MiR-130b-3p Suppress the Migration, Proliferation and Chemosensitization of Hepatocellular Carcinoma Cells

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Abstract: Hepatocellular carcinoma (HCC) is one of the most commonly diagnosed cancers globally, yet its pathogenesis remains incompletely understood. Among the various mechanisms contributing to HCC development, small RNAs, such as microRNAs (miRNAs), play a significant role. miRNAs are non-coding RNAs, typically 20-30 nucleotides long, that regulate gene transcription by binding to RNAs, affecting downstream signaling pathways. One such miRNA, hsa-miR-130b-3p, has been associated with cancer development, including HCC, although the full extent of its involvement remains unclear. This study aimed to explore the link between hsa-miR-130b-3p and HCC using bioinformatics analyses and *in vitro* assays. Publicly available databases were utilized for expression profiling, mRNA and lncRNA target prediction, pathway enrichment, and methylation analysis. *In vitro* experiments were conducted using a hsa-miR-130b-3p inhibitor in HepG2 cells to assess its effects on proliferation, migration, and oxaliplatin sensitivity. Our findings show that hsa-miR-130b-3p is upregulated in multiple cancers, including HCC, targeting cancer-related genes and interacting with various lncRNAs. Inhibition of hsa-miR-130b-3p reduced cancer cell proliferation and migration, while enhancing drug sensitivity to oxaliplatin. These results suggest that hsa-miR-130b-3p may play a role in HCC pathogenesis, but further studies are required to fully understand its mechanisms.

Keywords: HCC, small RNA, non-coding RNA, HepG2, small RNAs, mir130b.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common types of primary liver cancer and accounts for between 85% and 90% of primary liver cancer cases [1]. HCC is the most common malignancy in several regions of Africa and Asia, but there are increasing trends in the US as well [2]. Hepatocellular carcinoma is a heterogeneous disease that can be caused by various risk factors including hepatitis B, hepatitis C, diet and alcohol intake [1]. Various interventions have been executed to further circumvent HCC such as vaccination and surveillance in patients with cirrhosis and fibrosis [3]. Apart from that advances in the surgical process as well as therapeutic treatments have also greatly benefited HCC patients [3]. Nevertheless, despite all the efforts to manage HCC better, HCC is a complex and multifaceted disease. Therefore, there is still a lot to be explored to further understand the pathogenesis of this disease.

MicroRNAs (miRNA) are a class of small non-coding RNAs typically sized around 22 nucleotides in length [4]. These RNAs play important roles in gene regulation and maintaining cellular homeostasis. miRNA regulates gene regulation by binding to the 3' untranslated region (UTR) of certain genes, thus preventing transcription [5]. Some studies have also shown that miRNA can also bind beyond the 3' UTR and bind to other sites as well [5]. MiRNAs are often dysregulated in various diseases, especially in cancers [6]. It has been reported that miRNA-related genes can be amplified or deleted in different types of cancers [6]. Other epigenetic factors such as methylation have also been shown to cause dysregulation in miRNA profile [6].

In HCC, miRNAs have been shown to be involved in various cellular processes such as cell proliferation, invasion and metastasis [7]. Multiple miRNAs have been reported to be linked to HCC such as hsa-miR-106b-5p [8-10], hsa-miR-99a-5p [9, 10] and hsa-miR-199a-3p [9, 10]. Nevertheless, there are a lot more miRNAs that have yet to be fully elucidated, especially in their role in HCC. For instance, hsa-miR-130b-3p is a miRNA that has been reported to be involved in breast cancer [11], gestational diabetes [12], lung cancer [13] and prostate cancer [14], but their involvement in HCC is still unclear. Herein, we report a preliminary analysis on the role of this miRNA, hsa-miR-130b-3p and its involvement in HCC using publicly available datasets and *in vitro* cell culture work.

MATERIALS AND METHOD

MiRNA Expression Profile

The expression profile of the selected miRNA was determined using several online tools and databases.

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The expression profile of hsa-miR-130b-3p was determined using the EVAtlas database [15]. The individual expression of has-miR-130b-3p was determined using the miRTV tool as well [16].

mRNA Target Prediction and Enrichment Analysis

We utilized miRDB [17] for the mRNA target prediction that binds to miR-130b-3p. The resulting list was used as input for the downstream analysis. The enriched pathway was predicted based on the KEGG pathway [18] and the gene ontology analysis [19] using the Webgestalt online tool [20]. Then, the network analysis was performed using the Network Analyst Tool [21]. The generic protein-protein interaction was performed using the Imex Interactome [22] database with zero order network.

LncRNA Target Prediction

The binding of lncRNA to hsa-miR-130b-3p was predicted using the lncRNASNP2 database [23, 24]. The name of the miRNA was entered into the search tab and the results were presented in Table **1**.

Methylation Analysis

The methylation profile of the gene encoding has-miR-130b-3p, MIR130B was added as an input. We used the wanderer [25] tool that utilized the TCGA database.

Cell Culture and Transfection

HepG2 cells were previously obtained from ATCC and stored in UMBI's Biobank. The cells were cultured in DMEM medium (Nacalai Tesque, Japan) supplemented with 10% FBS (Sigma, USA) and 1% Penn-Strep (Nacalai Tesque, Japan). The cells were maintained in a 37 C incubator supplemented with 5% CO2. Three biological replicas were performed for each of the experiments, including cells treated with mIR-130b-3p inhibitor (INH; Integrated DNA Technologies, USA), cells transfected with a negative control (NC; Bioneer, Korea), and non-transfected cells (NTC). Transfection was performed using the jetOPTIMUS Transfection reagent according to the manufacturer's protocol (Polyplus, USA).

