Host miRNA Polymorphisms in Viral-induced Hepatocellular Carcinoma Outcomes: A Common Disease Underlying Liver Transplantation

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ABSTRACT

Persistent infections caused by either hepatitis B virus (HBV) and/or hepatitis C virus (HCV) are the principal etiologies of cirrhosis on a global scale, with the potential to progress to the development of hepatocellular carcinoma (HCC). Typically, for HCC detected in its early stages, liver transplantation (LT) represents the optimal therapeutic intervention, as it addresses both the malignancy and the associated liver ailment in a concurrent manner. MicroRNAs (miRNAs) are 18-25 nucleotide RNA molecules that are known for their regulating ability during various developing processes of each cell and tissue especially in multicellular organisms. Considering the regulatory potential of miRNAs, any alterations in their expression pattern such as mutations that produce single-nucleotide polymorphisms (SNPs), might cause anomalies like tumors. In this review manuscript a systematic approach was used to investigate the studies performed to evaluate the role of Host miRNA SNPs in the outcome of viral based (HBV and HCV) HCC. The search was directed in PubMed, Web of Science, and Scopus databases that resulted in 33 related original articles and 8 reviews that used for finding any missing reports. Therefore, in this review it is tried to discuss the importance and relation of SNPs in host miRNAs during viral induced HCC complications.

KEYWORDS: microRNAs; Single nucleotide polymorphisms; Hepatitis B virus; Hepatitis C virus; Hepatocellular carcinoma

INTRODUCTION

Liver transplantation (LT) continues to be the only recourse for patients experiencing end-stage liver disease. Viral infections have been the primary culprits in numerous global outbreaks, with infections of hepatitis B (HBV) and hepatitis C (HCV) representing serious public health challenges that impact millions of individuals worldwide. These infections are notorious for inducing chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). In addition, HCV relapse is the primary factor leading to graft failure in most transplantation programs. Despite current therapeutic strategies, sustained virologic responses are achieved in only one-third of treated patients, with common and severe adverse effects [1]. The progression from viral hepatitis to cirrhosis may take 10-20 years, and intermediately active hepatic inflammation resulting from these infections contributes to the inflammation-necrosis-regeneration process, which ultimately culminates in cirrhosis [2].

HCC, the most common primary liver tumor worldwide, is a significant public health issue. In 2018, it was responsible for 841,080 diagnosed cases and 781,631 deaths globally, with an age-adjusted incidence of 9.3 cases per 100,000 people per year. HCC is the sixth most frequent tumor and the fourth leading

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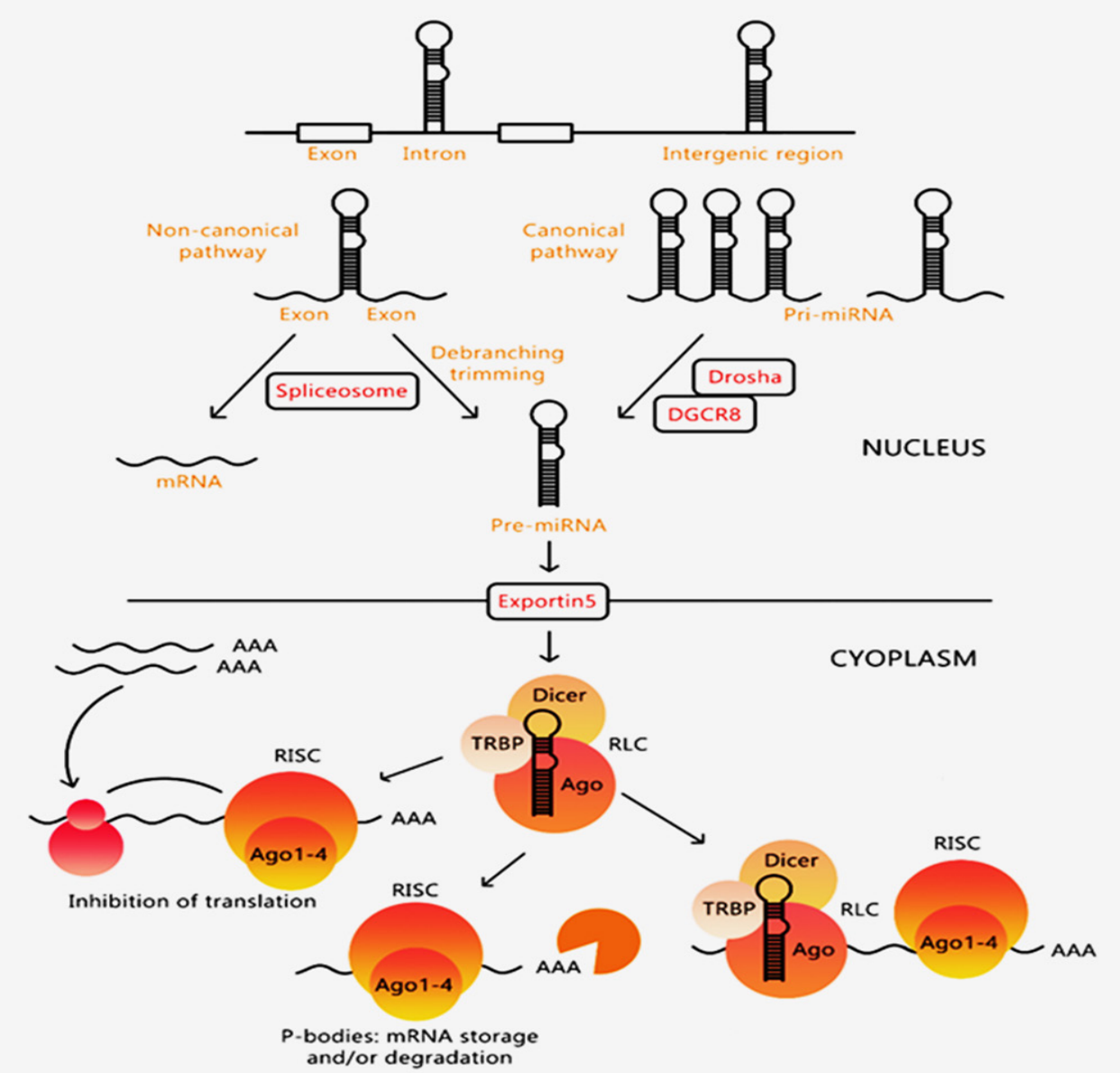

Figure 1: miRNA biogenesis starts by the production of the pri-miRNA transcripts. Then Drosha-DGCR8 complex cleaves the pri-miRNA molecules and produces the pre-miRNA which is exported to the cytoplasm via Exportin5-RanGTPase to yield the mature miRNA duplex. Finally, one of the strands of the mature miRNA duplex is loaded into RISC that is responsible for final mRNA expression regulation.

cause of cancer-related deaths [3]. This cancer often occurs in individuals with chronic liver disease and cirrhosis, and its incidence is on the rise [4-6]. The number of HCC patients receiving LT is increasing, and in most centers, LT for HCC represents 15-50% of all LT procedures [7, 8]. Despite the effectiveness of LT for HCC, due to the scarcity of organs, the careful selection and management of patients who can derive significant survival benefits from LT remains a fundamental concern. Therefore, limiting tumor recurrence after LT is a way to optimize this scarce resource [3].

