR-199a*, miR-199a, and miR-200a). Also, the authors reported that few miRs might be responsible for the dedifferentiation of the tumor [73]. In a different study, 381 probes for 238 mature and 143 precursor human miRs were used to carry out the expression profiling for HCC and liver cirrhosis. It was observed that 35 miRs were abruptly expressed in samples of HCC as compared to that of the cirrhotic liver. Among these deregulated miRs, few of them were reported to be well-characterized in various cancers [74]. Liu *et al* directed a similar study in 2011 to elucidate the molecular mechanistic profile of HBV-associated HCC. From 94 pairs of tumor and non-tumor tissue, miR-18a, miR-21, miR-30d, miR-34a, miR-93, miR-106a, miR-106b, miR-151, miR-222, miR-301 and miR-324-5p showed unusual expression. The findings suggested the relationship between abnormal expression of genes involved in the synthesis of miRs and the development of HCC [75].

Various studies are being conducted on the clinical samples of HCC. Jiang and researchers used ~200 samples of precursor and mature miRNAs from clinical HCC specimens, adjacent non-oncogenic tissues positive and negative for hepatitis and cirrhosis. 16 miRs were found to be deregulated in HCC samples as compared to adjacent non-oncogenic tissue samples. It was also reported that miRs linked with breast cancer, glioblastomas and pancreatic cancer (miR-221) and with pancreatic and thyroid cancer (miR-21) were also upregulated in the case of HCC [76].

To understand the series of progression from normal tissue to cirrhosis to HCC, a cohort study was designed by Pineau and collaborators. Pairwise comparisons were performed: cirrhosis vs. normal liver, HCC vs. normal liver, and HCC vs. non-cancerous

Table 3. Some important miRs and their targets.

S. No.	Name	Deregulation in HCC	Target	References
1.	miR-17-92	Oncogenic	HSP27	[60]
2.	miR-21	Oncogenic	PTEN	[61]
3.	miR-221	Oncogenic	CDKN1B/1C, DDIT4, BMF	[8, 62]
4.	miR-222	Oncogenic	PP2RA	[63]
5.	miR-224	Oncogenic	API-5	[63]
6.	miR-30d	Oncogenic	GNAI2	[63]
7.	miR-373	Oncogenic	PPP6C	[63]
8.	Let-7g	Tumor suppression	COL1A2, c-myc	[64, 65]
9.	miR-101	Tumor suppression	Mcl-1, FOS	[66, 67]
10.	miR-122	Tumor suppression	CyclinG1, CULT1	[68-70]
11.	miR-124	Tumor suppression	ROCK2, EZH2	[63]
12.	miR-125b	Tumor suppression	LIN28B	[71, 72]
13.	miR-29	Tumor suppression	Mcl-1, BCL2	[63]
14.	miR-29b	Tumor suppression	MMP-2	[63]
15.	miR-99a	Tumor suppression	IGF-1R, mTOR	[63]

cirrhotic tissues and it was concluded that a set of 12 miRs is responsible for the transition of normal tissue to hepato-cancerous one. Various similar studies were conducted to identify the cancer-specific miRs linked with humans [62]. A meta-analysis was conducted in which expression profile of miRs associated with breast, colon, prostate, liver and lung cancers. It was interesting to know that more than 60% of miR was differentially expressed in the case of HCC as compared to the other 4 forms of tumor. Aberrant expression of miR-154 was also an interesting finding in this meta-analysis as any other study did not previously report it. It was found to be suppressed in HCC affecting cell proliferation by modifying the progression of the cell cycle [77].

4.2. Oncogenic miRs in HCC

4.2.1. miR-17-92

MiR-17-92 is a cluster composed of miR-17-3p, miR-17-5p, miR-18a, miR-19a, miR-19b, miR-20a and miR-92-1 [60]. Overexpression of the miR-17-92 cluster has been demonstrated in various human malignancies, including B-cell lymphoma, lung cancer, stomach solid tumors and hepatocellular carcinoma [63, 78]. Qu and team used miR-knockdown strategy and demonstrated that knockdown of this miR reduces hepatocyte proliferation and anchorage-dependent growth by 50%. Upregulation of miR-17-5p was confirmed by conducting various *in-vitro* and *in-vivo* experiments, exemplifying that overexpression of this miR is directly linked to enhancement in the migratory and proliferation capacity of HCC cells and *vice-versa* [79].

Using the differential in-gel electrophoresis (DIGE) approach and other proteomic tools, authors identified heat shock protein-27 (HSP-27) as a major effector activated by miR-17-5p. The possible mechanism behind human HCC could be the activation of heat shock protein-27 (HSP-27) by miR-17-5p through p38 MAPK pathway [60].

4.2.2. miR-21

It is well-characterized tumorigenic miR, overexpressed in various tumors namely brain, breast, colon, esophagus, head and neck, lung, prostate and pancreatic tumors [61, 77]. Meng and co-workers brought into light the overexpression of miR-21 in HCC in both *in vivo* and *in vitro* models. *In vitro* inhibition is associated with an increase in cell proliferation, migration, and invasion. MiR-21 modulates the expression of PTEN (tumor suppressor) to exert its oncogenic activity. Suppression of PTEN by miR-21 leads to the phosphorylation of FAK (effector that regulates cell-cycle progression, cell survival, and migration). This tyrosine phosphorylation is followed by increased levels of MMP-2 and MMP-9, which in turn contributes to the pathogenesis of HCC [80].