Wound Healing Assay

HepG2 cells were seeded in a 24-well plate at $6.5x10^5$ cells per well overnight before transfection. Then, the scratch was introduced at the middle of each of the wells using a 10ul pipette tip. Wound closure was observed and recorded starting from 0h, 24 hours and 48 hours. The percentage of wound closure was calculated using 0h as the baseline for each of the treatment groups.

MTT Assay

HepG2 cells were seeded in a 96-well plate 8 x 10^4 cells per well overnight before transfection. Then, the cells were transfected, and the viability of the cells was measured using MTT assay at 24 hours and 48 hours. In brief, 20 ul of 5 mg/mL of MTT reagent (Sigma, USA) was added to the wells and left to incubate at 4 hours. Then, the crystals were resuspended in DMSO before the absorbance was measured at 560nm using a microplate reader (Varioskan, Thermo Fisher).

Drug Sensitivity Assay

HepG2 cells were seeded in a 96-well plate 8 x 10^4 cells per well overnight before transfection. Then, 10 uM of oxaliplatin (Medchemexpress, USA) was added to the transfected cells. The viability of the cells was measured using MTT assay as explained in the section above.

Statistical Analysis

Statistical analysis was conducted using T-test with p value<0.05 was considered significant. Graphpad Prism was used to perform all statistical analyses.

RESULTS

Hsa-miR-130b-3p is Upregulated in Liver Hepatocellular Carcinoma

To determine the expression of hsa-miR-130b-3p in various cancers, we utilized the TCGA database to get an overview of the miRNA expression in various cancers. As shown in Figure **1A**, the expression of hsa-miR-130b-3p was upregulated in various cancers including testicular germ cell cancer, squamous cell lung cancers, diffuse large B-cell lymphoma and also liver hepatocellular carcinoma. These results were also in agreement with the miRTV online tool as well as shown in Figure **1B**. We also determined the expression of has-miR-130b-5p which was also upregulated in liver cancer cases as well as in Figure **1C**. We also wanted to evaluate the presence of this miRNA in extracellular vesicles as it is well known that miRNA is abundant in the circulation. As shown in Figure **1B**, hsa-miR-130b-3p can be found in small extracellular vesicles (sEV) across different tissues, particularly in the lymph and bone marrow. This miRNA

