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The Role of miRNA-21 in the Metastasis of Hepatocellular Carcinoma as a Therapeutic Target

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ABSTRACT

Hepatocellular carcinoma (HCC) is a crucial health concern worldwide, representing a leading cause of cancer-related mortality and the most common form of primary liver cancer. The aggressive nature of HCC is mainly due to its high tendency for invasion and metastasis, processes regulated by a complex network of genetic and molecular pathways. Among the critical regulators of these processes is microRNA-21 (miR-21), a small non-coding RNA that implicated in various oncogenic activities. This review provides a comprehensive analysis of the role of miR-21 in promoting HCC metastasis, with a particular focus on its interaction with key signaling pathways, including the PTEN/PI3K/AKT, PDCD4/AP-1, RECK/MMP, and TIMP-3 axes. By targeting tumor suppressors, miR-21 facilitates epithelial-to-mesenchymal transition (EMT), invasion, and metastasis of HCC cells. Understanding the molecular mechanisms regulated by miR-21 not only sheds light on the pathogenesis of HCC but also highlights potential therapeutic targets for combating this aggressive cancer.

Keywords: Hepatocellular carcinoma; Cancer; Epigenetics; miR-21

INTRODUCTION

Cancer is a collection of illnesses distinguished by the unregulated proliferation and division of abnormal cells with the capability of invading surrounding tissues and spreading via the lymphatic system and bloodstream to other body organs, a process known as metastasis[1]. This uncontrolled growth arises when cells bypass the normal regulatory mechanisms that govern cell division and death, leading to the formation of tumors. Genetic mutations and epigenetic alterations often transform normal cells into cancerous cells. These changes can result from various factors, including environmental carcinogens, radiation, and viral infections[2-4]. Several types of primary liver cancer exist, such as intrahepatic cholangiocarcinoma, hepatocellular carcinoma, hepatoblastoma, and fibrolamellar carcinoma, depending on the cancer originates[5-8.]

HCC is the most common liver cancer caused by genetic changes in liver cells (hepatocytes). In 2018, it accounted for the third-highest number of cancer-related deaths globally, with over 780,000 fatalities recorded. Annually, around 800,000 new HCC cases

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are diagnosed [9]. One of the main characteristics of this disease is its high rate of progression compared to other cancers, while its survival rate remains exceptionally poor[10, 11].

Hepatocellular carcinoma is characterized by three types of clinical symptoms, which can occur in 90 to 95 percent of people with the disease: upper right quadrant abdominal pain, palpable abdominal mass, and weight loss. Hepatomegaly (liver enlargement) and abnormalities in liver consistency are also evident. Other common symptoms include weakness, fatigue, indigestion, anorexia, shortness of breath, vomiting, splenomegaly (enlarged spleen), fever, and jaundice. In the advanced and terminal stages, patients typically present with ascites, peripheral edema, and hepatic encephalopathy[12].

Various risk factors contribute to the development of HCC. One of these is chronic hepatitis B infection, which exerts its pathogenic effects through HBV-associated immune pathogenesis[13]. Similarly, HCV can induce HCC by causing chromosomal alterations in fibrotic liver cells, leading to tumor formation. HCV also promotes DNA damage during the process of cirrhosis and sustains chronic inflammation. This inflammatory state can dysregulate the TGF-β signaling pathway, shifting its role from inhibiting tumorigenesis to promoting fibrosis and the development of cancerous hepatocytes[14].

Furthermore, consuming alcoholic beverages serves as a risk factor for HCC. Alcohol's metabolites are responsible for toxic effects on the liver, affecting intracellular signaling pathways and gene expression, which leads to fat accumulation, fibrogenesis, and the activation of both innate and adaptive immunity[15]. Fungal infections, such as those caused by Aspergillus flavus, can lead to the formation of toxic compounds in the human body. Aflatoxin B1, one of the most potent tumorigenic substances, is capable of inducing hepatocellular carcinoma (HCC) by inhibiting cell growth and altering immune system function[16]. Furthermore, recent research indicates that nonalcoholic fatty liver disease (NAFLD) accounts for 2.38–13% of HCC cases, primarily by inducing liver cirrhosis [17]. Additionally, obesity is another significant risk factor affecting HCC development.

