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MiR-22 as a metabolic silencer and liver tumor suppressor

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A B S T R A C T

With obesity rate consistently increasing, a strong relationship between obesity and fatty liver disease has been discovered. More than 90% of bariatric surgery patients also have non-alcoholic fatty liver diseases (NAFLDs). NAFLD and non-alcoholic steatohepatitis (NASH), which are the hepatic manifestations of metabolic syndrome, can lead to liver carcinogenesis. Unfortunately, there is no effective medicine that can be used to treat NASH or liver cancer. Thus, it is critically important to understand the mechanism underlying the development of these diseases. Extensive evidence suggests that microRNA 22 (miR-22) can be a diagnostic marker for liver diseases as well as a treatment target. This review paper focuses on the roles of miR-22 in metabolism, steatosis, and liver carcinogenesis. Literature search is limited based on the publications included in the PubMed database in the recent 10 years.

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1. Introduction

MicroRNA 22 (miR-22) is highly conserved across vertebrate species and its expression is ubiquitously expressed in various organs.1–3 The miR-22 gene is located on chromosome 17p13, its cDNA catalyzed by RNA polymerase II is ~1.3 kb. In addition, its transcription start site lacks TATA box.4 Many studies have revealed that miR-22 is implicated in the development of various types of cancer including liver, colon, prostatic, breast cancer, gastric cancers, and many others. In general, miR-22 is considered as a metabolic silencer and a tumor-suppressor. However, its oncogenic effect has been documented as well. Furthermore, miR-22 has many biological functions including inflammatory and immune regulation; arterial smooth muscle cell proliferation and migration regulation; and cardiac and vascular remodeling.5–9 In this review paper, we summarize the role of miR-22 in liver disease development.

2. MiR-22 as a metabolic silencer

MiR-22 is an important regulator of dyslipidemia. It has been shown that miR-22 deficiency prevents high-fat diet (HFD)-induced dyslipidemia by inhibiting the expression of genes (sterol regulatory element binding protein-1 (Srebp-1), CC motif chemokine ligand 2 (Ccl2), interleukin 6 (Il-6), and interferon gamma (Ifng). Thus, miR-22 promotes lipogenesis and inflammation.10 MiR-22 along with miR-34a are up-regulated in the liver of diabetic db/db mice. miR-22 reduces the levels of E1A binding protein p300 (Ep300) as well as transcription factor 7 (Tcf7), and miR-34a decreases the protein level of its target gene Wnt Family Member 1 (Wnt1). Overexpression of miR-22 and miR-34a inhibits Wnt signaling, which leads to increased lipid accumulation in HepG2 cells.11

Fibroblast growth factor 21 (FGF21) is a master metabolic regulator that has a remarkable ability to reverse diabetes and obesity. In addition, FGF21 has regenerative capability and repairs injured tissue. Activation of FGF21 leads to AMPK and ERK1/2 activation. Given the role of FGF21 in metabolism and proliferation, its functions require regulation to avoid metabolism-driven overgrowth, which can be tumorigenic. A recent study has established the relationship between miR-22 and FGF21 and its receptor...
fibroblast growth factor receptor 1 (FGFR1) expression. The levels of miR-22 and FGFR21, FGFR1, as well as peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) were inversely correlated in human and mouse fatty livers, suggesting that hepatic miR-22 acts as a metabolic silencer. Further mechanistic analysis revealed that miR-22 directly targeted FGFR1. However, miR-22 decreased FGFR21 by reducing the occupancy of transcriptional factors peroxisome proliferator-activated receptor α (PPARα) and PGC1α to their binding motifs. Thus, miR-22 can be considered as a metabolic silencer by inhibiting the expression of FGFR21 and its receptor. The genes regulated by miR-22 to reduce metabolism are summarized in Table 1.