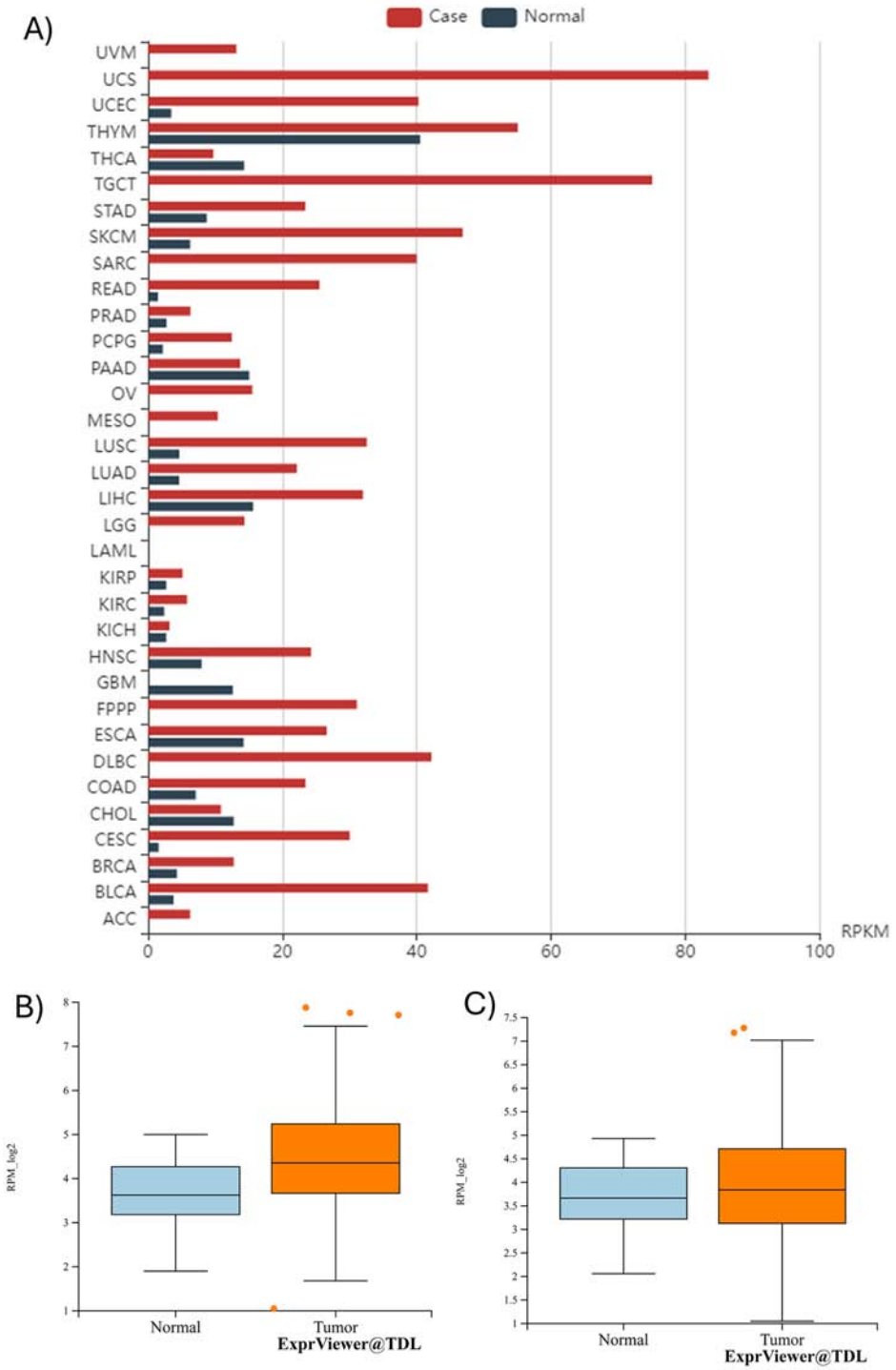

Figure 1: A) Overall distribution of the expression of hsa-miR-130b-3p in various cancers using the TCGA dataset. Data obtained using the EVAtlas tool [15]. **B**) Expression of hsa-miR-130b-3p **C**) hsa-miR-130b-5p in LIHC using the miRTV tool [16].

can also be found in sEVs from various sources apart from cell lines such as breast milk, plasma and serum as in Figure **2A**.

Certain Locations of the MIR130B Gene are Methylated

Methylation is well known to play a role in the expression of genes including miRNA-related genes. Therefore, we determined the methylation profile of the MIR130B gene using the TCGA dataset. As shown in Figure **2C**, there are 9 probes corresponding to this particular gene. Approximately 4 of the probes in the normal tissue had a delta beta value of less than 0.5, while the rest were more methylated. For the tumor tissues, the distribution of methylation was more dynamic as compared to the normal tissue. Generally,

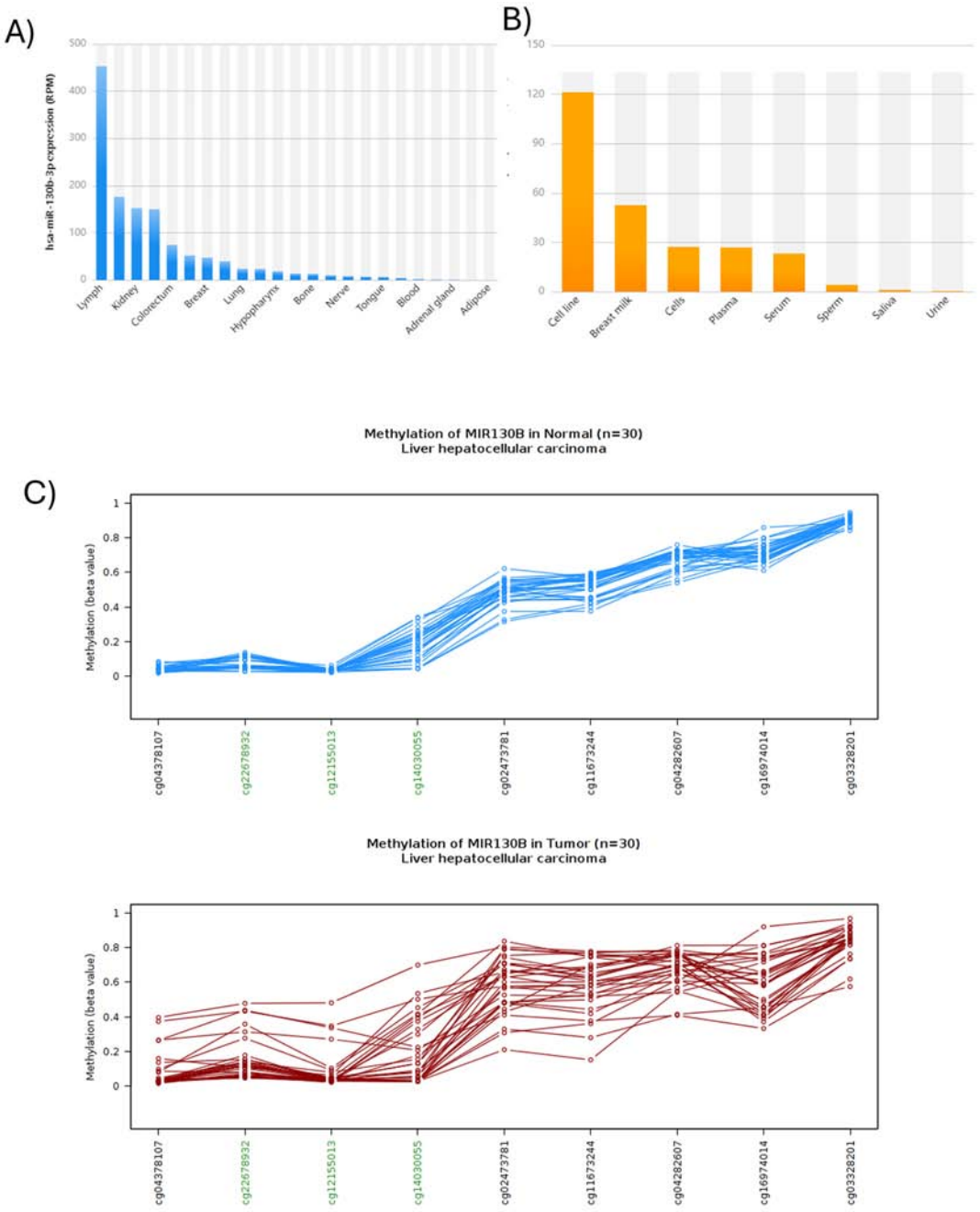

Figure 2: A) Expression of hsa-miR-130b-3p in sEVs from different tissues and from **B**) different sources. Data obtained using the EVATlas tool [15]. **C**) Methylation profile of the MIR130B gene in normal liver tissue (top) and liver cancer tissue (bottom). Figures and data obtained from the methylation Wanderer tool [25].