4.2.3. miR-221

miR-221 is another oncogenic microRNA that is seen to be upregulated in case of HCC [62, 81]. Amplification in the number of cells (particularly those in S-Phase of the cell cycle) is observed when miR-221 is being overexpressed. Inhibiting this miR with its anti-miR-221 agent show the opposite effect, suggesting its potential role in HCC. Fornari and team worked to provide evidence that this miR directly targets cell cycle inhibitors namely CDKN1B/p27 and CDKN1C/p57 in HCC cells [82]. The involvement of this miR in the progression of HCC has been clearly described by various researchers. Pineau and team in the year 2010 reported the role of miR-221 in HCC using the mosaic mouse model. They stated that the direct functional target of this miR is DNA damage-inducible transcript 4 (DDIT4), a tumor suppressor. By stimulation of the tuberous sclerosis tumor suppressor TSC1/2 complex, DDIT4 regulates mTOR kinase. They showed the possible linkage between PTEN-PI3K-AKT-mTOR pathway and HCC development [62]. A study reported the anti-apoptotic effect of miR-221 and mentioned that silencing the miR increases apoptotic cell death in liver cancer. MiR-221 is also found to regulate BMF, pro-apoptotic member of

Bcl-2 family. Inhibition of miR-221 increases the expression of BMF and cleavage of caspases-3 and vice versa. The authors reported that susceptibility of HCC to apoptotic stimuli is modulated by BMF *via* caspases dependent pathway [76]. Hence, it can be concluded with a note miR-221 plays an important role in hepatotumorigenesis through various cascades.

4.2.4. miR-222

Pineau and co-workers publicized that miR-221 and 222 are highly upregulated miRs in HCC samples by profiling study, designating them oncogenic miRs [62]. For investigating the role of miR in detail, a cohort study was designed by Wong *et al.* 2010 using 99 primary HCC tumors and 94 tumor-adjacent cirrhotic livers to early and late HCC stages. *In vitro* study reported that miR-222 considerably attenuate cell migration, invasion and motility in liver cancer cell lines without affecting cell proliferation, suggesting it to be a metastatic associated miRNA. AKT signaling was one important contributing factor in the regulation of HCC metastasis and venous invasion. Inhibition of miR leads to a decrease in AKT phosphorylation, suggesting the potential role of miR-222 in HCC [83].

4.3. Tumor Suppressive miRs and HCC

4.3.1. Let-7g

The let-7 family has 11 close members, out of which, let-7g is one of the most important tumor-suppressive miRNAs in various human cancers. It is positioned on chromosome 3p21.1 and is significantly downregulated in human HCC samples as compared to metastasis-free samples [64, 65]. Type 1 collagen A2 (COLIA2) is reported to be the direct target of let-7g, as the quantity of COLIA2 is contrariwise correlated with levels of let-7g. The addition of COLIA2 reverses the action inhibitory effect of let-7g on HCC cells [84]. Wong and team brought into light the anti-proliferative activity of let-7g by transfecting HepG2 cells with let-7g mimics. Downregulation of oncogene c-Myc significantly inhibits cell proliferation. It is observed that expression of both mRNA and protein of c-Myc is dramatically decreased after the transfection, providing evidence that downregulation of c-Myc occurs at both transcriptional and post-transcriptional levels. Interestingly, Wong and co-workers reported that the overexpression of let-7g results in the upregulation of p16INK4A through direct regulation of c-Myc in c-Myc-1-p16 regulatory cascade, leading to suppression of tumor [63].

4.3.2. miR-29

miR-29 is an independent prognostic factor reported in human HCC. Its investigation was initiated with a miRNA profiling study, which stated that the downregulation of miR-29 is observed in liver cancer and is associated with poor prognosis and survival of the patient [85]. A large spectrum of targets for this family has been identified including CDC42, TCL1, PIK3R1, and Mcl-1. In line with these findings, the functional targets of miR-29 are found to be Mcl-1 and Bcl-2. Suppression of endogenous expression of these targets by miR-29 results in the activation of the mitochondrial pathway. Abnormal expression of Bcl-2 and Mcl-1 in miR-29 overexpressing HepG2 cells override the apoptosis initiated by chemotherapeutic agent or serum starvation, providing evidence for the involvement of miR-29 in apoptosis [86].

4.3.3. miR-122

miR-122 contributes its 70% share to the total liver miRNA population. It is expressed abundantly and is highly tissue-specific [87]. This being the reason, that the researcher has investigated the diagnostic and prognostic role of miR-122 in hepatotumorigenesis. Intriguingly, scientists have reported that expression of this miR in liver cancer is etiology-dependent and its suppression is linked with large and less differentiated tumors leading to poor survival of patients suffering from HCC. Several studies provide evidence for the downregulation of miR-122 in HCC, signifying that it is tumor-

suppressive miRNA [68-70]. *In vitro* studies mark its imperative role in cell migration and invasion, providing support to the statement that it is involved in HCC. It is reported to modulate the expression of cyclin G1, which negatively regulates p53 by drafting PP2A to Mdm-2 dephosphorylation. This miR-122/cyclin G1-bonding increases stability of p53, consequently, affecting the sensitivity of cancer cells to doxorubicin-dependent apoptosis [82].

4.3.4. miR-101

The onco-inhibitory property of miR-101 was firstly studied by Su and co-workers, who reported that the expression of miR-101 suppresses colony formation *in vitro* and tumor formation *in vivo* [66]. Myeloid cell leukemia sequence-1 (Mcl-1) was identified, using luciferase reporter assays and western blot analysis, as a significant target of miR-101. Mcl-1 is an anti-apoptotic member belonging to the Bcl-2 family. Interestingly, overexpression of miR-101 by serum starvation or any therapeutic agent in HCC cells induces apoptosis. Mcl-1 repression resembles the apoptosis-promoting effect of this particular miR. Mcl-1, which lacks the 3'UTR sequence, when overexpressed eradicates the apoptotic effect of miR-101 [66, 67].