During the process of transcription and translation inside the cells, a wide range of noncoding RNAs (ncRNAs) including microRNAs (miRNAs) are produced. The common ability of miRNAs is to regulate their target gene expression through complementarity ratio. The changes in the sequence of miRNAs like single nucleotide polymorphisms (SNPs) have several effects on their regulatory process.

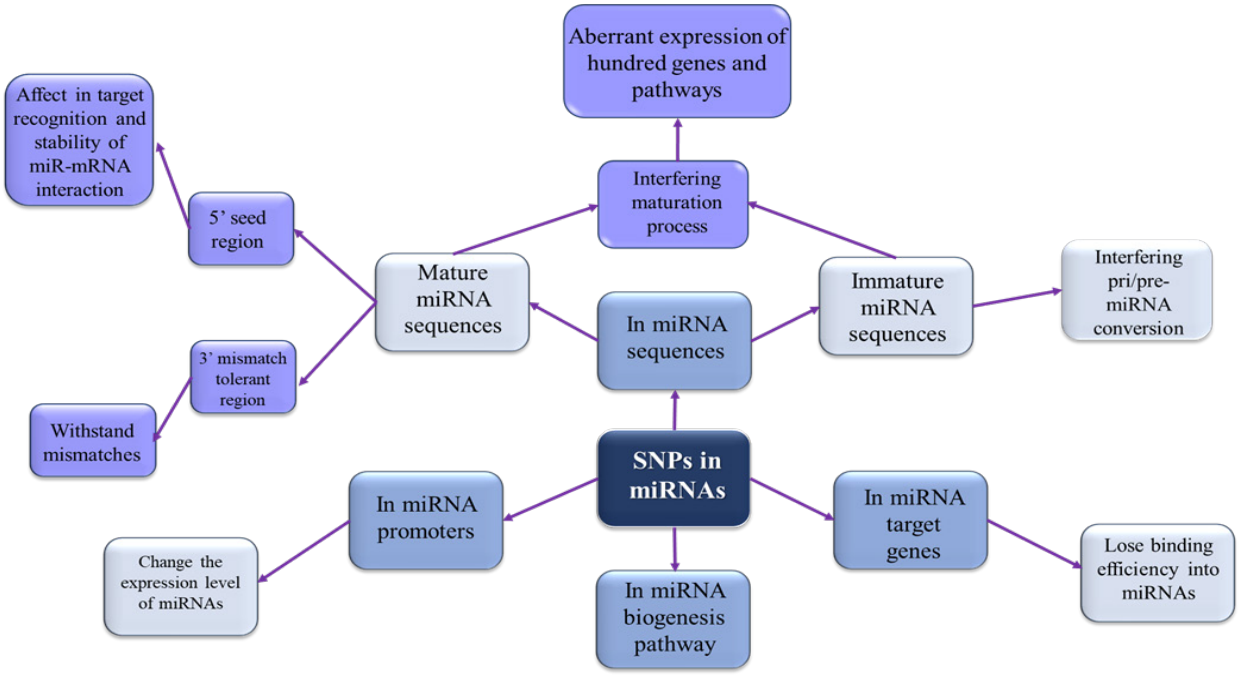

Figure 2: Different stages that SNPs might affect miRNAs

SNPs are the most communal and widespread genetic variation that can alter the sequence of miRNAs in different stages of their production as well primary-miRNAs (pri-miRNAs), precursor miRNAs (pre-miRNAs), and finally mature miRNAs [9]. Although SNPs by itself might not directly affect on the production of some cancers, studies point that these small changes in the miRNA sequences might facilitate tumorigenesis. Even the SNPs in miRNAs are detected in the functional quality of gene processing, miRNA-target binding status, the outcome of cancer treatment and patients' prognose [10]. Furthermore, miRNAs have been detected to participate in the development of tumor microenvironments such as autonomous recruitment of cell-free mechanisms and stabilizing oncogenic properties [11]. Then, mutations in the sequence of miRNAs would be interesting for researchers in the way of finding treatments for cancers.

The purpose of this review is to investigate the impact of single nucleotide polymorphisms (SNPs) related to host-miRNA and their association with hepatitis B virus (HBV) and hepatitis C virus (HCV) infections on the development of hepatocellular carcinoma (HCC), a leading cause of liver transplantation. By exploring the genetic variations that affect miRNA functions in the context of HBV and HCV infections, this review aims to provide insights into the molecular mechanisms underlying the development and progression of HCC. Ultimately, a better understanding of the interplay between host genetic factors and viral infections may contribute to the development of more effective strategies for preventing and treating HCC.

MATERIALS AND METHODS

The databases of PubMed, Web of Science, and Scopus, were used for searching the results in January 2022 by using "microRNAs", "single nucleotide polymorphisms", "hepatitis B virus", "hepatitis C virus", "hepatocellular carcinoma" these searches resulted in 65 original article that by removing the unrelated ones, the number of related articles became 33. In our searches 9 related review articles were found which used to check for any missing article.

Table 1: Summary of HBV associated HCC miRNAs and their mutations.

miRNA	SNP	Patients	Effect on the carrier	Reference
miR-146a	rs2910164	504 controls and 479 HCC patients, 88.9% of patients were HBV associated HCC	In miR-146a G/C SNP, GG genotype was related with an increase in the risk of HCC in males	[12]
miR-146a	rs2910164	504 controls and 479 HCC patients, 88.9% of patients were HBV associated HCC	In miR-146a, G allele increases the risk of HCC-related cell proliferation	[12]
miR-146a	rs2910164	Chinese population	This SNP is related with immune regulation during HBV infection	[13]
miR-499a	rs3746444	Chinese population: CHBV infected patients, HBV-infected HCC, non-infected ones and controls	CC genotype: a risk factor for HBV associated HCC	[14]
miR-499a	rs3746444	Small sample-size study	A allele relates to increased risk of HBV-associated HCC	[15]
miR-499a miR-423	rs3746444 rs6505162 (A/C/T)	984 HCC patients compared the genotype frequencies with a similar number of controls and 760 individuals of HCC group, were infected with HBV	rs6505162 had no effect on HCC risk, independent of the HBV infection status, TC + CC (in a dominant model) linked to the risk of HBV-associated HCC, in comparison to the TT genotype	[16]
miR-499a	rs3746444	Meta-analysis including case–control studies	Increased susceptibility to HCC among HBV-infected individuals	[17]
miR-196a2 C/T	rs11614913	199 CHBV-infected individuals without HCC, 361 CHBV-infected individuals with HCC, and 391 healthy controls	Increased risk of HBV-associated HCC in males carrying the C allele and the CC genotype	[18]
miR-196a2	rs11614913	Small case–control sample (266 individuals in each group), 110 in HCC group and 32 in control group were HBV infected	That CT + TT genotypes increase the risk of HCC development	[15]
miR-196a2	rs11614913	532 controls and 271 HCC patients with 58% HBV infection	CT and TT genotypes a reduced risk of HCC, the miR-196a2C>T SNP reports protection in HBV-related HCC	[19]
miR-196a2	rs11614913	A control and a of HCC patients' group (both ~1,000, including 771 HBV-associated HCC patients)	CT + TT genotypes and the T allele linked to lower chance of HBV associated HCC development	[20]
miR-196a2	rs11614913	A meta-analysis: 11 studies in Chinese populations	Associated with a decreased risk of HBV associated HCC	[21]