probes in the later CpG sites had a higher methylation in tumor tissues than in normal tissues.

Cancer-Related Pathways are Enriched among the Predicted Target Genes

To predict the target genes for hsa-miR-130b-3p, we utilized the miRDB database. The database yielded in 917 predicted target genes with target scores ranging from 100-50. From this list, 5 genes had a target score of 100 which includes CLIP-1, GJA1, CPEB1, SLAIN1 and SKIDA1. We then performed pathway enrichment using the KEGG database of all 917 target genes. Among the most significantly enriched pathways, as shown in Figure **3B** include the circadian rhythm pathway, colorectal cancer pathway, mTOR signalling pathway and the Wnt signalling pathway. For the gene ontology analysis, most of the genes were located in the membrane and were involved in protein-binding activity. We also determined the network analysis using the iMEX interactome

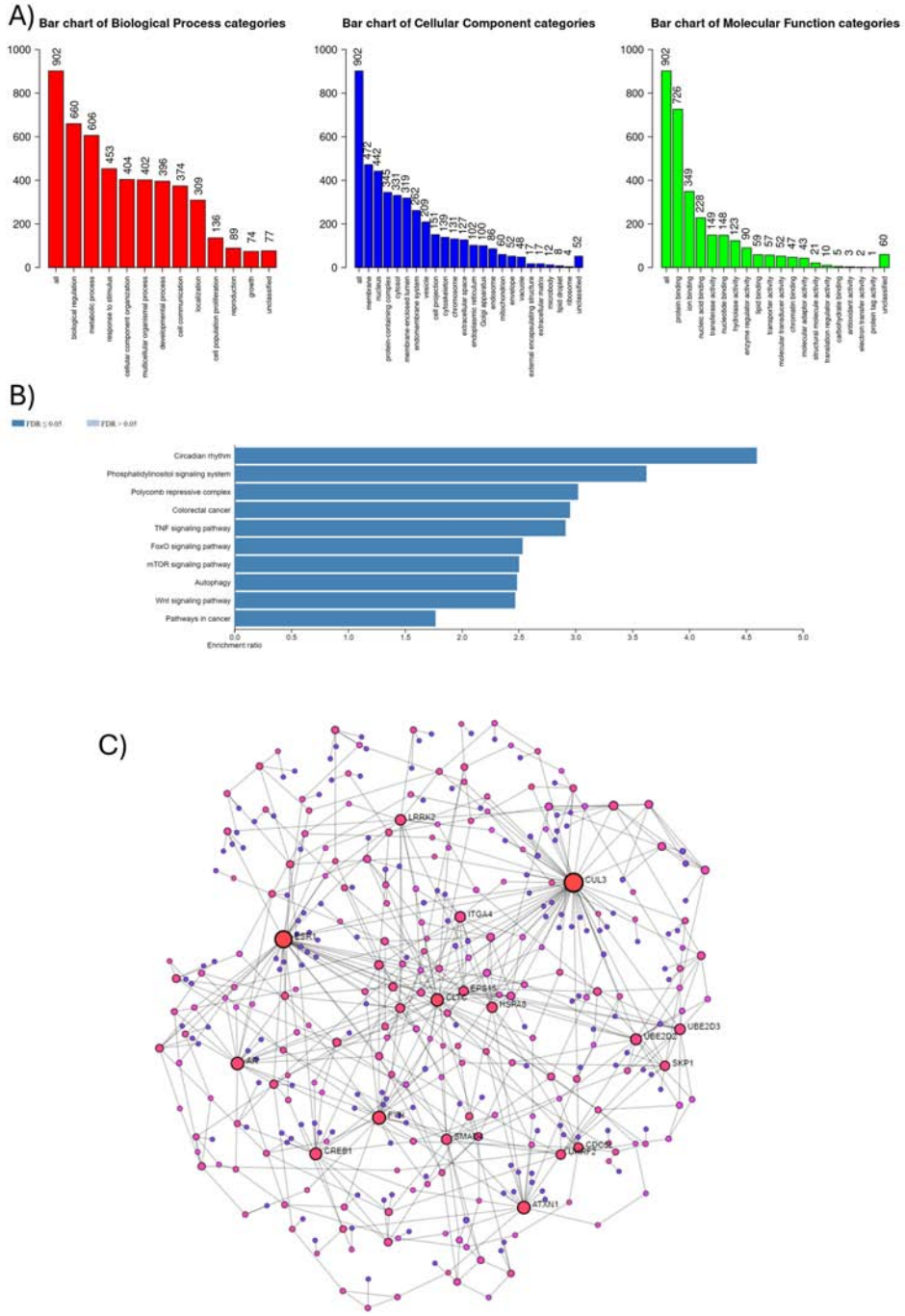

Figure 3: A) Gene ontology analysis of the selected target genes and **B**) Enriched pathways of the selected target genes. Data was obtained using Webgestalt tool [20]. **C**) Network analysis of the selected target genes. Data was obtained using the Network Analyst tool [21].

database, as depicted in Figure **3C**, among the hub genes that are highly interconnected among the genes include CUL3, ITGA4 and HSPA8.