### 3. MiR-22 in hepatic steatosis and fibrosis

In consistency with the negative role of miR-22 in regulating hepatic lipid metabolism, miR-22 is increased in various drug-induced steatosis including drugs like valproate, doxycycline, cyclosporin A, and tamoxifen. miR-22 is a potential biomarker for drug-induced steatosis and can be used to predict the effect of a drug on steatosis development. Hepatic miR-22 overexpression also enhances diet and alcohol-induced steatosis. In contrast, reducing miR-22 level up-regulates hepatic FGFR21 and FGFR1, leading to AMPK and ERK1/2 activation, which effectively improve alcoholic steatosis in mouse models. Furthermore, miR-22 levels are inversely correlated with the bone morphogenetic protein 7 (BMP7) levels in human livers. BMP7 inhibits the progress of liver cirrhosis by inhibiting the expression of transforming growth factor beta 1 (TGF-β1), blocking the nuclear accumulation of SMAD family member 2/3 (Smad2/3), or increasing BMP7 levels in human liver biopsy samples. BMP7 also inhibits galectin-1 and 9, which are implicated in the progression and poor prognosis of patients with HCC. Galectin-9 is known as a marker of cancer progression and poor prognosis of patients with HCC.

A combination of serum miR-22 and miR-210, which distinguish F0 fibrosis from any fibrosis, can be noninvasive diagnostic biomarkers to detect the presence of liver fibrosis in children with cystic fibrosis. Furthermore, miR-22 levels are inversely correlated with the levels of liver fibrosis, portal hypertension, as well as sodium retention caused, possibly by upregulation of BMP7. Thus, increased miR-22 promotes liver cirrhosis through directly targeting BMP7. In consistency, microarray screening study showed that “mumu_circ_34116/miR-22-3P/BMP7” signal axis might be involved in the activation of hepatic stellated cells. Furthermore, transfection experiment validated that the expression of alpha-smooth muscle actin (α-SMA) is significantly elevated because of inhibitory expression of mumu_circ_34116.

However, miR-22 inhibits galectin-1 and 9, which are implicated in the development of hepatic fibrosis. Down-regulation of galectin-1 can improve liver fibrosis by reducing α-SMA, desmin, alamine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. Serum galectin-9 levels are positive correlation with liver fibrosis. Thus, the role of miR-22 in liver diseases can be complicated. Whether miR-22 via reducing galectins can treat hepatic fibrosis remains to be studied.

### 4. MiR-22 and viral hepatitis

Serum miR-22 and miR-1275 are up-regulated in hepatitis B virus (HBV) patients. The level of those miRNAs are positively correlated with the serum γ-glutamyl transpeptidase levels. In consistency, serum level of miR-22 and miR-122 are increased in chronic HBV patients. Additionally, their expression levels are positively associated with hepatitis B surface antigen (HBsAg) levels and ALT levels. Similarly, elevated circulating miR-22 is found in human immunodeficiency virus (HIV)/hepatitis C virus (HCV) patients and is involved in the etiology of liver injury in HIV patients. Further, elevated circulating miR-22 and miR-122 indicates viral replication and liver injury in HBV patients.

### 5. Long non-coding RNA (lncRNA) MiR22HG as a tumor suppressor for hepatocellular carcinoma (HCC)

Based on genome-wide lncRNA expression profiles in HCC tissues and paired adjacent non-tumor tissues, lncRNA NR_028502.1 located in 17p13.3, a chromosomal region that is frequently deleted or hypermethylated in liver cancer, is down-regulated in HCC. In consistency, serum level of miR-22 and miR-122 are increased in chronic HBV patients. MiR22HG overexpression inhibits proliferation, invasion, and metastasis in HCC cells. In part, lncRNA MiR22HG acts a tumor suppressor for HCC through deriving miR-22-3p to target high mobility group box 1 (HMGB1), thereby inactivating HMGB1 downstream pathways.