Additionally, obesity is another significant risk factor affecting HCC development[18,19].

The occurrence of fatty liver disease in industrialized countries is closely related to a person's diet. Diets high in vegetables, white meat, and fish can lower the risk of liver cancer, whereas diets high in red meat products increase the risk[20, 21]. In addition to diet, there is a robust and significant link between diabetes mellitus and HCC, wherein hyperinsulinemia, hyperglycemia, activation of insulin-like growth factor pathways, and insulin resistance have been implicated in HCC emergence[22]. Furthermore, smoking can increase inflammatory and pro-inflammatory products such as TNF-alpha, IL-1, and IL-6, which are able to damage liver cells. Smoking significantly suppresses the P53 protein, a tumor suppressor factor[23], demonstrating that older individuals are more susceptible to developing HCC than younger individuals[24].

Beyond these established risk factors, increasing attention has been directed toward epigenetic regulators, particularly microRNAs (miRNAs). MiRNAs are small, non-coding RNAs that post-transcriptionally regulate gene expression by binding to target messenger RNAs. They are essential for a wide range of biological processes, including cell proliferation, differentiation, apoptosis, and stress responses. Dysregulation of specific miRNAs has been strongly implicated in cancer development and progression, where they can act as either oncogenes or tumor suppressors.

Among these, miR-21 has emerged as one of the most consistently upregulated oncogenic miRNAs in HCC. miR-21 contributes to the aggressive phenotype of HCC by targeting multiple tumor suppressor genes and driving processes such as epithelial-to-mesenchymal transition (EMT), invasion, and metastasis. Given the lack of effective treatment options and the high mortality rate of HCC, understanding the molecular mechanisms of miR-21 offers new opportunities for therapeutic intervention. Therefore, this review aims to comprehensively examine the role of miR-21 in invasion, migration, and metastasis of HCC through its effects on key cellular pathways.

MicroRNA-21

Cellular RNAs can be broadly classified into messenger RNAs (mRNAs), which encode proteins, and non-coding RNAs, which do not. Among non-coding RNAs, miRNAs represent a well-studied class of small, endogenous RNAs that regulate gene expression at the post-transcriptional level. MiRNAs typically bind to complementary sequences in the 3' untranslated region (UTR) of target mRNAs, leading either to mRNA degradation or translational repression[25]. Through this mechanism, miRNAs regulate approximately 30% of human genes, influencing diverse biological pathways. They play essential roles in tumorigenesis, metabolic reprogramming, and altered energy metabolism in rapidly dividing tumor cells[26,27]. Accordingly, dysregulation of miRNAs can contribute to uncontrolled cell proliferation and cancer development, while normal miRNA function is also crucial for maintaining cellular homeostasis [28-31].

Among these, microRNA-21 (miR-21) is one of the most extensively studied oncogenic miRNAs. The *MIR21* gene, located on chromosome 17q23.2 in humans, encodes miR-21, which is highly conserved across species. MiR-21 regulates multiple cellular processes, including differentiation, apoptosis, and proliferation, by binding to the 3' UTRs of specific mRNAs. Beyond its role in normal physiology, miR-21 exhibits anti-apoptotic properties, enhances cell survival under stress, and modulates immune responses. It also contributes to developmental processes by influencing tissue differentiation and organogenesis [32].

However, aberrant upregulation of miR-21 is strongly associated with a variety of diseases, particularly cancer, where it functions as an oncogene by downregulating multiple tumor suppressor genes[32,33]. Dysregulated expression of miR-21 has been reported in HCC, as well as in breast, lung, colorectal cancers, and multiple myeloma. In these malignancies, miR-21 promotes cancer progression by regulating pathways involved in cell cycle control, apoptosis resistance, invasion, and migration. Notable targets of miR-21 include Phosphatase and Tensin Homolog (PTEN), Tropomyosin 1 (TPM1), Programmed Cell Death Protein 4 (PDCD4), B-cell lymphoma 2 (BCL2), and various Matrix Metalloproteinases (MMPs)[34-36].