FBJ murine osteosarcoma viral oncogene homolog (FOS) is an oncogene, expressed in liver cancer. MiR-101 represses the expression of v-fos by binding to its 3'UTR region at the post-transcriptional level. Modulation in the expression of miR-101 inhibits HGF-induced cell invasion *via* repression of FOS expression [88].

4.3.5. miR-125b

MiR-125b is decontrolled in a variety of human carcinomas including breasts [89], oral [90], bladder [91] and thyroid [92] cancers. Various researchers studied the suppression of HCC tumors by miR-125b. In a study, Zhao and Wang reported that the expression of miR-125b decreases in the HCC tissues and cell lines and its expression even inhibits the proliferation of HepG2 cells. The authors used target prediction method to predict potential target genes of miR-125b and it was observed that SIRT7 is the direct target of miR-125b. It was also mentioned that upregulation of miR-125b inhibits the expression of SIRT7 and *vice versa* [68]. Jia and team examined the expression of miR-125b in HepG2, Huh, and SMMC7721 cells and reported the downregulation in the expression profile of miR-125B in tumor cells. The possible mechanism was the inhibition of proliferation and cell cycle progression of HCC cells. The authors also reported that Mcl-1 (a member of Bcl-2 family) and IL6R (cell surface receptor which mediates inflammation) are the direct targets of miR-125b and are suppressed upon the action of miR-125b [72, 93]. Jiang and researchers designed a study to determine the potential of miR-125b in acquired 5-Fluorouracil (5-FU) resistance in various HCC cell lines by transfecting miR-125b. Reduced expression of miR-125b is observed in 5-FU-resistant cells. Additionally, uptake and production of lactose are knowingly increased in 5-FU-resistant cells [94].

4.4. miRs and its Therapeutic Potential in HCC

Developing evidence put forward the imperative role of miRs in HCC initiation, progression, and metastasis through multiple related genes and cascades. Various approaches have been developed to target oncogenic miRs and restore the expression of tumor-suppressive miRs. miR sponges, anti-miR oligonucleotides (AMOs) and miR inhibitors have been widely utilized to reduce the level of oncogenic miRs in HCC. Similarly, tumor-suppressive genes can be restored by various vectors and liposomes to target such tumors [64]. Viral vector system has been developed to deliver tumor suppressive miRs in *in vivo* cell models using anti-miRNA oligonucleotides and animal models using an anti-oligonucleotide, which targeted miR-191. Reduction in expression levels of miR-191 showed a significant reduction in tumor size. Apart from its

therapeutic benefits, miRs also maximized the effect of chemotherapeutic drugs by sensitizing tumors [95-97].

CONCLUSION

lncRNAs and miRs, both, play an active role in various physiological processes involved in different disease states, including hepatocellular carcinoma. The existing records reflect the role of ncRNAs in HCC initiation, progression, and treatment, but there are numerous questions unanswered. Research about ncRNA is still in its infancy stage and has a wide scope ahead. Scientists have been able to characterize only a smaller portion of HCC-related ncRNAs, which might provide innovative approaches for the detection and treatment of HCC but still, a larger portion is still unexplored. Structural and functional identification can pave a mode of designing newer therapeutic agents for the management of HCC.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

We would like to thank Central Council for Research in Unani Medicine (CCRUM), New Delhi, India for providing us the grant (F. No. 3-31/2014-ccrum/Tech).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENT

We highly appreciate the efforts of Dr. Hemlata Nimesh (Assistant Professor, Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh, India) in drafting this review article. Authors are also thankful to Mr. Dhondhup Namgyal (Research Scholar, Amity Institute of Neuropsychology and Neurosciences, Amity University, Noida, Uttar Pradesh, India) for his insightful comments.

REFERENCES

- Abdel-Hamid NM, Abass SA, Mohamed AA, Muneam Hamid D. Herbal management of hepatocellular carcinoma through cutting the pathways of the common risk factors. *Biomed Pharmacother* 2018; 107: 1246-58.
<http://dx.doi.org/10.1016/j.biopha.2018.08.104> PMID: 30257339
- Wang Z, Li J, Ji Y, An P, Zhang S, Li Z. Traditional herbal medicine: a review of potential of inhibitory hepatocellular carcinoma in basic research and clinical trial. *Evid Based Complement Alternat Med* 2013; 2013: 268963.
<http://dx.doi.org/10.1155/2013/268963> PMID: 23956767
- Ding B, Lou W, Xu L, Fan W. Non-coding RNA in drug resistance of hepatocellular carcinoma. *Biosci Rep* 2018; 38(5): BSR20180915.
<http://dx.doi.org/10.1042/BSR20180915> PMID: 30224380
- Callegari E, Elamin BK, Sabbioni S, Gramantieri L, Negrini M. Role of microRNAs in hepatocellular carcinoma: a clinical perspective. *OncoTargets Ther* 2013; 6: 1167-78.
PMID: 24039437
- George J, Patel T. Noncoding RNA as therapeutic targets for hepatocellular carcinoma. *Seminars in liver disease*. Thieme Medical Publishers 2015; 35: 063-74.
<http://dx.doi.org/10.1055/s-0034-1397350>
- Fang Y, Fullwood MJ. Roles, functions, and mechanisms of long non-coding RNAs in cancer. *Genom Proteom Bioinf* 2016; 14: 42-54.
<http://dx.doi.org/10.1016/j.gpb.2015.09.006>
- Hauptman N, Glavač D. Long non-coding RNA in cancer. *Int J Mol Sci* 2013; 14(3): 4655-69.
<http://dx.doi.org/10.3390/ijms14034655> PMID: 23443164
- He Y, Meng XM, Huang C, *et al.* Long noncoding RNAs: Novel insights into hepatocellular carcinoma. *Cancer Lett* 2014; 344(1): 20-7.
<http://dx.doi.org/10.1016/j.canlet.2013.10.021> PMID: 24183851

