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miR-122 and hepatocellular carcinoma: from molecular biology to therapeutics

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microRNA-122 (miR-122) is a liver-specific miRNA and a key regulator in liver development as well as in liver diseases. The loss of miR-122 is associated with Hepatitis C virus (HCV) [1] infection, hepatocellular carcinoma (HCC) [2], and HCC resistance to treatment [3]. Several genes, such as Snail 1 and Snail 2 in epithelial-mesenchymal transition, WNT1 Gene from WNT signaling pathway, CREB1, and BCL9, have been validated as the targets of miR-122. Even though long non-coding RNAs (lncRNAs) ANRIL and RNA-binding protein AUF1 are proved to suppress miR-122 expression and to promote HCC progression, the regulation of miR-122 expression is still not fully understood.

In most studies linking lncRNAs and miRs with HCC, lncRNAs are often regarded as miR sponges, which share the same binding sequences of certain miRs with mRNAs and compete with them to sponge the miRs; however, in an interesting study published in EbioMedicine, Cheng et al. [4] found a CpG island located in the miR-122 promoter region, which support a novel regulatory mechanism for miR-122 expression.

Methylation and miRs regulation are two key epigenetic alterations in HCC progression. DNA methylation occurs when methyl groups are included to the DNA strand and repress DNA transcription. Hypermethylation of tumor suppressor genes or hypomethylation of oncogenes leads to tumorigenesis. Villanueva et al. conducted a methylome profiling among 304 HCC patients treated with surgical resection and validated a signature of 36 DNA methylation biomarkers that predicts poor survival accurately, indicating promoter DNA methylation can predict HCC prognosis [5]. Even though more and more studies reveal the role of miRs in HCC by deregulating tumor suppressor genes or oncogenes, the connection between DNA methylation and miRs are not well studied.

Cheng and colleagues wisely noticed that lncRNA HOTAIR which recruits the polycomb repressive complex 2 with its H3 lysine27 histone methylation activity, is overexpressed and decreases the expression of miR-122 in HCC tissues. As a well-known oncogene in most tumors, both *in vitro* and *in vivo* experiments demonstrated that knockdown of HOTAIR inhibited HCC cells proliferation, induced cell cycle arrest and suppressed tumor progression by negatively regulating miR-122 and consequently suppressing Cyclin G1. To further reveal the interaction between lncRNA HOTAIR and miR-122, Cheng et al. used bisulfite sequencing analysis, chromatin immunoprecipitation, and western blots and concluded that lncRNA HOTAIR epigenetically suppressed miR-122 expression *via* DNA methyltransferase-mediated DNA methylation. The study of Cheng and colleagues provides an important novel glimpse of the mechanistic link between two essential non-coding RNAs in HCC: HOTAIR and miR-122, and proposes the HOTAIR/miR-122/Cyclin G1 negative regulatory axis as a promising molecular target for HCC intervention.

At present time RNA molecules are developed for diagnosis and treatment of various diseases. [6]. Based on the importance of miR-122 in HCV infection and HCC progression, several clinical trials of miR-122 are ongoing. In one of the clinical trials, a miR-122 inhibitor (miravirsen) has been used as a novel therapeutic strategy against HCV infection (ClinicalTrials.gov identifier: NCT01200420). The results demonstrated that the use of miravirsen in patients chronically infected with HCV genotype 1 had prolonged dose-dependent reductions in HCV RNA levels without viral resistance [7]. Other investigators are trying to explore the role of miR-122 as a real-time detection marker of drug-induced liver injury following chemotherapy (ClinicalTrials.gov identifier: NCT03039062), or to evaluate the expression level of miR-122 after antivirals treatment, a novel and completely oral hepatitis C therapy (ClinicalTrials.gov identifier: NCT03414554 and NCT03687229), or to investigate the dysregulation of circulating miR-122 and its prognostic and predictive values for clinical outcomes in patients with acute liver failure (ClinicalTrials.gov identifier: NCT03000621). Moreover, animal models that target miR-122 have been generated or developed; an orthotopic mouse model demonstrated that miR-122-regulated thymidine kinase expression achieved effective anti-tumor results and increased the safety of intratumoral delivery of adenovirus-mediated thymidine kinase in addition to systemic ganciclovir for miR-122-deficient HCC [8]. A novel MS2 bacteriophage virus-like particle-based miR-122 delivery system cross-linked with the HIV TAT peptide effectively can penetrate the cytomembrane and inhibits HCC cell lines proliferation [9]. A graphene-P-gp loaded with miR-122-InP@ZnS quantum dots nanocomposites was also developed to reverse chemodrug resistance by inducing apoptosis in HCC [10].

The work of Cheng and colleagues demonstrates a negative regulatory axis of HOTAIR/miR-122/Cyclin G1 in HCC and raises several

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questions for further studies. In the clinical trials of miR-122 and mouse models for miR-122-targeted therapy, what are the expression pattern and biological role of HOTAIR? Will HOTAIR be a novel target for the treatment of HCV infection, HCC, and HCC chemoresistance? Can HOTAIR overcome the resistance to miravirsen caused by mutations in the viral genome after long-term treatment in HCV patients? As HCV-related HCC patients represent a major percentage of HCC, especially in China, are HOTAIR and miR-122 engaged in promoting HCV-related HCC as well? Additional investigations are needed to evaluate and compare the expression of HOTAIR and miR-122 in healthy donors, HCV-infected patients, and HCV-related HCC patients.

Considered key regulatory role of miR-122 in HCV infection and HCC progression, the mechanism between HOTAIR and miR-122 will provide new useful insights into HCC therapies.

Conflict of interest

None

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