In the context of HCC, genomic studies have consistently identified miR-21 overexpression as a driver of tumor progression[37, 38]. By inhibiting tumor suppressors such as PDCD4 and KLF5, miR-21 facilitates EMT, invasion, and metastatic dissemination of HCC cells[39]. Collectively, these findings highlight miR-21 as a central regulator of hepatocarcinogenesis and an important candidate for therapeutic targeting.

Invasion, migration, and metastasis of cancer cells

Despite advances in cancer diagnosis and therapy, metastasis remains the primary cause of cancer-related mortality worldwide[40-42]. Metastasis is defined as the dissemination of tumor cells from the primary site to distant organs, where they establish secondary tumors. This process underlies nearly 90% of cancer deaths and represents one of the most malignant hallmarks of cancer[43]. Targeting metastasis remains a major clinical challenge because it depends on complex interactions between tumor cells and their surrounding microenvironment [44].

In HCC, local invasion, the initial step of metastasis, is observed in a considerable proportion of patients [45, 46]. Once HCC cells acquire invasive capacity, they can infiltrate adjacent tissues, enter the bloodstream or lymphatic system, and subsequently colonize distant organs. Figure 1 illustrates both the major risk factors contributing to HCC development and the central role of miR-21 in facilitating invasion and metastasis. To reduce the morbidity and mortality associated with HCC, it is crucial to identify and inhibit the molecular drivers of invasion and metastatic spread. The following subsections describe the mechanisms by which miR-21 promotes these processes through regulation of multiple signaling pathways.