### 6. MiR-22 as a tumor suppressor

MiR-22 expression levels were analyzed in different types of cancer using information available from the TCGA Data Portal. The studies that have normal specimen number greater than 15 were included in the analysis. The data showed that in comparison with normal specimens, miR-22 levels were differentially expressed based on cancer types. In comparison with normal specimens, its level was reduced in HCC, breast invasive carcinoma, and lung squamous cell carcinoma (Fig. 1A and B).

We further analyzed the relationships between miR-22 levels and HCC clinical features. The data showed that the level of miR-22 was inversely associated with the depth of HCC invasion. T3 and T4 cancers had lower miR-22 level compared with T1 and T2 (Fig. 2A and E). In addition, HCC patients at stage III or IV had lower miR-22 level than those at stages I and II (Fig. 2B and E). Furthermore, miR-22 expression level was positively correlated with overall survival and disease-free survival (Fig. 2C–E). Thus, miR-22 can be considered as tumor suppressor for HCC.

It has been shown that low expression of miR-22 is associated with poor prognosis in hepatoma patients. In addition, reduced hepatic or serum miR-22 is shown in HBV-associated HCC patients. However, no significant difference of serum miR-22 levels was found between benign liver disease and non-HBV-related HCC patients. In consistency with our data analysis, miR-22 levels were negatively correlated with tumor size, lymph node metastasis, TNM

| Table 1 | MiR-22 as a metabolic silencer. |
|----------------|-------------------------------|
| Regulated genes | Function |Refs. |
| Sreb1, Cc2, Il-6, Ifng | Lack of miR-22 prohibits fat mass formation and dyslipidemia caused by a high-fat diet |10 |
| Ep300, Tcf7 | MiR-22 inhibits Wnt signaling leading to increased lipid accumulation in HepG2 cells |11 |
| FGFR1, FGFR2 | Increased hepatic miR-22 and reduced PGE2 are found in hepatic steatosis |12 |

Abbreviations: miR-22, microRNA 22; Sreb-1, sterol regulatory element binding protein-1; Cc2, CC motif chemokine ligand 2; Il-6, interleukin 6; Ifng, interferon gamma; Ep300, E1A binding protein p300; Tcf7, transcription factor 7; FGFR1, fibroblast growth factor receptor 1; FGFR2, fibroblast growth factor factor 2.

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stage, pathological type, differentiation grade, liver cirrhosis, serum alpha-fetoprotein (AFP) and HBV DNA copy number. Moreover, another study also shows that serum miR-22 and miR-199a-3p combined with AFP have a high accuracy in early detection of HCC in patients with chronic hepatitis C (Table 2).33

Fig. 1. MiR-22 expression level in different cancers. The miR-22 expression level (log2) was analyzed using TCGA Data Portal and data are shown as box plot (white box: normal specimens; gravy box: cancer specimens).

Fig. 2. The associations between miR-22 levels and HCC clinical features. The correlation between miR-22 expression level (log2) and (A) the depth of tumor invasion and (B) tumor stages. Kaplan-Meier curves showed the relationships between miR-22 levels and (C) overall survival and (D) disease-free survival. P values were calculated by the log-rank test. Clinical features and P values are summarized in (E).

Table 2
MiR-22 as a liver cancer diagnostic marker.

| Diagnostic indicator                                      | Disease                        | Refs.   |
|----------------------------------------------------------|--------------------------------|---------|
| Reduced expression of miR-22                             | Poor prognosis in hepatoma in patients | 31      |
| Reduced hepatic or serum miR-22                          | HBV-associated HCC patients.   | 32      |
| Serum miR-22 and miR-199a-3p in combination with AFP    | Early phase of HCC in patients with chronic HCV | 33      |

Abbreviations: miR, microRNA; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; AFP, alpha-fetoprotein.
7. The mechanism by which miR-22 acts as a tumor suppressor

Several mechanisms by which miR-22 acts as a liver cancer suppressor have been uncovered. miR-22 inhibits the development of HCC through directly targeting lncRNA NEAT1 and AKT serine/threonine kinase 2 (AKT2), which are overexpressed in human HCC specimens in comparison with adjacent normal tissue. Both NEAT1 and AKT2 are implicated in the development of HCC by increasing proliferation and invasion while inhibiting apoptosis in HCC cells.1,2

MiR-22 can also directly target the heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1), a potential diagnostic marker for HBV-related HCC.3 As an oncogene, HNRNPA1 promotes HBV-related HCC via the EGFR signaling pathway. Additionally, HNRNPA1 is negatively correlated with the overall survival of HCC patients.