Table 1: Continued ...

miRNA	SNP	Patients	Effect on the carrier	Reference
miR-196a2 C/T miR-34b/c T/C	rs11614913 rs4938723	3,325 participants (1,021 of them with HBV associated HCC)	Both SNPs: HBV associated HCC susceptibility strongly influenced	[22]
miR-196a2 C/T	rs11614913	Turkish population: a small case–control study	C allele and CC genotype: potential markers for individuals at high risk for HBV associated HCC	[23]
miR-146a G/C miR-196a-2 C/T miR-499 T/C	rs2910164 rs11614913 rs3746444	A meta-analysis	SNPs in miR-146a and miR-196a-2: role in genetic susceptibility to HCC, miR-146a C variant related to decrease in HCC risk among Asian and male populations; miR-196a-2 T variant associated with susceptibility to HCC in Caucasian populations	[24]
miR-196a2 miR-196a2 A/C	rs11614913 rs12304647	1,035 HBV-infected individuals in Korean population: 404 patients by HBV recovery, 313 HBV-infected patients with chronic hepatitis, 305 HBV-infected patients with liver cirrhosis, and 417 HBV-patients with HCC	In HBV-infected patients with chronic hepatitis or cirrhosis, CC genotype of rs12304647 linked to a reduced risk of HCC, no significant influence of rs11614913 on HCC development	[25]
miR-196a2 C/T miR-196a2 A/C miR-146a C/G	rs11614913 rs12304647 rs2910164	Case–control study: 3 Malaysian ethnical groups (Malays, Chinese, and Indians): 103 CHBV-infected with liver cirrhosis and HCC, 423 CHBV-infected patients	No significant influence of rs11614913 and rs2910164 on the HBV associated diseases, compared to CC genotype, AA + AC genotype of rs12304647 linked to reduced risk of cirrhosis/HCC	[26]
miR-196a2 C/T miR-149 C/T miR-146a C/G miR-499a C/T	rs11614913 rs2292832 rs2910164 rs3746444	Korean case–control study: 159 HCC patients who 127 were HBV infected	In miR-149, CT genotype and CT + CC reduced the risk of HCC in HBV-infected and non-infected, in miR-499a, an AG + GG reduced the risk of HBV-associated HCC, no influence on HBV-associated HCC for miR-146a and miR-196a2	[27]
miR-196a2 C/T miR-499 A/G	rs11614913 rs3746444	Meta-analysis: 13 studies involving 3,964 cases and 5,875 healthy controls	miR-196a2 C/T, but not miR-499 A/G, may be linked with decreased HBV related HCC	[28]
miR-146a G>C miR-149 C>T miR-196a2 C>T miR-499 A>G	———	271 patients with HCC and 532 healthy controls	Significant difference in miR-196a2C>T in the patient's group, individuals with HBV and miR-196a2 CT and TT genotypes had a significantly reduced risk of HCC, miR-196a2C>T had protective effect in patients with HBV associated HCC	[29]

Table 1: Continued ...

miRNA	SNP	Patients	Effect on the carrier	Reference
miR-608 C/G miR-149 C/T	rs4919510 rs2292832	Large-scale population: 993 patients with HCC and 992 healthy subjects	No link between rs4919510 and HBV associated HCC, miR-149 TT genotype linked with increased risk of HBV associated HCC in men	[30]
miR-149	rs2292832	327 liver biopsy proven HCC, 327 controls	The TC + CC, comparing with TT increased the chance of HCC in HBV-infected individuals	[31]
miR-499 A>G miR-149 C>T miR-196a 2T>C miR-146a G>C	rs3746444 rs2292832 rs11614913 rs2910164	Iranian population: 100 HCC patients (70 males and 30 females) and 120 healthy controls (70 males and 50 females)	miR-499 A>G, frequencies of AG genotype and G allele higher in female HCC patients than controls and the frequency of the A allele was higher in HBV-positive HCC patients, in miR-196a2 T>C, the frequencies of the CT and CC genotypes and the C allele higher in HBV-positive HCC patients than in controls	[32]
miR-146a G/C miR-499 A/G miR-149 C/T miR-196a 2C/T	rs2910164 rs3746444 rs2292832 rs11614913	Iranian population (liver transplant patients with HCC): 60 HCC patients and 120 healthy controls	CC genotype and C allele of miRNA-146a significantly associated with the increased risk of transplant rejection and significantly more frequent in male with acute rejection, no significant association between the genotypes and alleles of rs3746444, rs2292832, and rs11614913 and HCC in liver transplanted patients	[33]
miR-149 C/T miR-101-1 C/G/T	rs2292832 rs7536540	Thai population: 95 healthy controls, 90 CHBV-infected individuals, and 104 HCC patients	No significant association between miR-149 and miR-101-1 and the risk of HCC	[34]
miR-101-1 miR-101-2 C/T miR-101-2 C/T miR-338 C/T	rs7536540 rs17803780 rs12375841 rs62073058	Korean individuals	miR-101-1 related with the risk of liver cirrhosis and HCC, and rs12375841 and the haplotype ht2 (T-C) of miR-101-2 linked with HBV clearance	[35]
miR-646 G/T	rs6513497	771 HCC, 81.1% HBV infected	In males, GT genotype and G allele detected as protective factors against HBV associated HCC	[36]

Table 1: Continued ...

miRNA	SNP	Patients	Effect on the carrier	Reference
miR-499a C/T miR-423 A/C/T miR-26a1 C/T miR-608 C/G miR-604 C/T miR-492 C/G miR-149 C/T miR-146a C/G miR-196a2 C/T miR-30a A/G	rs3746444 rs6505162 rs7372209 rs4919510 rs2368392 rs2289030 rs2292832 rs2910164 rs11614913 rs1358379	HBV-associated liver diseases in Saudi Arabia: 1,352 HBV-infected patients and 600 healthy controls	SNPs in miR-149, miR-146a, miR-196a2, and miR-30a were significantly more common in patients, miR-30a, miR-149, miR-146a, miR-423, miR-492 and miR-196a2 associated to HBV clearance, miR-196a2, miR-30a, miR-26a1, miR-608, miR-149, and miR-423 linked to HBV associated cirrhosis, or HBV-associated HCC, no statistically significant relation reported for miR-604 or miR-499a on HBV related diseases	[37]
miRs-371-372-373 cluster	C/T rs28461391 A/C rs3859501 C/T rs12983273	1,439 Korean individuals	rs3859501 and the ht2 (C-A-C) relate to decrease in the risk of HBV associated HCC, none of SNPs has statistically significant effect on HBV clearance	[38]
miR-219-1	C/T rs421446 A/G rs107822 C/T rs213210	Korean population	All SNPs and both haplotypes (C-A-C and T-G-T) are associated with HBV clearance, no significant link with HBV associated HCC	[39]
miR-604 C/T	rs2368392	Korean patients: 1,439 with past or present HBV infection, divided into four groups (natural recovery, CHBV carrier/no cirrhosis, liver cirrhosis/HCC)	T allele linked to HBV chronic infection, Patients with CHBV this allele reduced the risk of HCC, rs2368392 is related to persistent infection, but not related to hepatocarcinogenesis	[40]
MCM7 (miR-106b-25 cluster)	rs999885	_____	AG/GG genotypes and G allele linked to a better HCC prognostic	[41]
The 3'UTR of IFNAR1 gene (binding site of miR-1231)	rs17875871	HCC individuals and controls (420 in each group)	Study of GAGA ins/del, deletion was related to increased risk of HBV associated HCC	[42]