Hsa-miR-130b-3p is Predicted to Bind to Several Long Non-Coding RNAs

Since miRNA can also competitively bind to long non-coding RNAs, we performed a prediction search to determine which targets does hsa-miR-13b-3p can bind to. As shown in Table **1**, according to the lncSNP2 database, this miRNA can bind to 12 different lncRNAs. The binding with the highest score is to a lncRNA named NONHSAT210947.1.

Inhibition of hsa-miR-130b-3p Reduced Proliferation and Migration of HepG2 Cells

Since multiple studies have shown that hsa-miR-130b-3p is upregulated in several cancers, we inhibited

Table 1: Potential lncRNA Targets that can Bind to has-miR-130b-3p as Predicted by lncRNASNP2 Tool [23]

lncRNA	miRNA	Interaction	lncRNA Chr	Binding Start	Binding End	Energy (kCal/Mol)	Score
NONHSAT210947.1	hsa-miR-130b-3p	miRNA: 3' uacGGGAAAGUAG--UAACGUGAc 5' :|: ||||| |||||||| lncRNA:5' aaaTCTGTTCATCTAATTGCACTt 3'	chr6	105810466	105810489	-18	166
NONHSAT174605.1	hsa-miR-130b-3p	miRNA: 3' uacGGGAAAGUAGUAACGUGAc 5' |:| |: |||||||||| lncRNA:5' cttCTCGATTCTCATTGCACTg 3'	chr16	74031582	74031603	-23.52	163
NONHSAT218862.1	hsa-miR-130b-3p	miRNA: 3' uacggGAAAGUAGUAACGUGAc 5' | ||: |:||||||| lncRNA:5' ttttaCATTTTTTATTGCACTt 3'	chr8	128268803	128268824	-12.82	161
NONHSAT200974.1	hsa-miR-130b-3p	miRNA: 3' uacGGGAAAGUAGUAACGUGAc 5' | :||| ::||||||| lncRNA:5' ccaCATTTTCTCTGTTGCACTt 3'	chr4	11307377	11307398	-16.200001	159
NONHSAT031007.2	hsa-miR-130b-3p	miRNA: 3' uacGGGAAAGUAGUAACGUGAc 5' |:| | | ||||||||| lncRNA:5' tttCTCACTAAACATTGCACTa 3'	chr12	117453097	117453118	-14.34	159
NONHSAT149544.1	hsa-miR-130b-3p	miRNA: 3' uacgggaAAGUAGUAACGUGAc 5' ||:||| ||||||| lncRNA:5' aaattgcTTTATC-TTGCACTt 3'	chr1	110347094	110347114	-14.55	157
NONHSAT056183.2	hsa-miR-130b-3p	miRNA: 3' uacggGAAAGUAGUAACGUGAc 5' ||| :| | ||||||| lncRNA:5' attagCTTCTAACTTTGCACTg 3'	chr17	78105789	78105810	-15.19	157
NONHSAT180481.1	hsa-miR-130b-3p	miRNA: 3' uacggGAAAGUAGU----AACGUGAc 5' ||||:|||| ||||||| lncRNA:5' cccgaCTTTTATCAATGAGTTGCACTa 3'	chr19	46919428	46919402	-17.280001	156
NONHSAT175404.1	hsa-miR-130b-3p	miRNA: 3' uaCGGGAAAGUAGUAACGUGAc 5' |:|:|||: ||||||| lncRNA:5' gaGTCTTTTT----TTGCACTg 3'	chr17	57120344	57120361	-18.709999	147
NONHSAT002478.2	hsa-miR-130b-3p	miRNA: 3' uacGGGAAAGUAGUAACGUGAc 5' | | | | | ||||||| lncRNA:5' agtCACATCCTTGTTTGCACTg 3'	chr1	37814038	37814059	-18.190001	147

NONHSAT173188.1	hsa-miR-130b-3p	miRNA: 3' uacggGAAAGUA-- GUAACGUGAc 5' || ||| : ||||||| lncRNA:5' acaaaCTGCCATGGTTTTGCACTa 3'	chr16	67098921	67098944	-13.47	144
NONHSAT192168.1	hsa-miR-130b-3p	miRNA: 3' uacgggaaaguaguaACGUGAc 5' ||||||| lncRNA:5' ttccaggggcgatTTGCACTa 3'	chr22	25687531	25687552	-11.45	140