MiR-22 is reduced in folate deficiency-conditioned HCC cell lines including SK-Hep1 and Mahlavu.4 MiR-22 overexpression reduces the number of spheres in both liver cancer Sk-Hep1 and Mahlavu (MDA-MB-453) cells, and the opposite is observed by inhibiting miR-22. It has been shown that reduced miR-22 causes folate deficiency-induced cancer stem-like phenotypes via increasing histone deacetylase 4 (HDAC4), zinc finger E-box binding homeobox 2 (ZEB2), and octamer-binding transcription factor 4 (OCT4), but decreasing paired related homeobox 1 (PRRX1).5

MiR-22 also silences galectin-1 and 9, which specifically bind to β-galactoside sugars. Galectin-1 is overexpressed in HCC and promotes HCC progression.6-8 The expression of miR-22 is negatively correlated with the expression of galectin-1. The expression of galectin-1 is increased in hepatic stellate cells (HSCs) isolated from HCC tissues. MiR-22 inhibits the HSC-induced T cell apoptosis and cytokine production promoted by HSC-derived galectin-1 in HCC.9 Moreover, elevated galectin-1 and low CD3 expression levels is associated with poor prognosis in HCC patients. Further, Galectin-9 is increased while miR-22 is decreased in human liver cancer tissues and cell lines. MiR-22 inhibits lymphocyte apoptosis and tumor cell proliferation in HCC cells via silencing galectin-9.10

MiR-22 can directly target cell cycle gene expression.11 Cyclin A2 (CCNA2) is a direct miR-22 target gene in both liver and colon cancer cells.12 MiR-22 overexpression as well as chemicals that induce miR-22 expression can reduce CCNA2 protein and increase the number of G0/G1 in human liver cancer Huh7 and colon cancer HCT116 cells.13

Silencing multiple protein deacetylases is another mechanism by which miR-22 has anti-cancer effects. HDAC1 is a novel miR-22 target recently uncovered by our group using colon cancer cells.14 In a miR-22-dependent manner, histone deacetylase (HDAC) inhibitors reduce HDAC1, HDAC4, and sirtuin 1 (SIRT1), which are highly expressed in the liver and colon cancer specimens. Upon miR-22 induction, reduced HDAC1, HDAC4, and SIRT1 occupied the transcriptional regulatory region of the retinoic acid receptor beta (RARβ) and nuclear receptor subfamily 4 group A member 1 (NURR77) genes leads to increased H3K9 acetylation of the RARβ and NURR77 genes. Therefore, miR-22-reduced protein deacetylases simultaneously induce NURR77 and RARβ expression, as well as, their nuclear export converting their transcriptional effect into apoptotic effect.15

Nuclear factor κB (NF-κB) regulates many biological processes including liver tumorigenesis.16 MiR-22 inhibits NF-κB activity through targeting NF-κB coactivator 1 (NCOA1).17 The mechanisms by which miR-22 functions as a HCC suppressor is summarized in Table 3 and Fig. 3.