Table 1: Continued ...

miRNA	SNP	Patients	Effect on the carrier	Reference
DICER1 (miR-574-3p binding) RAN (miR-199a-3p binding) PIWIL1 (miR-1264 binding)	C/T rs1057035 A/C/G rs3803012 C/T rs10773771	Polymorphisms studied in infected individuals *in vivo* and *in vitro*	CT/CC genotypes of rs1057035 and rs10773771 decreased the risk of HBV associated HCC, rs3803012 AG/GG genotypes deals with persistent infection of HBV	[43]
KRAS G/T (miR-let-7 and miR-181 binding)	rs712	_____	rs712TT genotype is related to occurrence of HBV associated HCC	[44]
RAD52 A/G RAD52 A/T RAD52 A/T RAD52 G/T RAD52 C/T	rs1051669 rs10774474 rs11571378 rs7963551 rs6489769	relation of HBV associated HCC risk and 5 SNPs situated at RAD52	rs7963551 C allele decrease HCC progress, rs7963551 CC/AC linked with increased expression of RAD52, finally, SNPs dealing with binding sites of miRNAs might have significant relation to HBV associated HCC risk	[45]
PD1 A/G	rs10204525	_____	PD-1 expression rate is decreased via miR-4717 function in lymphocytes of patients in CHBV infection and GG genotype, also liked with increased levels of TNF-α and IFN-γ and finally have important impact on the HBV infection	[46]
DGCR8 A/G AGO1 A/G GEMIN4 C/T	rs3757 rs636832 rs7813	_____	rs636832 A allele is linked to decreased risk of CHBV infection, comparing to the AA genotype, AG + GG increased the risk of CHBV infection, AA genotype a protective aspect for CHBV disease, no significant relations for other studied SNPs	[47]

RESULTS

miRNAs' General Features and the SNPs Affecting the Biogenesis and Action of miRNAs

miRNAs are small non-coding RNAs that are 18 to 25 nucleotide long and regulate many different biological processes including substantial roles in viral infections and cancers pathogenesis. For instance, a number of miRNAs have been detected in serum and tissues of HBV based tumors and dysregulated miRNA expression is detected in all steps of carcinogenesis during HCC [48]. Studying the miRNA profiles showed different expression patterns between healthy and HCC infected and benign and malignant HCC tissues [49]. Therefore, here we first discuss the biogenesis

pathway of miRNA production and then focus on the mutations that might affect this process.

miRNAs Biogenesis

miRNAs are well-known for their ability in gene expression modifications post-transcription in almost all of the eukaryotes such as human beings. The role of these molecules is detected in viral infections and act as mediators of the host response. These responses might later result in the intracellular defenses during infections or produce resistance to some viral infections as well as organize the survival and proliferation of viral particles inside the cells. Furthermore, viruses have been detected to produce miRNAs by recruitment of the host cell machinery for enforcing the generation of their own miRNAs which finally, contribute to host cell apoptosis prevention that facilitates malignant transformation [50].

In order to recognize how polymorphisms influence the mechanism of miRNAs gene expression regulation which results in the alteration in the biological processes that are regulated by them, it is vital to review the mechanism of generation of the miRNAs. miRNAs are coded by different parts of genome, for example, they might be result from a specific gene or a part of one gene sequence. Anyway, in human beings commonly miRNAs are transcribed by the action of RNA PolII (polymerase II) in the nucleus that produce pri-miRNA molecules, a long RNA transcript composed of 500–3,000 bases (see Fig. 1). These molecules have common features of regular mRNAs such as 5' cap and poly A tail, and secondary structures of multiple stem-loops (hairpins). Then, an enzymatic complex in the nucleus named Drosha and its cofactor, DGCR8 (DiGeorge syndrome critical region 8 protein, RNase III like enzyme) detects pri-miRNA molecules and cleaves them into pre-miRNA with a 2-nucleotide overhang in the 3' end [51].

These newly digested RNA molecules which are 60–70 nucleotide-long, are transported to the cytoplasm by the aid of a nuclear membrane translocator molecule called exportin-5 (Exp-5) which gains its energy through Ran-GTPase. After translocating into the cytoplasm, pre-miRNA molecules are detected by another RNase III like enzyme, Dicer/TRBP (transactivation response RNA-binding protein) and cut into mature miRNA molecules (19–25 bases long) duplexes (miRNA/miRNA*). Then, one of the two strand of this mature miRNA-duplex enters into a functional complex called RNA-induced silencing complex (RISC). In this complex, via Argonaut proteins (AGO1-4), the process of silencing the target mRNAs starts through binding of miRNAs into their target mRNAs in the 3' UTR (untranslated region). The strand that is responsible for entering RISC complex is called "guide strand" and the other strand that is called "passenger strand" or sometimes is shown as "miRNA*" commonly degrades. The determinant factor for selecting the strand to enter the RISC complex is the extent of complementarity in the 5' ends of miRNA duplexes. The less the complementarity in the 5' end, the more chance for entering the RISC complex [52] (see Fig. 1).

The sequences in the miRNAs that are in charge of binding to 3' UTR of the targets are composed of a 6-8 nucleotide that is located within 2 to 8 nucleotides counting from the miRNA's 5' end and is called "seed sequence". Also, it is reported that a partial complementarity between mRNA-miRNA at seed sequence renders to inhibition of the translation process, whereas the perfect complementarity ends up in the degradation of the targets of mRNAs [53].

By considering the production pathway of miRNAs, it is obvious that polymorphisms in miRNA genes are able to interfere with any part of the process of miRNA biogenesis such as pri-miRNA or pre-miRNA stages, or even worse in the quality of miRNA–mRNA interactions and can act as a two-sided blade which can increase or decrease the affinity of this attachment. Also, the fact that certain miRNA is capable of regulating several mRNAs and conversely, several miRNAs might be in charge of regulating one mRNA, even make the effect of SNPs more complicated [54]. Therefore, some

Table 2: Summary of HCV associated HCC miRNAs and their mutations.