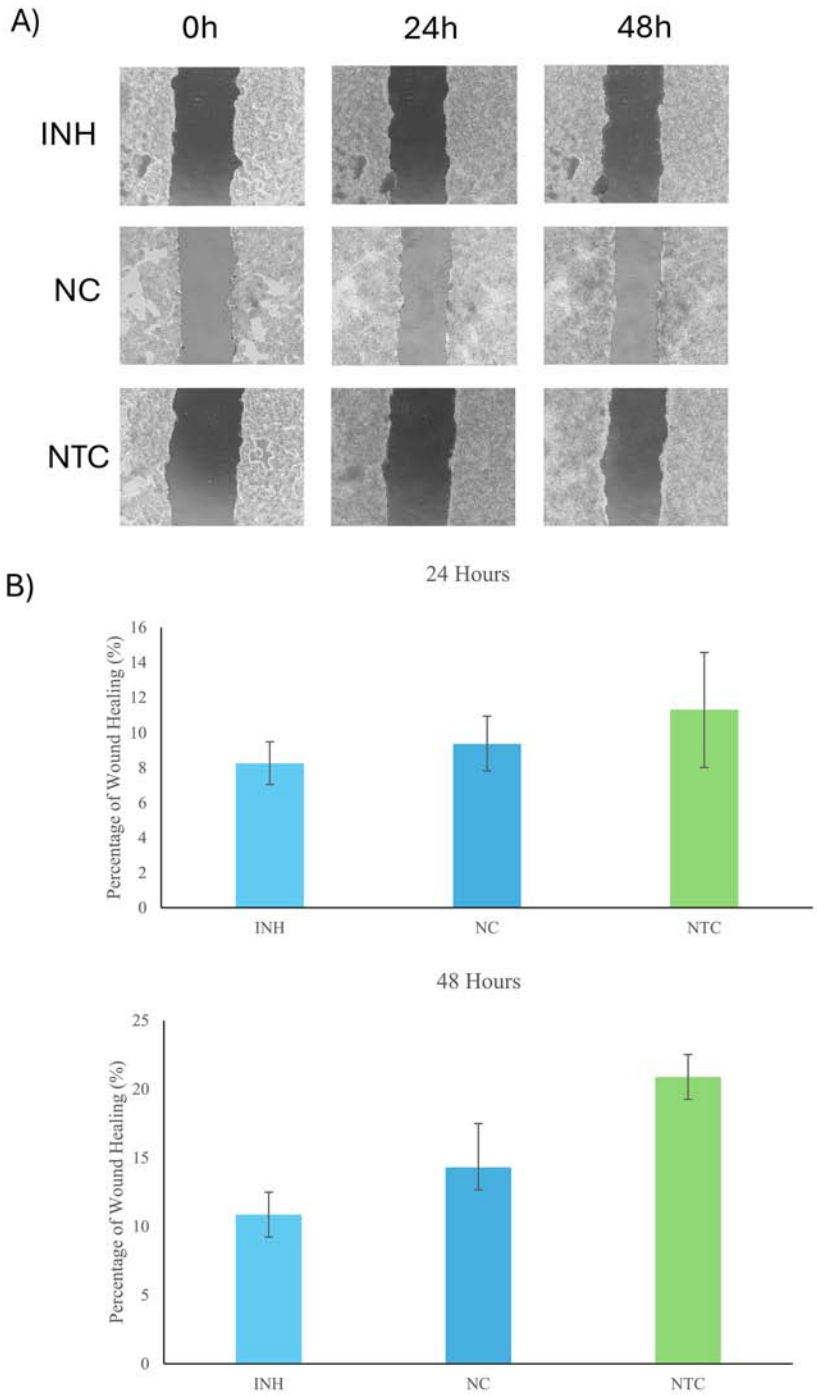

Figure 4: A) Microscopic pictures of the wound healing analysis. Images were taken at 0, 24 and 48 hours. **B**) Percentage of wound healing closure at 24 hours and 48 hours.