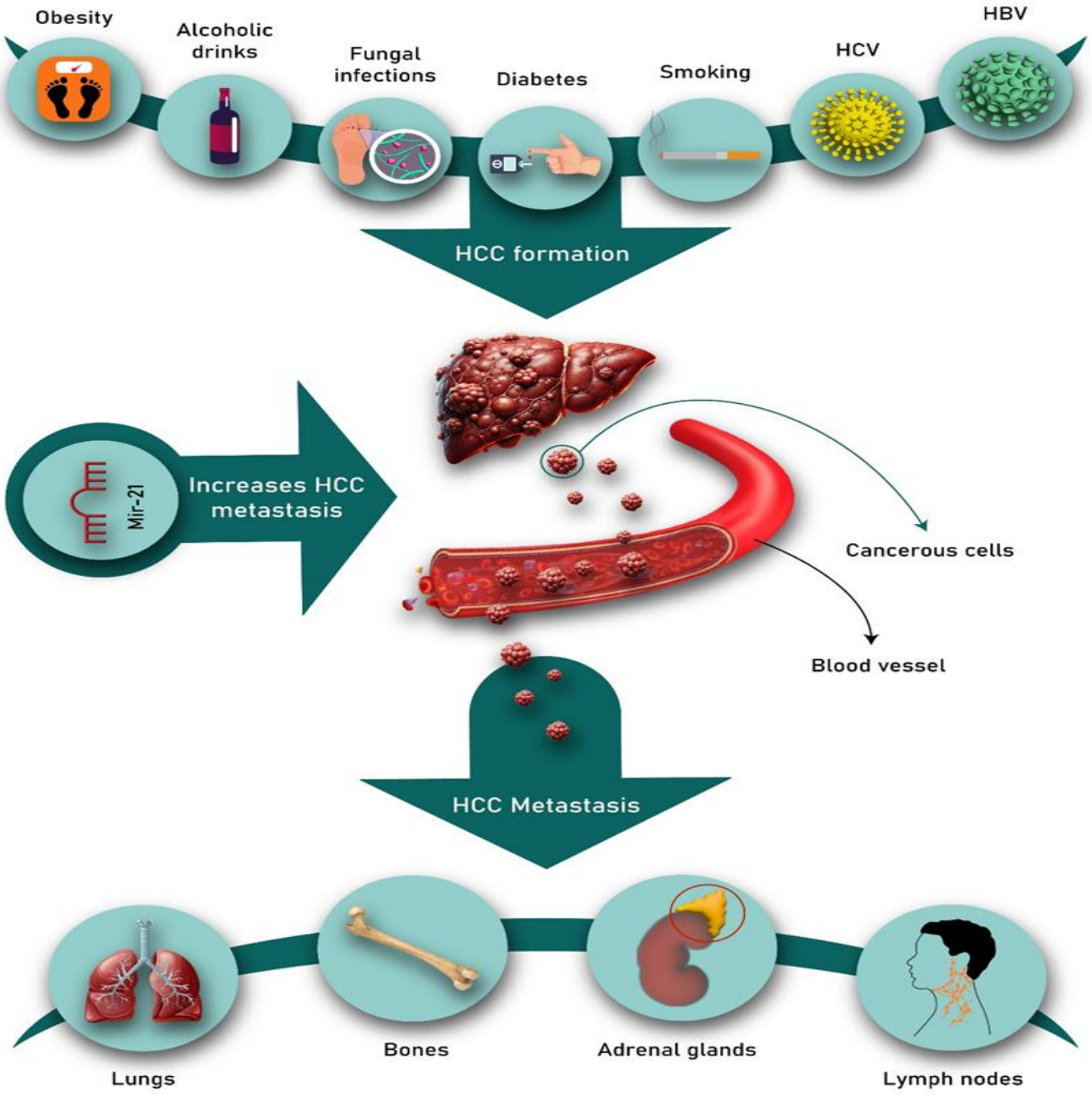

Figure 1. Several factors contribute to HCC formation, including obesity, drinking alcoholic beverages, fungal infections, diabetes, smoking, HCV, and HBV. Besides the potential of HCC to spread out in the body, miR-21 acts as a contributor to cancerous cell migration through blood vessels, ultimately having them spread to other body organs, encompassing lungs, bones, adrenal glands, and lymph nodes, forming secondary tumors.

The role of MiR-21/PDCD4/c-jun/AP-1/MMP-2, 9-axis in HCC metastasis

To understand the role of miR-21 in HCC metastasis, it is first necessary to consider the contribution of MMPs. These proteolytic enzymes degrade components of the extracellular matrix (ECM), thereby facilitating tumor cell invasion into surrounding tissues and entry into the bloodstream[47,48]. MMPs are also involved in angiogenesis, apoptosis, and inflammation[49,50]. Among the 25 known MMPs, gelatinases (MMP-2 and MMP-9) are of particular importance. They degrade type IV collagen, fibronectin, and other ECM proteins, promoting tumor invasion[51]. Excessive activity of MMP-2 and MMP-9 disrupts normal cellular pathways, accelerates tumor progression, and supports angiogenesis through the induction of pro-angiogenic factors such as tumor necrosis factor-alpha (TNF-α) and vascular endothelial growth factor (VEGF)[52, 53].

The expression of MMP-2 and MMP-9 is tightly regulated by intracellular signaling pathways. One critical regulator is Programmed Cell Death Protein 4 (PDCD4), a tumor suppressor that inhibits the activity of the transcription factor AP-1. Under normal conditions, PDCD4 prevents AP-1–mediated upregulation of MMPs, thereby limiting invasion and metastasis. However, when miR-21 is overexpressed, it directly targets and suppresses PDCD4, removing this inhibitory control [54]. The result is increased AP-1 activity, which in turn elevates the transcription of MMP-2 and MMP-9, driving invasion and angiogenesis.

Beyond this linear regulation, a feedback loop amplifies the oncogenic effects of miR-21. Activated AP-1 can further enhance miR-21 expression, creating a self-reinforcing cycle in which miR-21 suppresses PDCD4, AP-1 activity rises, and MMP expression continues to increase[34,55]. This positive feedback loop accelerates tumor progression, angiogenesis, and metastasis in HCC.

Taken together, the miR-21/PDCD4/AP-1/MMP axis plays a pivotal role in promoting HCC invasion and metastasis. Importantly, this pathway exemplifies how miR-21 amplifies oncogenic signaling by targeting tumor suppressors, thereby creating a cycle of sustained MMP activation and aggressive tumor behavior.