miRNA	SNP	Patients	Effect on the carrier	Reference
miR-146a G/C	rs2910164	HCV-associated disease in Chinese individuals	No significant relation between GG genotype and G allele and risk of HCC in both HCV-negative or HCV-positive subjects	[13]
miR-146a G>C miR-196a2 C>T miR-499 A>G	————	260 cases with HCC and 281 health controls in China	miR-196a2C>T linked with decrease in risk of HBV-related HCC, but not HCV infected ones, miR-146aG>C and miR-196a2C>T related with of HCC risk	[55]
miR-146a G>C miR-196a2 C>T miR-499 A>G	————	Chinese individuals	miR-196a2 CC, CT and TT genotypes increased risk of HCC significantly	[56]
miR-146a C>G miR-149 T>C miR-196a2 T>C miR-499 T>C	rs2910164 rs2292832 rs11614913 rs3746444	Case-control in Chinese individuals: 274 patients with HCC	Patients with HCC were more likely to be males, have older age, have a history of alcohol drinking, and be infected with HBV and HCV infection, TC and CC genotypes of rs11614913 associated with increased risk of HCC	[57]
IFNL4/IL28B C/T (alter miR-122 expression)	rs12979860	United States population with different origin (Asian, African American, Caucasian, and Hispanic)	Both CT and TT genotypes are related to higher levels of IFN-stimulated genes comparing to CC genotype	[58]
IFNL4/IL28B C/T (alter miR-122 expression)	rs12979860	Liver biopsy and serum samples from 133 patients with CHC: 66 patients with SVR, and 64 didn't response to treatment	CC genotype is linked to increase in the liver miR-122 expression	[59]
IFNL4/IL28B C/T IFNL4 IL28B G/T (alter miR-122 expression)	rs12979860 rs8099917	Japanese individuals	In no-tumor liver samples + HCV infection cause reduction in miR-122 expression, TG genotype relates to decrease in miR-122 expression in mentioned samples	[60]
IFNL4/IL28B G/T	rs8099917	126 patients with chronic HCV, 51 virologic response or nonresponse	Relation between TT genotype and an increase in miR-122 expression level	[61]
IFNL4/IL28B	rs12979860 rs8099917	*in vitro* assay	Both studied SNPs control HCV infection development	[62]

Table 2: Continued ...

miRNA	SNP	Patients	Effect on the carrier	Reference
IFNL3/IL28B A/C (disturbs the binding miR-208b and miR-499a-5p)	rs4803217	*in vitro* assay	G allele has negative effect on the action of both miRNAs and cause IFLN3 high expression and linked to HCV clearance, T allele facilitates the infection process, both miRNAs can be possible targets for HCV infection treatment	[63]
IFNL3/IL28B A/C (disturbs the binding miR-208b and miR-499a-5p)	rs4803217	_____	G allele contributes to HCV clearance and T allele is related to infection process	[64]
miR-101-1 C/G/T miR-221 A/G	rs7536540 rs17084733	Egyptian population	Suggest that miR-101-1 and miR-221 might be used as biomarkers of HCV-associated HCC	[65]
TGFBR1 A/G (placed at miR-let-7 and miR-98-binding sites)	rs868	*in vitro* study	Impact on RNA load of HCV and hepatic inflammation, interaction between rs868 and infection caused by HCV is not studied by detail	[66]
miR-196a2 C/T miR-499 A/G	rs11614913 rs3746444	Egyptian Patients, 75 HCV-related HCC, 75 HCV cirrhotic patients and 75 healthy controls	GG genotype significantly lower in HCC patients, a significant difference in miR-499 genotypes frequency compared between HCC and cirrhosis groups, GG genotype was significantly lower in HCC cases than cirrhosis group, G allele significantly lower in HCC than other groups and significantly lower in HCC than normal group, G allele associated with lower risk of HCV related HCC	[67]
miR-196a-2 C>T miR-499 A>G	rs11614913 rs3746444	Egyptian patients: HCC and control groups each 50 individuals	miR-499 SNP might affect the susceptibility to HCC, miR-196A-2 SNP may affect the HCC risk in Egyptians with HCV infection	[68]

researchers focused on the effects of SNPs in the miRNAs in viral associated diseases and pointed out that these SNPs change the susceptibility of host for viral infections or viral clearance and even the extent of chronicity of the viral diseases or development of viral dependent cancers [37].

miRNA Mutagenesis and Tumorigenesis

Cancers are produces by the accumulation of various genetic disorders especially the ones that affect the function of tumor suppressor genes (TS-genes) and activate proto-oncogenes. In between, some miRNAs are detected to act like tumor suppressors (TS-miRs) and oncogenes (onco-miRs). Subsequently, the fluctuations in their expression levels alter tumor susceptibility. Basically, any deregulation in the pattern of miRNA expression might be the basis of malignancies that are produced by different mechanisms such as epigenetic and structural chromosome abnormalities [9, 69].

Another point that is important to consider is that the SNPs happening in the miRNA sequences change the pattern of gene expression rather than altering the protein's performance. Finally, the SNPs that affect miRNAs functionality can be summarized in different stages [70] that is shown in Fig. 2.

By the way, it should be considered that some of phenotypically neutral mutations that happen in the seed sequence facilitate the transition into new miRNAs that even might have more specific functions. However, any changes, even those that results a new miRNA, are the reason of a variation in the balance of regulatory process regulated by related miRNAs [71].

Viral (HBV and HCV) Associated HCC and Related miRNAs

Viral infections such as HBV and HCV are the concern of health organization around the world. Nearly 30% of the population of the world are infected or at least are carriers of HBV. HBV infection is one of the main reasons of different types of liver damages as well as HCC, which in some countries like China, turned to an endemic problem [72].

Contemplating that, miRNAs can be extracted and evaluated in different tissue types and body fluids such as serum, plasma, and urine, they are always the first line candidates for non-invasive evaluating, prognosis and diagnosis methods in different diseases such as cancers. Incidentally, the SNPs in miRNA sequences can impede the efforts made for development an effective panel of miRNA biomarkers for viral diseases such as HCC. Various researches have specified that during HBV infection of the host cells, the cellular content of miRNAs alter and even different stages of HBV infection has its own content of miRNAs. For instance, the miRNA expression pattern is specific in early hepatic tumors versus other stages of disease. Noticing the recent mentioned points, turn miRNAs into perfect candidates for hepatic disease, HBV infections, and HCC development [73]. Different studies have been detected the miRNA expression pattern of HCC patients and hepatoma cell lines via profiling methods that might be helpful in evolving novel insights into HCC pathogenesis and development. For the sake of this reason, some studies have discussed the miRNAs related to viral and non-viral HCC (reviewed in [74, 75]). Therefore, here the polymorphisms that is related to these miRNAs are overviewed.

HCC Key miRNAs and Their Mutations

Many researches have tried to introduce the most important miRNAs during different stages of viral based HCC. Among them, it seems that miR-122 is of special importance. Here, the function and subsequently the outcome of mutations in this miRNA is discussed in detail. The rest of miRNAs and their mutations is listed in Table 1.

Normally, miR-122 act as TS-miRNA and expresses in high amounts in the liver tissue. This miRNA sequence is placed on chromosome 18 (18q21.31) and lies in the intergenic area and while it is important for normal function of the liver, during HBV infection, its expression is suppressed [76].

The function of miR-122 A/C SNP (rs4309483) and miR-122 C/T SNP (rs4503880) on the risk of HCC with and without infection of HBV were described in a study which was done on 1,300 HBV associated HCC, 1,344 patients with HBV infection (without HCC), and 1,344 patients that were HBV cleared. The result of their study showed that rs4309483 SNP in miR-122 is related to the increased risk of HBV associated HCC and also is a protective agent against chronic HBV (CHBV) infection and these might be interpreted that although this SNP hinders CHBV infection but when the infection is launched the carcinogenesis is simplified by the existence of this SNP [41, 74].