- [9] Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. *Nature* 2004; 429(6990): 457-63.
<http://dx.doi.org/10.1038/nature02625> PMID: 15164071
- [10] Jones PA, Takai D. The role of DNA methylation in mammalian epigenetics. *Science* 2001; 293(5532): 1068-70.
<http://dx.doi.org/10.1126/science.1063852> PMID: 11498573
- [11] Karpf AR, Jones DA. Reactivating the expression of methylation silenced genes in human cancer. *Oncogene* 2002; 21(35): 5496-503.
<http://dx.doi.org/10.1038/sj.onc.1205602> PMID: 12154410
- [12] Herceg Z, Paliwal A. Epigenetic mechanisms in hepatocellular carcinoma: how environmental factors influence the epigenome. *Mutat res-rev mutat* 2011; 727: 55-61.
<http://dx.doi.org/10.1016/j.mrrev.2011.04.001>
- [13] Bhan A, Soleimani M, Mandal SS. Long noncoding RNA and cancer: a new paradigm. *Cancer Res* 2017; 77(15): 3965-81.
<http://dx.doi.org/10.1158/0008-5472.CAN-16-2634> PMID: 28701486
- [14] Huang JL, Zheng L, Hu YW, Wang Q. Characteristics of long non-coding RNA and its relation to hepatocellular carcinoma. *Carcinogenesis* 2014; 35(3): 507-14.
<http://dx.doi.org/10.1093/carcin/bgt405> PMID: 24296588
- [15] Liu YR, Tang RX, Huang WT, *et al.* Long noncoding RNAs in hepatocellular carcinoma: novel insights into their mechanism. *World J Hepatol* 2015; 7(28): 2781-91.
<http://dx.doi.org/10.4254/wjh.v7.i28.2781> PMID: 26668690
- [16] Gibb EA, Brown CJ, Lam WL. The functional role of long non-coding RNA in human carcinomas. *Mol Cancer* 2011; 10: 38.
<http://dx.doi.org/10.1186/1476-4598-10-38> PMID: 21489289
- [17] Gong Z, Zhang S, Zhang W, *et al.* Long non-coding RNAs in cancer. *Sci China Life Sci* 2012; 55(12): 1120-4.
<http://dx.doi.org/10.1007/s11427-012-4413-9> PMID: 23233227
- [18] Li G, Zhang H, Wan X, *et al.* Long noncoding RNA plays a key role in metastasis and prognosis of hepatocellular carcinoma. *Bio-Med Res Int* 2014; 2014: 780521.
<http://dx.doi.org/10.1155/2014/780521> PMID: 24757675
- [19] Parasramka MA, Maji S, Matsuda A, Yan IK, Patel T. Long non-coding RNAs as novel targets for therapy in hepatocellular carcinoma. *Pharmacol Ther* 2016; 161: 67-78.
<http://dx.doi.org/10.1016/j.pharmthera.2016.03.004> PMID: 27013343
- [20] Miyoshi N, Wagatsuma H, Wakana S, *et al.* Identification of an imprinted gene, Meg3/Gtl2 and its human homologue MEG3, first mapped on mouse distal chromosome 12 and human chromosome 14q. *Genes Cells* 2000; 5(3): 211-20.
<http://dx.doi.org/10.1046/j.1365-2443.2000.00320.x> PMID: 10759892
- [21] Tang J, Zhuo H, Zhang X, *et al.* A novel biomarker Linc00974 interacting with KRT19 promotes proliferation and metastasis in hepatocellular carcinoma. *Cell Death Dis* 2014; 5(12): e1549.
<http://dx.doi.org/10.1038/cddis.2014.518> PMID: 25476897
- [22] Chen P, Wan D, Zheng D, Zheng Q, Wu F, Zhi Q. Long non-coding RNA UCA1 promotes the tumorigenesis in pancreatic cancer. *Biomed Pharmacother* 2016; 83: 1220-6.
<http://dx.doi.org/10.1016/j.biopha.2016.08.041> PMID: 27562722
- [23] Zhou B, Zhuang XM, Wang YY, *et al.* Long non-coding RNA UCA1 increases chemoresistance of tongue cancer cells by regulating autophagy signaling. *Int J Oral Maxillofac Surg* 2017; 46: 139.
<http://dx.doi.org/10.1016/j.ijom.2017.02.482>
- [24] Liu H, Wang G, Yang L, Qu J, Yang Z, Zhou X. Knockdown of long non-coding RNA UCA1 increases the tamoxifen sensitivity of breast cancer cells through inhibition of Wnt/ β -catenin pathway. *PLoS One* 2016; 11(12): e0168406.
<http://dx.doi.org/10.1371/journal.pone.0168406> PMID: 27977766
- [25] DiStefano JK. Long noncoding RNAs in the initiation, progression, and metastasis of hepatocellular carcinoma. *Noncoding RNA Res* 2017; 2(3-4): 129-36.
<http://dx.doi.org/10.1016/j.ncrna.2017.11.001> PMID: 30159431
- [26] Mehra M, Chauhan R. Long noncoding RNAs as a key player in hepatocellular carcinoma. *Cancer Biomark* 2017; 9: pii: 1179299X17737301.
<http://dx.doi.org/10.1177/1179299X17737301>
- [27] Zhang H, Chen Z, Wang X, Huang Z, He Z, Chen Y. Long non-coding RNA: a new player in cancer. *J Hematol Oncol* 2013; 6(1): 37.
<http://dx.doi.org/10.1186/1756-8722-6-37> PMID: 23725405
- [28] Du Y, Kong G, You X, *et al.* Elevation of highly up-regulated in liver cancer (HULC) by hepatitis B virus X protein promotes hepatoma cell proliferation *via* down-regulating p18. *J Biol Chem* 2012; 287(31): 26302-11.