It is interesting to note that the potential tumor-promoting effect of miR-22 has also been revealed in an animal model. MiR-22 inhibits the expression of methionine adenosyltransferase 1A (Mat1a) and methylenetetrahydrofolate reductase (Mthfr) in early preneoplastic livers of rats treated by 2-acetylaminofluorene. The reduced expression of Mat1a and Mthfr genes by miR-22 and miR-29b is a main driver to promote liver carcinogenesis in the studied model.18

8. The mechanisms by which the expression of miR-22 is regulated

Knockout hepatic nuclear respiratory factor 1 (Nrf1a) causes oncogenic activation of NF-E2-related factor 2 (Nrf2) and leads to the development of NASH and hepatoma. Thus, Nrf1a functions as a dominant tumor suppressor. It has been shown that both Nrf1α and Nrf2 regulate miR-22 expression via binding to the antioxidant response element (ARE) site of the miR-22 promoter.19

There are several chemicals that can induce the expression of miR-22 including catalpol, an iridoid glucoside. Catalpol induces miR-22 and reduces cell proliferation, invasion, and migration. Catalpol also increases apoptotic rates and G0/G1 phase of Huh7 and HCLMM2 cells. Catalpol exerts anti-tumor effects through up-regulating miR-22-3p, which reduces the metastasis associated 1 family member 3 (MTA3) expression by directly targeting MTA3.20 MiR-22 is induced in human liver cancer Huh7 cells treated with sodium butyrate21,22 Sodium butyrate treatment or forced miR-22 overexpression increases the ROS production and reduces SIRT1 expression. Down-regulation of miR-22 counteracts the effects of butyrate in Huh7 cells including the induction of apoptosis via ROS production, cytochrome c release, and activation of caspase-3. Furthermore, anti-miR-22 also reverses the inhibition of cell growth and proliferation mediated by sodium butyrate.23

In addition to butyrate, other short-chain fatty acids (SCFAs) that have histone deacetylase (HDAC) inhibitory property such as propionate and valerate as well as synthetic HDAC inhibitor suberanilohydroxamic acid (SAHA) can also induce miR-22 as demonstrated using colon cancer cells.24 In contrast, SCFAs that lack HDAC inhibitory effect such as formate and acetate do not have an effect in inducing miR-22.25 Additionally, retinoic acid (RA), which is produced by butyrate-induced aldehyde dehydrogenase 1 family member A1(ALDH1A1), also induces miR-22. Furthermore, when HDAC inhibitors are used in combination with RA, the induction of miR-22 reaches to a higher level than a single chemical treatment. Such induction is mediated via retinoic acid receptor β (RARβ) binding to a direct repeat 5 (DR5) motif found in the regulatory region of the miR-22.26

Bile acids via its receptor farnesoid X receptor (FXR) induces miR-22 by direct binding to an invert repeat 1 (IR-1) motif located in the regulatory region of the miR-22.27 Both endogenous FXR ligand chenodeoxycholic acid and synthetic FXR ligand GW4064 increase miR-22 in Huh7 liver and HCT116 colon cells.28 In addition, semi-synthetic bile acid, obeticholic acid, which is in clinical trials to treat NASH, also increases miR-22 expression in Huh7 liver cells.29 Furthermore, by inducing FGF21 signaling, miR-22 inhibitors can improve the effect of obeticholic acid in improving insulin sensitivity as demonstrated in Western diet-induced obese mice.30 The liver is a testosterone-responsive organ. Testosterone regulates liver metabolism, inhibits hepatic immune responses and even promotes liver carcinogenesis.31-33 Testosterone treatment of female mice induces hepatic miR-22, miR-690, miR-122, let-7A, miR-30D, and let-7D. An androgen response element (ARE) has been found in the miR-122 promoter, but not in the other five induced miRNAs. Therefore, the mechanism by which testosterone induces miR-22 remains to be uncovered. The induction of miR-22 leads to reduced expression of estrogen receptor α and aromatase, thus resulting in estrogen signal inhibition.34

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The chemicals that have anti-cancer effects and can increase the expression level of miR-22 are summarized in Table 4 and Fig. 3. It is interesting to note that most of those miR-22 inducers have metabolic stimulating effects, and yet miR-22 functions as a metabolic silencer.