Also, it is worth mentioning that the polymorphisms which happen in the binding sites of the targets of miRNAs, change the efficiency of this attachment and subsequently alters the regulatory mechanisms of target genes and finally might change the sensitivity to cancer in the patients. Supporting this theory was

the study which reported polymorphism that happens in the binding site of miRNA-122 (in IL1-A) increase the risk of HCC [29]. Also, rs3783553 and rs4309483 polymorphisms have effects in decreasing the cancer-promoting effect of HBV preS deletion in the subjects harboring HBV-infection and expression of miRNA-122 that results in the production a protection against CHB infection, respectively [30]. Finally, rs2999200 and rs6551952 SNPs can significantly influence on the basic expression level of miRNA-122 [79].

Some of mutations that is explained in Table 1 have seems to be more critical. For instance, besides the effect of miR-146a rs2910164 on HCC development, this SNP has influence on both acute and chronic liver failures and CHBV infected patients. Also, patients with rs2910164GG genotype show decreased vulnerability to HBV infection, lower TNF-α production, and increased survival frequency [80]. Besides the role of miR-196a2 rs11614913 on HCC progression, there is no significant relation with the number, size, stage, or growth phase of the tumors, and even metastasis to the lymph nodes [18].

Also, by understanding the conflicts that is detected in studies in Table 1, this fact should be determined that novel and more robust investigations in order to study the impact of this SNP on HBV associated HCC patients should be executed by considering that in complicated diseases such as HBV associated HCC, multiple alternatives exist. Furthermore, conflicting findings that is observed in the studies even in the same studied SNP in the context of HBV associated HCC, might be related to different factors such as ethnic background of the studied population, HBV genetic variants that is prevalently circulate in a specific population, and the size of population in the study [74].

HCV infection can cause HCV related diseases such as HCC and the susceptibility of individuals in establishing HCV related diseases is determined by the quality of interaction of HCV and the host, the genetic characteristics of viruses, and finally is related to the environmental and different physio-metabolic factors [81]. Table 2 summarizes the studies that consider miRNA related SNPs in HCV associated hepatic diseases and HCC.

CONCLUSIONS AND PERSPECTIVES

The fact that introduces miRNAs as intricate regulators of gene expression patterns, is accompanied by another fact that SNPs in the sequence of these regulating molecules might cause drastic changes in the functionality of miRNAs. Although many miRNAs are detected to be involved in tumorigenesis via sequential changes in the expression pattern of genes, polymorphisms in the miRNAs act as a double-sword blade especially in cancers. Therefore, SNPs in the sequences responsible for encoding the miRNAs might increase the incidence of viral persistence and even HCC development. Several studies pointed out that the importance of these SNPs in HBV or HCV persistence/clearance or HCC development. In conclusion, some of mutations reviewed in this manuscript seem to have specific importance in viral-associated HCC (Table 1 and Table 2). It should be taken into consideration that by continuing the researches, new SNPs will be detected that might be more critical in viral diseases and cancers. By the way, focusing on the described SNPs in this manuscript might be helpful in providing critical insights in stablishing innovative therapies against viral diseases or cancers such as HCC through imposing deliberate alterations in the pattern of miRNAs function.

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REFERENCES

1. Crespo G, Mario Z, Navasa M, Forns X. Viral Hepatitis in Liver Transplantation. *Gastroenterology* 2012;**142**:1373-83.

2. Lin J, Wu JF, Zhang Q, *et al*. Virus-related liver cirrhosis: Molecular basis and therapeutic options. *World J Gastroenterol* 2014;**20**:6457-69.
3. Santopaolo F, Lenci I, Milana M, *et al*. Liver transplantation for hepatocellular carcinoma: Where do we stand? *World J Gastroenterol* 2019;**25**:2591-602.
4. Ince N, Wands JR. The Increasing Incidence of Hepatocellular Carcinoma. *N Engl J Med* 1999;**340**:798-9.
5. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? Hepatology (Baltimore, Md) 2014;**60**:1767-75.
6. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med* 2003;**139**:817-23.
7. Villa V, Lo CM. Liver transplantation for hepatocellular carcinoma in Asia. *The Oncologist* 2007;**12**:1321-31.
8. Adam R, Karam V, Delvart V, *et al*. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012;**57**:675-88.
9. SiamiGorji S, Jorjani I, Tahamtan A, Moradi A. Effects of microRNAs polymorphism in cancer progression. *Med J Islam Repub Iran* 2020;**34**:3.
10. Ryan BM, Robles AI, Harris CC. Genetic variation in microRNA networks: The implications for cancer research. *Nat Rev Cancer* 2010;**10**:389-402.
11. Suzuki HI, Katsura A, Matsuyama H, Miyazono K. MicroRNA regulons in tumor microenvironment. *Oncogene* 2015;**34**:3085-94.
12. Xu T, Zhu Y, Wei Q-K, *et al*. A functional polymorphism in the miR-146a gene is associated with the risk for hepatocellular carcinoma. *Carcinogenesis* 2008;**29**:2126-31.
13. Cong N, Chen H, Bu WZ, *et al*. miR-146a G>C polymorphisms and risk of hepatocellular carcinoma in a Chinese population. *Tumor Biol* 2014;**35**:5669-73.
14. Xiang Y, Fan S, Cao J, *et al*. Association of the microRNA-499 variants with susceptibility to hepatocellular carcinoma in a Chinese population. *Mol Biol Rep* 2012;**39**:7019-23.
15. Li D, Peng J, Tan Y, *et al*. Genetic variations in microRNA genes and susceptibility to hepatocellular carcinoma MicroRNA and hepatocellular carcinoma. *Genet Mol Res* 2015;**14**:1926-31.
16. Ma Y, Wang R, Zhang J, *et al*. Identification of miR-423 and miR-499 Polymorphisms on Affecting the Risk of Hepatocellular Carcinoma in a Large-Scale Population. *Genet Test Mol Biomarkers* 2014;**18**:516-24.
17. Yu H, Wang Y, Wang S, Sun N. Association between miR-499 rs3746444 and the susceptibility of hepatocellular carcinoma. *Cell Mol Biol* 2016;**62**:42-5.
18. Qi P, Dou TH, Geng L, *et al*. Association of a variant in MIR 196A2 with susceptibility to hepatocellular carcinoma in male Chinese patients with chronic hepatitis B virus infection. *Hum Immunol* 2010;**71**:621-6.
19. Kou JT, Fan H, Han D, *et al*. Association between four common microRNA polymorphisms and the risk of hepatocellular carcinoma and HBV infection. *Oncol Lett* 2014;**8**:1255-60.
20. Zhang J, Wang R, Ma YY, *et al*. Association between single nucleotide polymorphisms in miRNA196a-2 and miRNA146a and susceptibility to hepatocellular carcinoma in a Chinese population. *Asian Pac J Cancer Prev* 2013;**14**:6427-31.
21. Tian T, Wang M, Zhu W, *et al*. MiR-146a and miR-196a-2 polymorphisms are associated with hepatitis virus-related hepatocellular cancer risk: A meta-analysis. *Aging* 2017;**9**:381-92.
22. Han Y, Pu R, Han X, *et al*. Associations of pri-miR-34b/c and pre-miR-196a2 Polymorphisms and Their Multiplicative Interactions with Hepatitis B Virus Mutations with Hepatocellular Carcinoma Risk. *PLoS One* 2013;**8**:e58564.
23. Akkız H, Bayram S, Bekar A, *et al*. A functional polymorphism in pre-microRNA-196a-2 contributes to the susceptibility of hepatocellular carcinoma in a Turkish population: a case-control study. *J Viral Hepat* 2011;**18**:e399-407.
24. Xu Y, Li L, Xiang X, *et al*. Three common functional polymorphisms in microRNA encoding genes in the susceptibility to hepatocellular carcinoma: A systematic review and meta-analysis. *Gene* 2013;**527**:584-93.
25. Kim HY, Yoon JH, Lee HS, *et al*. MicroRNA-196A-2 polymorphisms and hepatocellular carcinoma in patients with chronic hepatitis B. *J Med Virol* 2014;**86**:446–53.
26. Riazalhosseini B, Mohamed Z, Apalasamy YD, *et al*. Association between microRNA-196A2 and microRNA-146A polymorphisms and progression to cirrhosis and hepatocellular carcinoma in patients with viral hepatitis B. *Pharmacogenet Genomics* 2016;**26**:74-9.
27. Kim WH, Min KT, Jeon YJ, *et al*. Association study of microRNA polymorphisms with hepatocellular carcinoma in Korean population. Gene 2012;**504**:92-7.
28. Zhu SL, Zhong JH, Gong WF, *et al*. Association of the miR-196a2 C>T and miR-499 A>G polymorphisms with hepatitis B virus-related hepatocellular carcinoma risk: an updated meta-analysis. *Onco Targets Ther* 2016;**9**:2111.
29. KOU JT, FAN H, HAN D, *et al*. Association between four common microRNA polymorphisms and the risk of hepatocellular carcinoma and HBV infection. *Oncol Lett* 2014;**8**:1255-60.