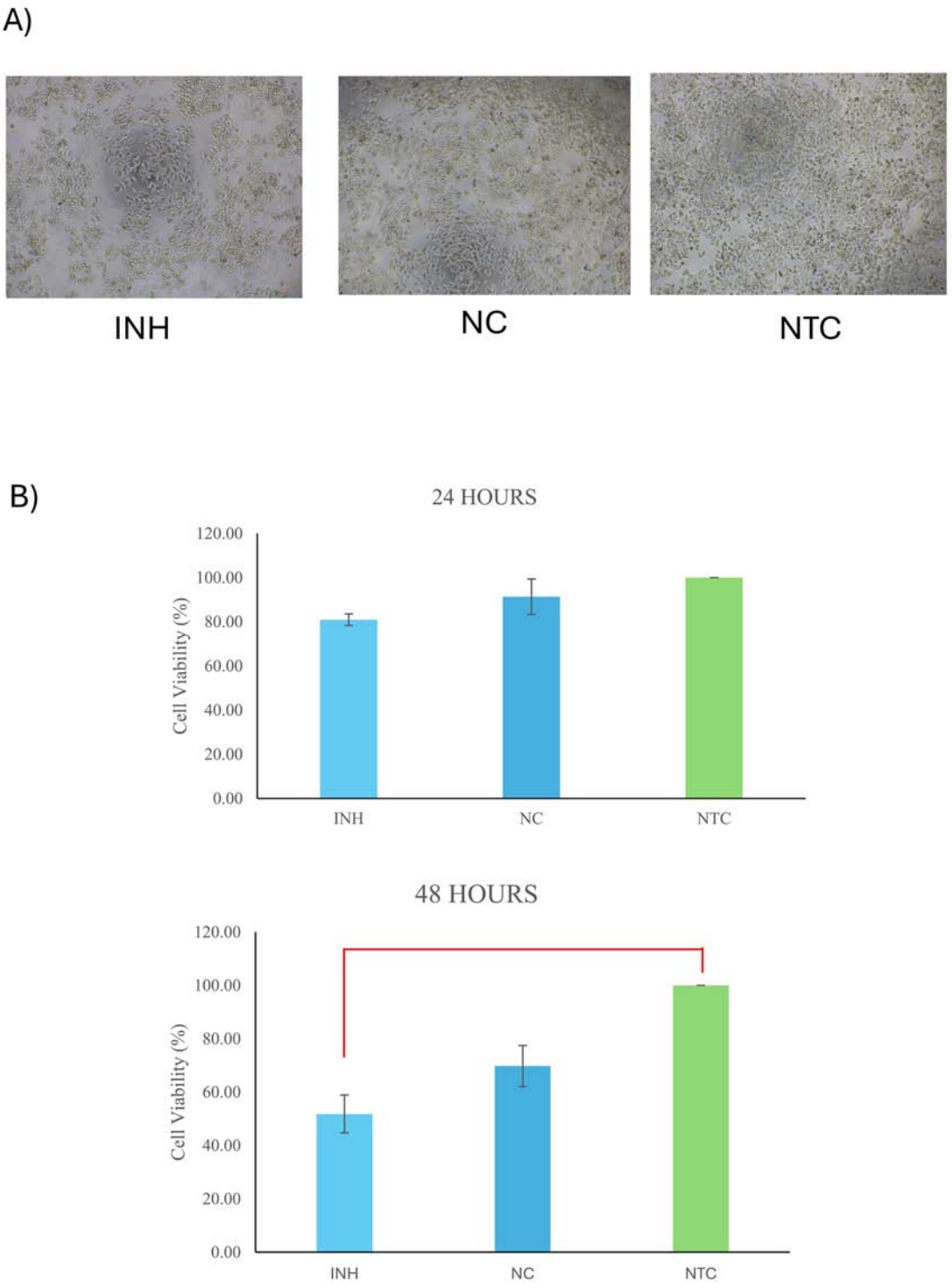

Figure 5: A) Microscopic pictures of HepG2 cells after treatment with the miR130b-3p inhibitor. **B**) Percentage of cell viability at 24 hours and 48 hours.

this miRNA to evaluate the functional effects in the liver cancer cell line, HepG2. As shown in Figure **5**, the morphology of the cells after inhibition for 24 hours did not result in significant differences. Based on our MTT analysis, after 24 hours, the reduction of cell viability was about 20%. After 48 hours, the cells with the miRNA inhibition exhibited a larger reduction in viability, to approximately 50%. For the migration, inhibition of hsa-miR-130b-3p resulted in a lower percentage of wound closure at both 24 and 48 hours as shown in Figure **4**. We also evaluated the effects of this miRNA in terms of its drug sensitivity activity. Based on Figure **6**, the inhibition of hsa-miR-130b-3p resulted in the cells being more sensitive toward the oxaliplatin treatment.