<http://dx.doi.org/10.1074/jbc.M112.342113> PMID: 22685290
- [29] Liz J, Esteller M. lncRNAs and microRNAs with a role in cancer development. *Biochimica et Biophysica Acta (BBA). Gene Regulatory Mechanisms* 2016; 1859: 169-76.
- [30] Klingenberg M, Matsuda A, Diederichs S, Patel T. Non-coding RNA in hepatocellular carcinoma: mechanisms, biomarkers and therapeutic targets. *J Hepatol* 2017; 67(3): 603-18.
<http://dx.doi.org/10.1016/j.jhep.2017.04.009> PMID: 28438689
- [31] Lai MC, Yang Z, Zhou L, *et al.* Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. *Med Oncol* 2012; 29(3): 1810-6.
<http://dx.doi.org/10.1007/s12032-011-0004-z> PMID: 21678027
- [32] Ying L, Chen Q, Wang Y, Zhou Z, Huang Y, Qiu F. Upregulated MALAT-1 contributes to bladder cancer cell migration by inducing epithelial-to-mesenchymal transition. *Mol Biosyst* 2012; 8(9): 2289-94.
<http://dx.doi.org/10.1039/c2mb25070e> PMID: 22722759
- [33] Yang X, Xie X, Xiao YF, *et al.* The emergence of long non-coding RNAs in the tumorigenesis of hepatocellular carcinoma. *Cancer Lett* 2015; 360(2): 119-24.
<http://dx.doi.org/10.1016/j.canlet.2015.02.035> PMID: 25721084
- [34] Huang D, Fang J, Luo G. Roles of long noncoding RNAs in hepatocellular carcinoma. *Open Life Sci* 2016; 11: 91-7.
<http://dx.doi.org/10.1515/biol-2016-0012>
- [35] Bayoumi AS, Sayed A, Broskova Z, *et al.* Crosstalk between long noncoding RNAs and microRNAs in health and disease. *Int J Mol Sci* 2016; 17(3): 356.
<http://dx.doi.org/10.3390/ijms17030356> PMID: 26978351
- [36] Matouk IJ, DeGroot N, Mezan S, *et al.* The H19 non-coding RNA is essential for human tumor growth. *PLoS One* 2007; 2(9): e845.
<http://dx.doi.org/10.1371/journal.pone.0000845> PMID: 17786216
- [37] Zhang L, Yang F, Yuan JH, *et al.* Epigenetic activation of the MiR-200 family contributes to H19-mediated metastasis suppression in hepatocellular carcinoma. *Carcinogenesis* 2013; 34(3): 577-86.
<http://dx.doi.org/10.1093/carcin/bgs381> PMID: 23222811
- [38] Zhang X, Rice K, Wang Y, *et al.* Maternally expressed gene 3 (MEG3) noncoding ribonucleic acid: isoform structure, expression, and functions. *Endocrinology* 2010; 151(3): 939-47.
<http://dx.doi.org/10.1210/en.2009-0657> PMID: 20032057
- [39] Yuan SX, Wang J, Yang F, *et al.* Long noncoding RNA DANCR increases stemness features of hepatocellular carcinoma by derepression of CTNBN1. *Hepatology* 2016; 63(2): 499-511.
<http://dx.doi.org/10.1002/hep.27893> PMID: 25964079
- [40] Wang F, Ying HQ, He BS, *et al.* Upregulated lncRNA-UCA1 contributes to progression of hepatocellular carcinoma through inhibition of miR-216b and activation of FGFR1/ERK signaling pathway. *Oncotarget* 2015; 6(10): 7899-917.
<http://dx.doi.org/10.18632/oncotarget.3219> PMID: 25760077
- [41] Zheng Q, Lin Z, Li X, *et al.* Inflammatory cytokine IL6 cooperates with CUDR to aggravate hepatocyte-like stem cells malignant transformation through NF- κ B signaling. *Sci Rep* 2016; 6: 36843.
<http://dx.doi.org/10.1038/srep36843> PMID: 27833137
- [42] Hu JJ, Song W, Zhang SD, *et al.* HBx-upregulated lncRNA UCA1 promotes cell growth and tumorigenesis by recruiting EZH2 and repressing p27Kip1/CDK2 signaling. *Sci Rep* 2016; 6: 23521.
<http://dx.doi.org/10.1038/srep23521> PMID: 27009634
- [43] Tsang WP, Wong TW, Cheung AH, Co CN, Kwok TT. Induction of drug resistance and transformation in human cancer cells by the noncoding RNA CUDR. *RNA* 2007; 13(6): 890-8.
<http://dx.doi.org/10.1261/ma.359007> PMID: 17416635
- [44] Thorenoor N, Faltejskova-Vychytilova P, Hombach S, *et al.* Long non-coding RNA ZFAS1 interacts with CDK1 and is involved in p53-dependent cell cycle control and apoptosis in colorectal cancer. *Oncotarget* 2016; 7(1): 622-37.
<http://dx.doi.org/10.18632/oncotarget.5807> PMID: 26506418
- [45] Nie F, Yu X, Huang M, *et al.* Long noncoding RNA ZFAS1 promotes gastric cancer cells proliferation by epigenetically repressing KLF2 and NKD2 expression. *Oncotarget* 2017; 8(24): 38227-38.
<http://dx.doi.org/10.18632/oncotarget.9611> PMID: 27246976
- [46] Peng L, Yuan XQ, Zhang CY, *et al.* The emergence of long non-coding RNAs in hepatocellular carcinoma: an update. *J Cancer* 2018; 9(14): 2549-58.