30. Wang R, Zhang J, Ma Y, *et al*. Association study of miR-149 rs2292832 and miR-608 rs4919510 and the risk of hepatocellular carcinoma in a large-scale population. *Mol Med Rep* 2014;**10**:2736-44.

31. Liu MF, Chen WQ, He YZ, Gu YL. Role of miR-149C>T polymorphisms on the risk of hepatocellular carcinoma in a Chinese population. *Genet Mol Res* 2014;**13**:7184-9.

32. Farokhizadeh Z, Dehbidi S, Geramizadeh B, *et al*. Association of MicroRNA Polymorphisms With Hepatocellular Carcinoma in an Iranian Population. *Ann Lab Med* 2019;**39**:58-66.

33. Dehbidi S, Farokhizadeh Z, Karimi MH, *et al*. Evaluation of microRNA gene polymorphisms in liver transplant patients with hepatocellular carcinoma. *Hepat Mon* 2020;**20**:1-9.

34. Pratedrat P, Sopipong W, Makkoch J, *et al*. Association between miR-196a2 polymorphism and the development of hepatocellular carcinoma in the Egyptian population. *Meta Gene* 2014;**20**:1833-9.

35. Bae JS, Kim JH, Pasaje CFA, *et al*. Association study of genetic variations in microRNAs with the risk of hepatitis B-related liver diseases. *Dig Liver Dis* 2012;**44**:849-54.

36. Wang R, Zhang J, Jiang W, *et al*. Association between a variant in MicroRNA-646 and the susceptibility to hepatocellular carcinoma in a large-scale population. *Sci World J* 2014;**2014**: 312704.

37. Al-Qahtani AA, Al-Anazi MR, Nazir N, *et al*. Association of single nucleotide polymorphisms in microRNAs with susceptibility to hepatitis B virus infection and HBV-related liver complications: A study in a Saudi Arabian population. *J Viral Hepat* 2017;**24**:1132-42.

38. Kwak MS, Lee DH, Cho Y, *et al*. Association of polymorphism in pri-microRNAs-371-372-373 with the occurrence of hepatocellular carcinoma in hepatitis B virus infected patients. *PLoS One* 2012;**7**:e41983.

39. Cheong JY, Shin HD, Kim YJ, Cho SW. Association of polymorphism in MicroRNA 219-1 with clearance of hepatitis B virus infection. *J Med Virol* 2013;**85**:808-14.

40. Cheong JY, Shin HD, Cho SW, Kim YJ. Association of Polymorphism in MicroRNA 604 with Susceptibility to Persistent Hepatitis B Virus Infection and Development of Hepatocellular Carcinoma. *J Korean Med Sci* 2014;**29**:1523.

41. Qi F, Huang M, Pan Y, *et al*. A genetic variant in the promoter region of miR-106b-25 cluster predict clinical outcome of HBV-related hepatocellular carcinoma in Chinese. *PLoS One* 2014;**9**:e85394.

42. Zhou C, Yu Q, Chen L, Wang J, Zheng S, Zhang J. A miR-1231 binding site polymorphism in the 3'UTR of IFNAR1 is associated with hepatocellular carcinoma susceptibility. Gene 2012;507:95–8. https://doi.org/10.1016/j.gene.2012.06.073.

43. [43] Liu L, An J, Liu J, Wen J, Zhai X, Liu Y, et al. Potentially functional genetic variants in microRNA processing genes and risk of HBV-related hepatocellular carcinoma. Mol Carcinog 2013;52:148–54. https://doi.org/10.1002/mc.22062.

44. [44] Xiong D, Song Y, Xiong W, Liang Y. An let-7 KRAS rs712 polymorphism increases hepatocellular carcinoma risk. Genetics and Molecular Research 2015;14:14050–5. https://doi.org/10.4238/2015.October.29.24.

45. [45] Li Z, Guo Y, Zhou L, Ge Y, Wei L, Li L, et al. Association of a functional RAD52 genetic variant locating in a miRNA binding site with risk of HBV-related hepatocellular carcinoma. Mol Carcinog 2015;54:853–8. https://doi.org/10.1002/mc.22156.

46. [46] Zhang G, Li N, Li Z, Zhu Q, Li F, Yang C, et al. MicroRNA-4717 differentially interacts with its polymorphic target in the PD1 3' untranslated region: A mechanism for regulating PD-1 expression and function in HBV-associated liver diseases. Oncotarget 2015;6:18933–44. https://doi.org/10.18632/oncotarget.3662.

47. [47] Shang M, Huang Y, Hu X, Wang J, Song X, Zhou Y, et al. Association between SNPs in miRNA-machinery genes and chronic hepatitis B in the Chinese Han population. Infection, Genetics and Evolution 2014;28:113–7. https://doi.org/10.1016/j.meegid.2014.09.015.

48. [48] Qi P, Cheng S qun, Wang H, Li N, Chen Y feng, Gao C fang. Serum microRNAs as biomarkers for hepatocellular carcinoma in Chinese patients with chronic hepatitis B virus infection. PLoS One 2011;6. https://doi.org/10.1371/journal.pone.0028486.

49. [49] Anwar S, Lehmann U. MicroRNAs: Emerging Novel Clinical Biomarkers for Hepatocellular Carcinomas. J Clin Med 2015;4:1631–50. https://doi.org/10.3390/jcm4081631.

50. [50] Lin SL, Ying SY. Gene silencing in vitro and in vivo using intronic micrornas. Methods in Molecular Biology, vol. 1733, Humana Press Inc.; 2018, p. 107–26. https://doi.org/10.1007/978-1-4939-7601-0_9.