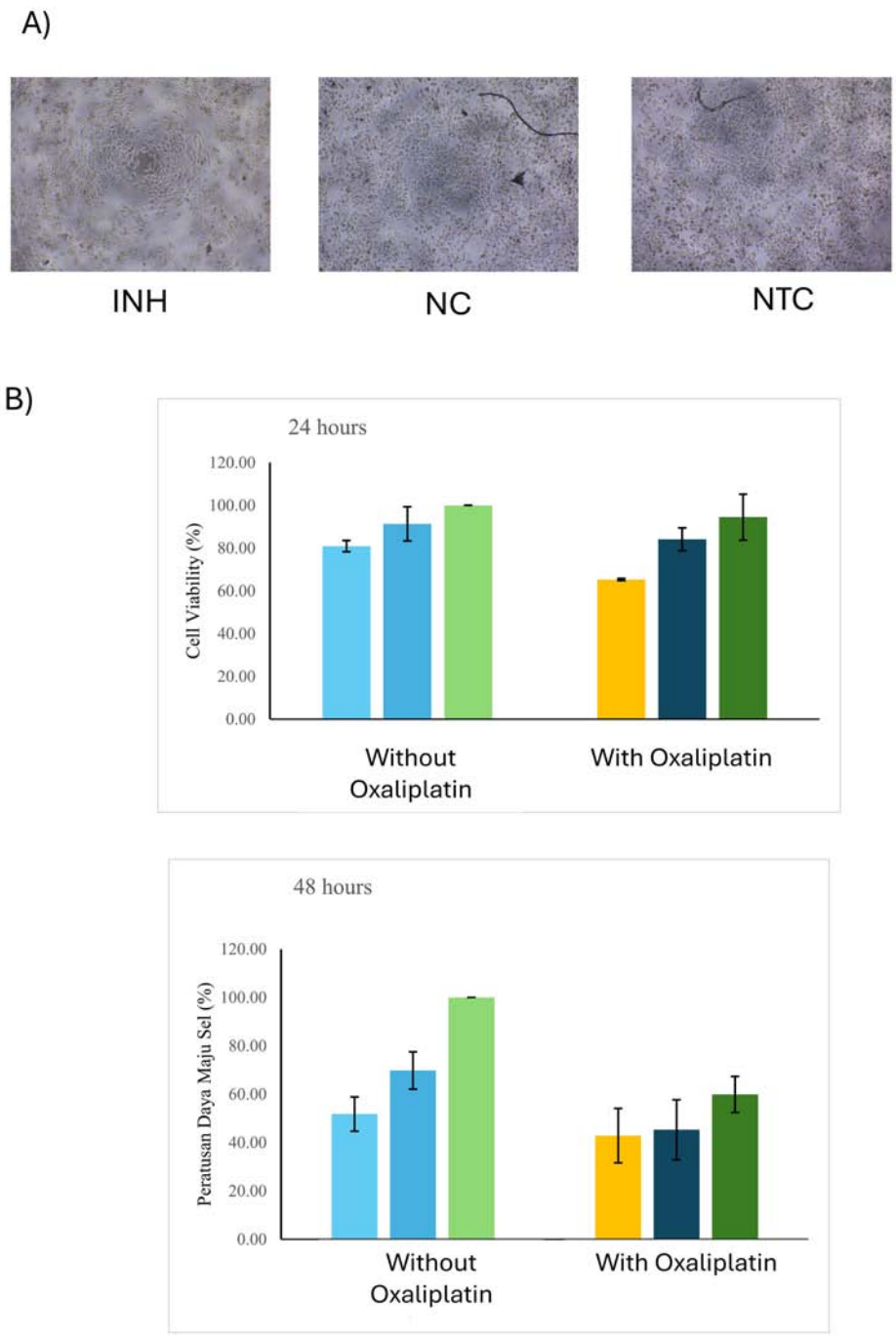

Figure 6: A) Microscopic pictures of HepG2 after treatment with oxaliplatin. **B**) Percentage of cell viability at 24 hours and 48 hours.

DISCUSSION

The expression of miRNAs can differ between different types of tissues and diseases. Our initial results show that miR-130b-3p was indeed upregulated in various cancers. This agrees with multiples studies that have previously reported the expression of miR130b-3p was upregulated. In hepatocellular carcinoma, a study by Liao *et al.* also showed that mir130b-3p was increased [26]. In fact, a study by Ma *et al*., showed that miR130b is also overexpressed in liver cancer stem cells [27]. An earlier study by Liu *et al*., also discovered that miR-130b is upregulated in the serum of liver cancer patients and can be potentially used as a diagnostic biomarker [28]. This is similar to our report where we showed that miR130b-3p can be found in circulating entities such as extracellular vesicles. In fact, some studies have even shown that miR-130b-3p has functional activities in exosomes released from cells. For example, a study by Yen *et al*.,

showed that exosomal -derived miR-130b-3p can promotes the tubular formation in oral cancer by targeting PTEN [29].

MiR130b-3p has been reported to target several downstream genes including PTEN [29, 30], HOXA5 [26] and SPIN90 [31]. Most of these targets will eventually lead to the pathogenesis of various cancers. For cancer-related pathways, a recent study by Yang *et al*., showed that miR-130b-3p regulated pancreatic cancer through the PI3K/AKT pathway [32]. Meanwhile in non-small cell lung cancer, it has been shown that miR-130b-3p can affect the TGF-b pathway [33]. Whereas in head and neck cancers, miR130b-3p regulated the MTORC1 pathway instead [34]. Our results indicated that the target genes of miR130b-3p could indeed affect multiple cancer signaling pathways and more in depths studies are needed especially in liver cancer.

Methylation is an epigenetic mechanism that can affect the expression of genes including microRNAs. There have been no in-depth studies evaluating the methylation profile of miR130b and cancer. One study by Ramalho-Carvalho *et al*., showed that the miR-130b~301b cluster was differentially methylated in prostate cancer cells [35]. A different study by Ahn *et al*., suggested that DNA methylation did not directly affect the expression of miR-130b-3p in breast cancer cells [31].

It is well known that miRNAs can act as sponges to other RNAs including lncRNAs. Based on our predictive analysis, miR130b-3p can bind to at least 12 lncRNAs, but we did not perform any further validation. A study by Chen *et al*., showed that miR130b can bind to LINC00857 in pancreatic cancer [36]. This study showed that the expression of LINC00857 was upregulated while the expression of miR130b was downregulated. Another study by Li *et al*., showcased that miR130b can bind to the lncRNA H19 and modulate keratinocyte differentiation [37]. A more recent study by Wang *et al*., showed that miR-130b can target the lncRNA MRPS30 in breast cancer cells [11]. This shows that the expression of miR130b is tissue or disease-dependent and involves myriads of factors.

There are several studies that have linked the expression of has-miR-130b-3p to drug resistance in several diseases. For instance, in a study by Miao *et al*., in 2017 showed that his miRNA mediated drug resistance involving Adriamycin in breast cancer cells [30]. The authors suggest that hsa-miR-130b-3p regulated the mechanism through the PI3K/AKT signaling pathway [30]. In relation to oxaliplatin, there are no studies to the best of our knowledge that has evaluated the effects of hsa-miR-130b-3p. Our initial reports did indeed show that the inhibition of this miRNA attenuated the effects of oxaliplatin in HepG2 cells.

CONCLUSION

Overall, this study has shown that hsa-miR-130b-3p is involved in HCC through multiple mechanisms such as binding to various target genes, lncRNAs and methylation regulation. Inhibiting this miRNA could further affect the physiological conditions of liver cancer cells. Therefore, while the results shown are promising, more in-depth studies are needed to fully understand the role of hsa-miR-130b-3p in HCC.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

THP contributed to data acquisition, formal analysis and initial draft. SFM contributed to funding acquisition, experimental design and final draft. NA contributed to data acquisition, formal analysis, experimental design and drafting of the manuscript.

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