The KLF5-inhibitory effect of miR-21 on HCC metastasis

Kruppel-like transcription factors (KLFs) are a family of transcriptional regulators with diverse roles in cancer. KLF5, in particular, has been reported to function as a tumor suppressor in certain contexts. It regulates cell growth, cell cycle progression, and angiogenesis, and its overexpression has been associated with improved prognosis in HCC[56]. Importantly, miR-21 directly targets KLF5 by binding to its 3'-UTR, leading to reduced expression and loss of tumor-suppressive activity. Wang et al.[39] demonstrated that miR-21 overexpression in HCC tissues and cell lines enhanced the invasive potential of cancer cells through KLF5 inhibition. Conversely, restoring KLF5 expression counteracted miR-21's pro-invasive effects, highlighting the central role of the miR-21/KLF5 axis in suppressing or promoting HCC progression.

However, other studies suggest that KLF5 may act as a tumor promoter in HCC. An et al. [57] reported that higher KLF5 levels correlated with poorer clinical outcomes in patients. Mechanistically, KLF5 has been shown to activate the PI3K/AKT/Snail pathway and induce EMT, a process in which epithelial cells acquire mesenchymal characteristics, thereby increasing their invasive and migratory potential[57-59]. KLF5 also enhances the expression of mesenchymal markers (Vimentin, N-Cadherin, Snail) while reducing epithelial markers (E-cadherin), and it can stimulate MMP-2 and MMP-9 expression, further promoting invasion. Intriguingly, Wang et al.[39] also reported evidence that miR-21 may inhibit tumor growth by downregulating KLF5, suggesting a context-dependent dual role.

Taken together, these findings indicate that miR-21 exerts complex effects on HCC by modulating KLF5. While some data support KLF5 as a tumor suppressor inhibited by miR-21, other studies implicate KLF5 as an oncogenic factor. This duality highlights the need for further research to clarify the precise contribution of the miR-21/KLF5 axis in HCC progression.

The role of miR-21/PTEN/PI3K/AKT/EMT pathway in HCC metastasis

One of the most vital signaling pathways hyper-activated in highly proliferative cancers is the Phosphatidylinositol 3-kinase/Activated Protein Kinase B (PI3K/AKT) pathway. It normally regulates EMT, which is principally responsible for the transient transformation of epithelial cells into mesenchymal phenotypes[60]. The transition from an epithelial to a mesenchymal phenotype can be mediated by AKT, which has been shown to enhance the expression of Snail, a mesenchymal marker that contributes to metastasis[61, 62]. When PTEN—one of the most important tumor suppressor genes [65]—is mutated or inactivated, as commonly occurs in various cancers, AKT becomes constitutively activated [63, 64]. This activation leads to enhanced cell survival and proliferation, thereby driving tumor progression. AKT activation also enhances glucose uptake and metabolism, which is crucial for meeting the high energy demands of rapidly proliferating cancer cells [63, 66].

PTEN normally exerts its tumor-suppressive function by negatively regulating PI3K, a kinase that promotes cell cycle progression and prevents apoptosis, thereby supporting tumor growth[67,68]. Consequently, following partial or complete inactivation of PTEN, higher levels of activated PI3K are detectable in various cancers, leading to increased tumor cell proliferation and spread [61].

MiR-21, a well-known regulator of PTEN, attenuates its function, inducing AKT activation and enhanced EMT. It also increases PI3K activity, resulting in tumor growth. Thus, miR-21 promotes the metastasis of HCC cells through the PI3K/AKT/PTEN axis[61]. Additional signaling pathways have been associated with miR-21 in the induction of cancer cell metastasis, such as the RHOB/PI3K/AKT/NF-κB/MMP pathway. Several studies have directly examined the association between miR-21 and PTEN in HCC. Meng et al. first demonstrated that inhibition of miR-21 in HCC cells restored PTEN expression, leading to decreased proliferation, migration, and invasion[69]. More recently, He et al. reported that in sorafenib-resistant HCC cells, miR-21 was upregulated, resulting in reduced PTEN levels and activated AKT signaling; inhibition of miR-21 re-sensitized these cells to sorafenib by restoring autophagy through the PTEN/AKT pathway[70]. In addition, exosomal miR-21 has been shown to contribute to tumor progression by transferring oncogenic signals between cells. For example, Cao et al. found that exosomal miR-21 downregulated PTEN and its pseudogene PTENp1, increased p-AKT, and enhanced the proliferation and migration of HCC cells[71]. Collectively, these findings support the critical role of the miR-21/PTEN/PI3K/AKT axis in promoting EMT and metastasis, and further highlight its potential as a therapeutic target in HCC.