9. Conclusion

The level of miR-22 rises in hepatic steatosis and declines in liver cancer. Thus, miR-22 inhibition can treat NAFLD, and yet miR-22 inducers or mimics can be useful treating liver cancer. Indeed, the cancer treatment effects of miR-22 inducers includes catalpol, butyrate, retinoic acid, and HDAC inhibitors have been revealed.

Metabolism driven by FGF21 leads to AMPK and ERK1/2 activation thereby supporting growth and cell proliferation. Surprisingly, metabolism enhancers such as bile acids, testosterone, and retinoic acid induce the expression of miR-22, which silences FGF21 and its receptor. The simultaneous induction of miR-22 as well as FGF21 signaling likely maintain FGF21 homeostasis and restrict persistent ERK1/2 activation. In other words, concomitant induction of FGF21 and miR-22 can be a way to maintain FGF21 homeostasis and thus insulin sensitivity. However, the reduction of

Table 3
The mechanisms by which miR-22 acts as a liver cancer suppressor.

| Cancer models                  | Target genes | Function of the target genes                        | Refs. |
|--------------------------------|--------------|-----------------------------------------------------|-------|
| Human HCC                      | NEAT1, AKT2  | Promote proliferation and invasion, inhibit Apoptosis | 54-56 |
| HBV-related HCC                | HNRNPA1, HDAC4, ZEB2, OCT4, PRKX1 | Regulates EGF receptor signaling, Regulate gene expression | 37,38 |
| Folate deficiency-conditioned HCC cells | Galectin-1, Galectin-9 | Promote T cell apoptosis and cytokine production | 39-41 |
| Human HCC                      | CCNA2        | Regulates cell cycle                                  | 42    |
| Huh7 and HCT116 cells          | HDAC1, HDAC4, SIRT1, NUR77, RARβ | Epigenetic and transcriptional regulation leading to apoptosis of cancer cell | 43 |
| HCT16 and DLD-1 cell           | NCOA1, NF-κB | Transcriptional regulation                            | 44    |
| Huh7 cell                      |              |                                                      |       |

Abbreviations: miR-22, microRNA 22; HCC, hepatocellular carcinoma; AKT2, AKT serine/threonine kinase 2; HBV, hepatitis B virus; HNRNPA1, heterogeneous nuclear Ribonucleoprotein A1; HDAC, histone deacetylase; ZEB2, Zinc finger E-box binding homeobox 2; OCT4, octamer-binding transcription factor 4; PRKX1, decreased paired related homeobox 1; CCNA2, cyclin A2; SIRT1, siruin 1; NUR77, nuclear receptor subfamily 4 group A member 1; RARβ, retinoic acid receptor beta; NCOA1, nuclear receptor coactivator 1; NF-κB, nuclear factor kappa B.

Table 4
MiR-22 inducers.

| MiR-22 inducers              | Refs. |
|------------------------------|-------|
| Catalpol                     | 47    |
| Bile acids, Chenodeoxycholic acid, GW4064, Obeticholic acid | 12,42 |
| Retinoic acid                | 43    |
| HDAC inhibitors: butyrate, propionate, valerate, suberanilohydroxamic acid | 42,43,48 |
| Testosterone                 | 55    |

Abbreviations: miR-22, microRNA 22; HDAC, histone deacetylase.
miR-22 may improve the efficacy of AMPK activators by increasing hepatic FGFR2. The expression level of miR-22 changes in a dynamic way as liver disease progresses. To use miR-22 as a drug target, the status of miR-22 needs to be monitored. To target delivery of miR-22 inducer or silencer should be considered to avoid unwanted effects.

Author's contributions

L. Wang reviewed literature and wrote the article. Y.-S. Wang contributed in data analysis and writing. E.M. contributed in data analysis. W.-C. Chang contributed in data analysis and writing. Y.-J. Wan reviewed literature and wrote the article.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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