- <http://dx.doi.org/10.7150/jca.24560> PMID: 30026854
- [47] Deng L, Yang SB, Xu FF, Zhang JH. Long noncoding RNA CCAT1 promotes hepatocellular carcinoma progression by functioning as let-7 sponge. *J Exp Clin Cancer Res* 2015; 34: 18. <http://dx.doi.org/10.1186/s13046-015-0136-7> PMID: 25884472
- [48] Yuan SX, Yang F, Yang Y, *et al.* Long noncoding RNA associated with microvascular invasion in hepatocellular carcinoma promotes angiogenesis and serves as a predictor for hepatocellular carcinoma patients' poor recurrence-free survival after hepatectomy. *Hepatology* 2012; 56(6): 2231-41. <http://dx.doi.org/10.1002/hep.25895> PMID: 22706893
- [49] Zhang Y, Guan DG, Yang JH, Shao P, Zhou H, Qu LH. ncRNaimprint: a comprehensive database of mammalian imprinted noncoding RNAs. *RNA* 2010; 16(10): 1889-901. <http://dx.doi.org/10.1261/rna.2226910> PMID: 20801769
- [50] Szymanski M, Erdmann VA, Barciszewski J. Noncoding RNAs database (ncRNAdb). *Nucleic Acids Res* 2007; 35(Database Issue): D162-4. <http://dx.doi.org/10.1093/nar/gk1994> PMID: 17169980
- [51] Zhao Y, Li H, Fang S, *et al.* NONCODE 2016: an informative and valuable data source of long non-coding RNAs. *Nucleic Acids Res* 2016; 44(D1): D203-8. <http://dx.doi.org/10.1093/nar/gkv1252> PMID: 26586799
- [52] Amaral PP, Clark MB, Gascoigne DK, Dinger ME, Mattick JS. lncRNAdb: a reference database for long noncoding RNAs. *Nucleic Acids Res* 2011; 39(Database issue): D146-51. <http://dx.doi.org/10.1093/nar/gkq1138> PMID: 21112873
- [53] Griffiths-Jones S, Bateman A, Marshall M, Khanna A, Eddy SR. Rfam: an RNA family database. *Nucleic Acids Res* 2003; 31(1): 439-41. <http://dx.doi.org/10.1093/nar/gkg006> PMID: 12520045
- [54] Yuan J, Wu W, Xie C, Zhao G, Zhao Y, Chen R. NPInter v2.0: an updated database of ncRNA interactions. *Nucleic Acids Res* 2014; 42(Database Issue): D104-8. <http://dx.doi.org/10.1093/nar/gkt1057> PMID: 24217916
- [55] Kin T, Yamada K, Terai G, *et al.* fRNAdb: a platform for mining/annotating functional RNA candidates from non-coding RNA sequences. *Nucleic Acids Res* 2007; 35(Database Issue): D145-8. <http://dx.doi.org/10.1093/nar/gk1837> PMID: 17099231
- [56] Dinger ME, Pang KC, Mercer TR, Crowe ML, Grimmond SM, Mattick JS. NRED: a database of long noncoding RNA expression. *Nucleic Acids Res* 2009; 37(Database Issue): D122-6. <http://dx.doi.org/10.1093/nar/gkn617> PMID: 18829717
- [57] Geng YJ, Xie SL, Li Q, Ma J, Wang GY. Large intervening non-coding RNA HOTAIR is associated with hepatocellular carcinoma progression. *J Int Med Res* 2011; 39(6): 2119-28. <http://dx.doi.org/10.1177/147323001103900608> PMID: 22289527
- [58] Niinuma T, Suzuki H, Nojima M, *et al.* Upregulation of miR-196a and HOTAIR drive malignant character in gastrointestinal stromal tumors. *Cancer Res* 2012; 72(5): 1126-36. <http://dx.doi.org/10.1158/0008-5472.CAN-11-1803> PMID: 22258453
- [59] Qi P, Du X. The long non-coding RNAs, a new cancer diagnostic and therapeutic gold mine. *Mod Pathol* 2013; 26(2): 155-65. <http://dx.doi.org/10.1038/modpathol.2012.160> PMID: 22996375
- [60] Weiler J, Hunziker J, Hall J. Anti-miRNA oligonucleotides (AMOs): ammunition to target miRNAs implicated in human disease?. *Gene Ther* 2006; 13(6): 496-502. <http://dx.doi.org/10.1038/sj.gt.3302654> PMID: 16195701
- [61] Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an anti-apoptotic factor in human glioblastoma cells. *Cancer Res* 2005; 65(14): 6029-33. <http://dx.doi.org/10.1158/0008-5472.CAN-05-0137> PMID: 16024602
- [62] Pineau P, Volinia S, McJunkin K, *et al.* miR-221 overexpression contributes to liver tumorigenesis. *Proc Natl Acad Sci USA* 2010; 107(1): 264-9. <http://dx.doi.org/10.1073/pnas.0907904107> PMID: 20018759
- [63] Wong CM, Kai AK, Tsang FH, Ng IO. Regulation of hepatocarcinogenesis by microRNAs. *Front Biosci (Elite Ed)* 2013; 5: 49-60. <http://dx.doi.org/10.2741/E595> PMID: 23276969