The role of miR-21/RHOB/PI3K/AKT/NF-κB/MMP pathway in HCC metastasis

RhoB, known as the Ras homolog gene family member B, belongs to the Rho family of small GTPases, which are essential regulators of a variety of cellular processes, including cell morphology, adhesion, and migration. It regulates actin organization and vesicle transport[72]. The overexpression of RhoB inhibits tumor formation and assists in metastasis prevention by repressing the Ras/PI3K/AKT pathway, which plays a key role in cell migration[73]. This pathway induces Nuclear Factor Kappa B (NF-κB) activation, contributing to hepatocyte survival and protection against cell death. Continuous NF-κB activation is strongly correlated with unfavorable prognostic features and properties of stemness in HCC[74]. Notably, NF-κB activation induces MMP expression, further enhancing invasion and metastasis[75,76]. This mechanism complements the previously described role of MMPs in HCC progression[75, 76]. PI3K/AKT can also indirectly induce MMP production through NF-κB at a post-transcriptional level; however, this pathway is inhibited upon RhoB overexpression[73]. Intriguingly, RhoB was identified by Connolly et al. in 2010 as a target of miR-21 [77]. Consequently, the miR-21-mediated decrease in RhoB expression enhances various in vitro cellular traits associated with increased metastatic capability [73, 77, 78].

Several studies beyond the current discussion have directly explored the functional interplay between miR-21 and RhoB across different biological contexts. In cancer cell lines (Huh-7, HepG2, and MDA-MB-231), overexpression of miR-21 promotes

metastatic traits, such as enhanced invasion and migration, by directly targeting RhoB, thereby suppressing its tumor-suppressive functions[79]. In endothelial cells, miR-21 has been shown to inhibit angiogenic processes: it reduces RhoB expression and impairs migration and tubulogenesis, acting via a conserved binding site within the RhoB 3'UTR[80]. Additionally, in models of pulmonary hypertension, miR-21 negatively regulates RhoB and Rho-kinase activity; mice lacking miR-21 display elevated RhoB levels and pronounced pulmonary hypertensive manifestation[81]. Collectively, these findings demonstrate that miR-21 promotes HCC metastasis and invasion by suppressing RhoB activation. However, the hSulf-1/MAPK/ERK/ZEB1/EMT and PTEN/MAPK/ERK pathways are other well-characterized axes through which miR-21 contributes to HCC progression and metastasis.

The role of miR-21/h-sulf-1/MAPK/ERK/ZEB1/EMT and miR-21/PTEN/MAPK/ERK pathways in HCC metastasis

Heparin-degrading Endosulfatase 1 (hSulf-1) negatively regulates growth factor signaling by desulfating and hydrolyzing the sulfate ester bonds of cell surface heparan sulfate proteoglycans (HSPGs), which are one of the main components of the extracellular matrix (ECM). N-acetyl glucosamine residues of HSPG coated on the cell surface must be sulfated to trigger the heparin-binding growth factor signaling. This desulfation interrupts the binding ability of heparin-binding growth factors to their specific receptors, thereby inhibiting cell proliferation and migration. Various cancers, including ovarian, breast, and HCC, show low levels of hSulf-1, which is involved in invasion, tumor growth, angiogenesis, and carcinogenesis[82-84]. Interestingly, miR-21 expression levels show an inverse association with hSulf-1. The miR-21-mediated decrease in hSulf-1 leads to increased binding of heparin-binding growth factors, such as extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK), to their receptors, ultimately promoting cell proliferation and migration[84]. The MAPK/ERK pathway plays a decisive role in HCC progression by regulating cell differentiation, survival, proliferation, and processes that are essential for tumor growth and metastasis[85,86]. Following its indirect activation by miR-21 (via the downregulation of hSulf-1), this pathway promotes the epithelial-mesenchymal transition (EMT) process by enhancing the expression of zinc finger E-box binding homeobox 1 (ZEB1), a transcription factor that functions as an oncogene[87]. Consequently, translation of mesenchymal markers increases, leading to enhanced invasion of tumor cells. Moreover, Bao et al. demonstrated that miR-21 regulates HCC cellular proliferation, invasion, migration, and tumor extension by suppressing the expression of PTEN in HCC cells. This represents a primary mechanism by which the MAPK/ERK pathway is activated to facilitate the spread of cancerous cells[84]. Therefore, the invasion and spread of HCC are attributed to miR-21 through the abovementioned mechanisms and pathways. Consequently, targeting these pathways brings them into focus as potential therapeutic strategies for HCC. Additionally, other pathways have been identified that contribute to HCC metastasis, including the RECK/MMP pathway, which is regulated by miR-21.