51. [51] Bartel DP. MicroRNAs: Genomics, Biogenesis, Mechanism, and Function. Cell 2004;116:281–97. https://doi.org/10.1016/S0092-8674(04)00045-5.

52. [52] Dweep H, Kubikova N, Gretz N, Voskarides K, Felekkis K. Homo sapiens exhibit a distinct pattern of CNV genes regulation: An important role of miRNAs and SNPs in expression plasticity. Sci Rep 2015;5:12163. https://doi.org/10.1038/srep12163.

53. [53] Drury RE, O'Connor D, Pollard AJ. The clinical application of MicroRNAs in infectious disease. *Front Immunol* 2017;**8**:1182.

54. Hu Y, Yu CY, Wang JL, *et al*. MicroRNA sequence polymorphisms and the risk of different types of cancer. *Sci Rep* 2014;**4**:1-8.

55. Zhou B, Dong LP, Jing XY, *et al*. Association between miR-146aG>C and miR-196a2C>T polymorphisms and the risk of hepatocellular carcinoma in a Chinese population. *Tumor Biol* 2014;**35**:7775-80.

56. Hao YX, Wang JP, Zhao LF. Associations between three common microRNA polymorphisms and hepatocellular carcinoma risk in Chinese. Asian Pacific Journal of Cancer *Prevention* 2013;**14**:6601-4.

57. Yan P, Xia M, Gao F, *et al*. Predictive role of miR-146a rs2910164 (C>G), miR-149 rs2292832 (T>C), miR-196a2 rs11614913 (T>C) and miR-499 rs3746444 (T>C) in the development of hepatocellular carcinoma. *Int J Clin Exp Pathol* 2015;**8**:15177-83.

58. Urban TJ, Thompson AJ, Bradrick SS, *et al*. IL28B genotype is associated with differential expression of intrahepatic interferon-stimulated genes in patients with chronic hepatitis C. *Hepatology* 2010;**52**:1888-96.

59. Estrabaud E, Lapalus M, Broet P, *et al*. Reduction of MicroRNA 122 Expression in IFNL3 CT/TT Carriers and during Progression of Fibrosis in Patients with Chronic Hepatitis C. *J Virol* 2014;**88**:6394-402.

60. Spaniel C, Honda M, Selitsky SR, *et al*. microRNA-122 Abundance in Hepatocellular Carcinoma and Non-Tumor Liver Tissue from Japanese Patients with Persistent HCV versus HBV Infection. *PLoS One* 2013;**8**:e76867.

61. Su TH, Liu CH, Liu CJ, *et al*. Serum microRNA-122 level correlates with virologic responses to pegylated interferon therapy in chronic hepatitis C. *Proc Natl Acad Sci USA* 2013;**110**:7844-9.

62. Hoffmann TW, Delfosse F, Helle F, *et al*. The expression of HCV-associated host factors is dependent on the hepatoma cell line used in HCV studies. *Arch Virol* 2014;**159**:527-34.

63. McFarland AP, Horner SM, Jarret A, *et al*. The favorable IFNL3 genotype escapes mRNA decay mediated by AU-rich elements and hepatitis C virus-induced microRNAs. *Nat Immunol* 2014;**15**:72-9.

64. Tian Z. Outflanking HCV. *Nat Immunol* 2014;**15**:6-8.

65. Shaker O, Alhelf M, Morcos G, Elsharkawy A. miRNA-101-1 and miRNA-221 expressions and their polymorphisms as biomarkers for early diagnosis of hepatocellular carcinoma. *Infect Genet Evol* 2017;**51**:173-81.

66. Sajjad EA, Radkowski M, Perkowska-Ptasińska, *et al*. Negative correlation between hepatitis C virus (HCV) and let-7 MicroRNA family in transplanted livers: The role of rs868 single-nucleotide polymorphism. *Ann Transplant* 2017;**22**:638-45.

67. Fteah AM, Ahmed AI, Mosaad NA, *et al*. Association of MicroRNA 196a and 499 polymorphisms with development of cirrhosis and hepatocellular carcinoma Post-HCV infection in Egyptian patients. Asian Pacific Journal of Cancer *Prevention* 2019;**20**:3479-85.

68. Abdel-Hamid M, Elshaer S, Darwish A. Association of MicroRNA related single nucleotide polymorphisms 196A-2 and 499 with the risk of hepatocellular carcinoma in Egyptian patients. *Meta Gene* 2018;**16**:139-42.

69. Dalmay T, Edwards DR. MicroRNAs and the hallmarks of cancer. *Oncogene* 2006;**25**:6170-5.

70. Hrdlickova B, de Almeida RC, Borek Z, Withoff S. Genetic variation in the non-coding genome: Involvement of micro-RNAs and long non-coding RNAs in disease. *Biochim Biophys Acta Mol Basis Dis* 2014;**1842**:1910-22.

71. Saunders MA, Liang H, Li WH. Human polymorphism at microRNAs and microRNA target sites. *Proc Natl Acad Sci USA* 2007;**104**:3300-5.

72. Trépo C, Chan HLY, Lok A. Hepatitis B virus infection. *The Lancet* 2014;**384**:2053-63.

73. Waidmann O, Bihrer V, Pleli T, *et al*. Serum microRNA-122 levels in different groups of patients with chronic hepatitis B virus infection. *J Viral Hepat* 2012;**19**:e58-65.

74. Ellwanger JH, Zambra FMB, Guimarães RL, Chies JAB. MicroRNA-related polymorphisms in infectious diseases-tiny changes with a huge impact on viral infections and potential clinical applications. *Front Immunol* 2018;**9**:1316.

75. Sarkar N, Chakravarty R. Hepatitis B virus infection, MicroRNAs and liver disease. *Int J Mol Sci* 2015;**16**:17746-62.

76. Mahmoudian-Sani MR, Asgharzade S, Alghasi A, *et al*. MicroRNA-122 in patients with hepatitis B and hepatitis B virus-associated hepatocellular carcinoma. *J Gastrointest Oncol* 2019;**10**:789-96.

77. Gao Y, He Y, Ding J, *et al*. An insertion/deletion polymorphism at miRNA-122-binding site in the interleukin-1a 3α untranslated region confers risk for hepatocellular carcinoma. *Carcinogenesis* 2009;**30**:2064-9.

78. Du Y, Han X, Pu R, *et al*. Association of miRNA-122-binding site polymorphism at the interleukin-1 α gene and its interaction with hepatitis B virus mutations with hepatocellular carcinoma risk. *Front Med China* 2014;**8**:217-26.

79. Gamazon ER, Innocenti F, Wei R, *et al*. A genome-wide integrative study of microRNAs in human liver. *BMC Genomics* 2013;**14**:395.

80. Jiang H, He X, Li J, *et al*. Association of a single-nucleotide polymorphism within the miR-146a gene with susceptibility for acute-on-chronic hepatitis B liver failure. *Immunogenetics* 2013;**65**:257-63.

81. Ellwanger JH, Kaminski V de L, Valverde-Villegas JM, *et al*. Immunogenetic studies of the hepatitis C virus infection in an era of pan-genotype antiviral therapies - Effective treatment is coming. *Infect Genet Evol* 2018;**66**:376-91.