- [64] Johnson SM, Grosshans H, Shingara J, *et al.* RAS is regulated by the let-7 microRNA family. *Cell* 2005; 120(5): 635-47. <http://dx.doi.org/10.1016/j.cell.2005.01.014> PMID: 15766527
- [65] Takamizawa J, Konishi H, Yanagisawa K, *et al.* Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. *Cancer Res* 2004; 64(11): 3753-6. <http://dx.doi.org/10.1158/0008-5472.CAN-04-0637> PMID: 15172979
- [66] Su H, Yang JR, Xu T, *et al.* MicroRNA-101, down-regulated in hepatocellular carcinoma, promotes apoptosis and suppresses tumorigenicity. *Cancer Res* 2009; 69(3): 1135-42. <http://dx.doi.org/10.1158/0008-5472.CAN-08-2886> PMID: 19155302
- [67] Xu Y, An Y, Wang Y, *et al.* miR-101 inhibits autophagy and enhances cisplatin-induced apoptosis in hepatocellular carcinoma cells. *Oncol Rep* 2013; 29(5): 2019-24. <http://dx.doi.org/10.3892/or.2013.2338> PMID: 23483142
- [68] Coulouarn C, Factor VM, Andersen JB, Durkin ME, Thorgerisson SS. Loss of miR-122 expression in liver cancer correlates with suppression of the hepatic phenotype and gain of metastatic properties. *Oncogene* 2009; 28(40): 3526-36. <http://dx.doi.org/10.1038/onc.2009.211> PMID: 19617899
- [69] Kutay H, Bai S, Datta J, *et al.* Downregulation of miR-122 in the rodent and human hepatocellular carcinomas. *J Cell Biochem* 2006; 99(3): 671-8. <http://dx.doi.org/10.1002/jcb.20982> PMID: 16924677
- [70] Bandiera S, Pfeiffer S, Baumert TF, Zeisel MB. miR-122-a key factor and therapeutic target in liver disease. *J Hepatol* 2015; 62(2): 448-57. <http://dx.doi.org/10.1016/j.jhep.2014.10.004> PMID: 25308172
- [71] Zhao L, Wang W. miR-125b suppresses the proliferation of hepatocellular carcinoma cells by targeting Sirtuin7. *Int J Clin Exp Med* 2015; 8(10): 18469-75. PMID: 26770454
- [72] Jia HY, Wang YX, Yan WT, *et al.* MicroRNA-125b functions as a tumor suppressor in hepatocellular carcinoma cells. *Int J Mol Sci* 2012; 13(7): 8762-74. <http://dx.doi.org/10.3390/ijms13078762> PMID: 22942733
- [73] Murakami Y, Yasuda T, Saigo K, *et al.* Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and non-tumorous tissues. *Oncogene* 2006; 25(17): 2537-45. <http://dx.doi.org/10.1038/sj.onc.1209283> PMID: 16331254
- [74] Gramantieri L, Ferracin M, Fornari F, *et al.* Cyclin G1 is a target of miR-122a, a microRNA frequently down-regulated in human hepatocellular carcinoma. *Cancer Res* 2007; 67(13): 6092-9. <http://dx.doi.org/10.1158/0008-5472.CAN-06-4607> PMID: 17616664
- [75] Liu AM, Zhang C, Burchard J, *et al.* Global regulation on microRNA in hepatitis B virus-associated hepatocellular carcinoma. *OMICS* 2011; 15(3): 187-91. <http://dx.doi.org/10.1089/omi.2010.0098> PMID: 21319996
- [76] Jiang J, Gusev Y, Aderca I, *et al.* Association of MicroRNA expression in hepatocellular carcinomas with hepatitis infection, cirrhosis, and patient survival. *Clin Cancer Res* 2008; 14(2): 419-27. <http://dx.doi.org/10.1158/1078-0432.CCR-07-0523> PMID: 18223217
- [77] Wang W, Peng B, Wang D, *et al.* Human tumor microRNA signatures derived from large-scale oligonucleotide microarray datasets. *Int J Cancer* 2011; 129(7): 1624-34. <http://dx.doi.org/10.1002/ijc.25818> PMID: 21128228
- [78] Sato F, Hatano E, Kitamura K, *et al.* MicroRNA profile predicts recurrence after resection in patients with hepatocellular carcinoma within the Milan Criteria. *PLoS One* 2011; 6(1): e16435. <http://dx.doi.org/10.1371/journal.pone.0016435> PMID: 21298008
- [79] Qu KZ, Zhang K, Li H, Afdhal NH, Albitar M. Circulating microRNAs as biomarkers for hepatocellular carcinoma. *J Clin Gastroenterol* 2011; 45(4): 355-60. <http://dx.doi.org/10.1097/MCG.0b013e3181f18ac2> PMID: 21278583
- [80] Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. *Gastroenterology* 2007; 133(2): 647-58. <http://dx.doi.org/10.1053/j.gastro.2007.05.022> PMID: 17681183
- [81] He H, Jazdzewski K, Li W, *et al.* The role of microRNA genes in papillary thyroid carcinoma. *Proc Natl Acad Sci USA* 2005; 102(52): 19075-80. <http://dx.doi.org/10.1073/pnas.0509603102> PMID: 16365291