The role of miR-21/RECK/MMP pathway in HCC metastasis

The reversion-inducing cysteine-rich protein with Kazal motifs (RECK) is a glycoprotein located on the cellular membrane. This glycoprotein is produced less in cancerous cells than in normal ones. By inhibiting RECK, miR-21 indirectly elevates MMP expression and activity, thereby supporting ECM degradation and metastatic dissemination[88,89]. Studies have identified RECK as a direct target of miR-21. For instance, Zhou et al. demonstrated that miR-21, in addition to inhibiting PDCD4 and PTEN, can promote HCC cell metastasis by suppressing RECK, thereby increasing MMP activity and expression[88]. MMPs subsequently enable the breakdown of the ECM, facilitating HCC cell metastasis. The mechanisms described above are not the only means by which miR-21 induces metastasis in HCC. Tissue inhibitor of metalloproteinases 3 (TIMP-3) is another protein through which miR-21 exerts its oncogenic effects in HCC patients.

The TIMP-3-inhibitory effect of miR-21 on HCC metastasis

As previously mentioned, MMP enzymes, especially MMP-2 and MMP-9, exert metastasis-promoting activities. Researchers have identified two types of endogenous regulators or inhibitors of MMP enzymes: general and specific inhibitors. The general inhibitor of these enzymes is alpha-2-macroglobulin, which inhibits these enzymes in serum and body fluids. There is another group called Tissue Inhibitors of Matrix Metalloproteinases (TIMPs), which are more specific. All MMPs, particularly MMP-9 and MMP-2, are tightly regulated by TIMPs [90, 91]. TIMP-1, 2, and 4 are secreted proteins, while TIMP-3 is anchored to the extracellular matrix[48]. The high level of production and secretion of TIMPs reduces tumor cell metastasis through MMP inhibition, thereby preventing the excessive degradation of the ECM [92]. Besides inhibiting MMP enzymes, TIMP-3 also prevents Vascular Endothelial Growth Factor (VEGF) from binding to Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2), which consequently inhibits angiogenesis and, ultimately, cancer cell metastasis[93]. In 2020, Li et al. demonstrated for the first time that TIMP-3 is a direct target of miR-21, and that this interaction promotes the migration and subsequent metastasis of HCC cells[94]**.** Therefore, targeting the miR-21/TIMP-3 axis may represent a promising therapeutic approach for limiting HCC progression and metastasis. However, further studies are needed to fully elucidate the relationship between miR-21 and TIMP-3.

Considering the findings reviewed in this study, miR-21's ability to target multiple tumor suppressor proteins—as discussed throughout this review—underscores its pivotal role in orchestrating the molecular events that lead to HCC progression (Figure 2). Therapeutic strategies aimed at inhibiting miR-21 or restoring the expression of these tumor suppressor proteins could potentially disrupt these pathological processes, thereby reducing the metastatic potential of HCC (Table 1).