- [82] Fornari F, Gramantieri L, Ferracin M, *et al.* MiR-221 controls CDKN1C/p57 and CDKN1B/p27 expression in human hepatocellular carcinoma. *Oncogene* 2008; 27(43): 5651-61. <http://dx.doi.org/10.1038/onc.2008.178> PMID: 18521080
- [83] Wong QW, Ching AK, Chan AW, *et al.* MiR-222 overexpression confers cell migratory advantages in hepatocellular carcinoma through enhancing AKT signaling. *Clin Cancer Res* 2010; 16(3): 867-75. <http://dx.doi.org/10.1158/1078-0432.CCR-09-1840> PMID: 20103675
- [84] Ji J, Zhao L, Budhu A, *et al.* Let-7g targets collagen type I $\alpha 2$ and inhibits cell migration in hepatocellular carcinoma. *J Hepatol* 2010; 52(5): 690-7. <http://dx.doi.org/10.1016/j.jhep.2009.12.025> PMID: 20338660
- [85] Zhao YJ, Ju Q, Li GC. Tumor markers for hepatocellular carcinoma. *Mol Clin Oncol* 2013; 1(4): 593-8. <http://dx.doi.org/10.3892/mco.2013.119> PMID: 24649215
- [86] Xiong Y, Fang JH, Yun JP, *et al.* Effects of microRNA-29 on apoptosis, tumorigenicity, and prognosis of hepatocellular carcinoma. *Hepatology* 2010; 51(3): 836-45. PMID: 20041405
- [87] Lin CJ, Gong HY, Tseng HC, Wang WL, Wu JL. miR-122 targets an anti-apoptotic gene, Bcl-w, in human hepatocellular carcinoma cell lines. *Biochem Biophys Res Commun* 2008; 375(3): 315-20. <http://dx.doi.org/10.1016/j.bbrc.2008.07.154> PMID: 18692484
- [88] Li S, Fu H, Wang Y, *et al.* MicroRNA-101 regulates expression of the v-fos FBJ murine osteosarcoma viral oncogene homolog (FOS) oncogene in human hepatocellular carcinoma. *Hepatology* 2009; 49(4): 1194-202. <http://dx.doi.org/10.1002/hep.22757> PMID: 19133651
- [89] Wang H, Tan G, Dong L, *et al.* Circulating MiR-125b as a marker predicting chemoresistance in breast cancer. *PLoS One* 2012; 7(4): e34210. <http://dx.doi.org/10.1371/journal.pone.0034210> PMID: 22523546
- [90] Shiiba M, Shinozuka K, Saito K, *et al.* MicroRNA-125b regulates proliferation and radioresistance of oral squamous cell carcinoma. *Br J Cancer* 2013; 108(9): 1817-21. <http://dx.doi.org/10.1038/bjc.2013.175> PMID: 23591197
- [91] Han Y, Liu Y, Zhang H, *et al.* Hsa-miR-125b suppresses bladder cancer development by down-regulating oncogene SIRT7 and oncogenic long non-coding RNA MALAT1. *FEBS Lett* 2013; 587(23): 3875-82. <http://dx.doi.org/10.1016/j.febslet.2013.10.023> PMID: 24396870
- [92] Visone R, Russo L, Pallante P, *et al.* MicroRNAs (miR)-221 and miR-222, both overexpressed in human thyroid papillary carcinomas, regulate p27Kip1 protein levels and cell cycle. *Endocr Relat Cancer* 2007; 14(3): 791-8. <http://dx.doi.org/10.1677/ERC-07-0129> PMID: 17914108
- [93] Gong J, Zhang JP, Li B, *et al.* MicroRNA-125b promotes apoptosis by regulating the expression of Mcl-1, Bcl-w and IL-6R. *Oncogene* 2013; 32(25): 3071-9. <http://dx.doi.org/10.1038/onc.2012.318> PMID: 22824797
- [94] Jiang JX, Gao S, Pan YZ, Yu C, Sun CY. Overexpression of microRNA-125b sensitizes human hepatocellular carcinoma cells to 5-fluorouracil through inhibition of glycolysis by targeting hexokinase II. *Mol Med Rep* 2014; 10(2): 995-1002. <http://dx.doi.org/10.3892/mmr.2014.2271> PMID: 24865963
- [95] Esau CC, Monia BP. Therapeutic potential for microRNAs. *Adv Drug Deliv Rev* 2007; 59(2-3): 101-14. <http://dx.doi.org/10.1016/j.addr.2007.03.007> PMID: 17462786
- [96] Borel F, Konstantinova P, Jansen PL. Diagnostic and therapeutic potential of miRNA signatures in patients with hepatocellular carcinoma. *J Hepatol* 2012; 56(6): 1371-83. <http://dx.doi.org/10.1016/j.jhep.2011.11.026> PMID: 22314424
- [97] Giordano S, Columbano A. MicroRNAs: new tools for diagnosis, prognosis, and therapy in hepatocellular carcinoma?. *Hepatology* 2013; 57(2): 840-7. <http://dx.doi.org/10.1002/hep.26095> PMID: 23081718