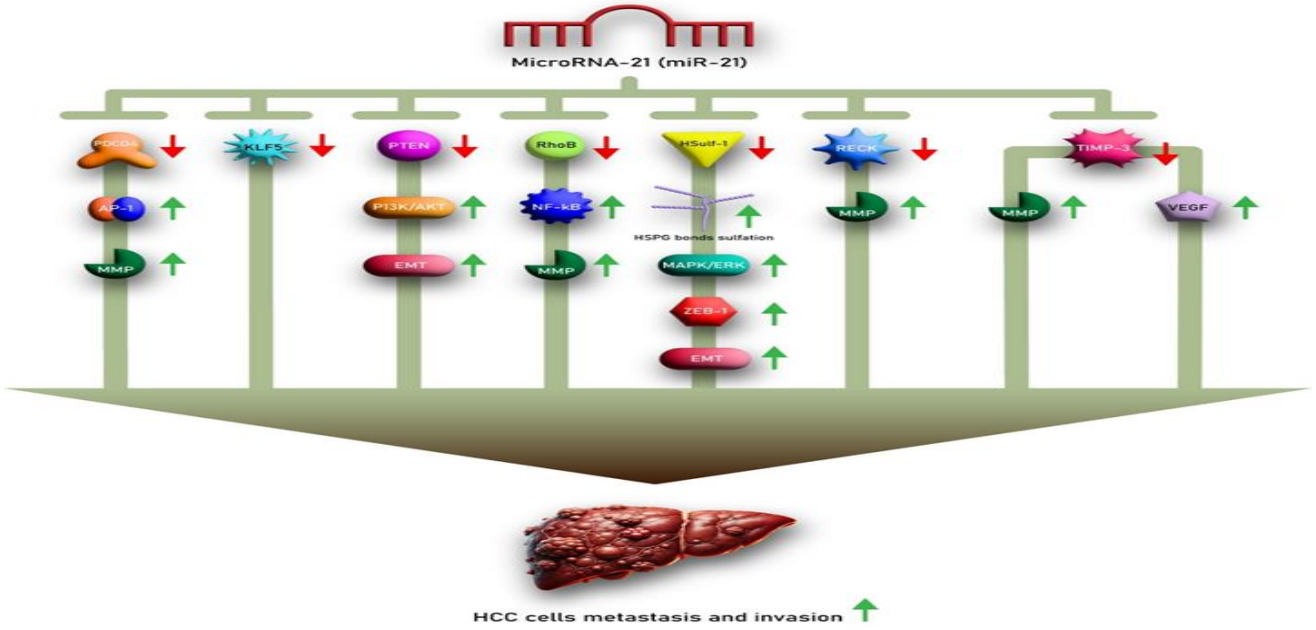

Figure 2. miR-21-associated signaling pathways enrolled in HCC metastasis. A) The inhibitory impact of miR-21 on PDCD4 causes AP-1 activation, and MMP arises as a result. B) Also, KLF5 reduces once miR-21 increases. C) MiR-21 lessens the amount of activated PTEN, further promoting the P13K/AKT pathway, leading to EMT activation. D) RhoB acts as a tumor suppressor reduced by the activity of miR-21, causing NF-κB activation and MMP enhancement. E) the reduction in hSulf-1 following the miR-21 enhancement causes lower desulfation and higher sulfation of HSPG bonds, resulting in MAPK/ERK activation, which mediates ZEB-1 activation and eventually EMT promotion. F) Reck decreases under the impact of miR-21, causing escalated levels of MMPs. G) Lower TIMP-3 amounts after being inhibited by miR-21 heighten MMPs and VEGF. A, B, C, D, E, F, and G processes ultimately lead to increased HCC metastasis.

Table 1. miR-21 direct targets in HCC and downstream consequences

Target (miR-21 direct)	Immediate downstream / pathway nodes	Primary phenotypic effects in HCC	Evidences	References
PDCD4	↓ PDCD4 → ↑ AP-1 (c-Jun) → ↑ MMP-2, MMP-9	Invasion, angiogenesis, metastasis	HCC tissues & cell lines; AP-1↔miR-21 feedback loop	(34, 54, 55)
KLF5	↓ KLF5; context-dependent effects on PI3K/AKT/Snail, MMP-2/9	Invasion/migration; context may vary	HCC tissues & cell lines; mixed tumor-suppressive vs oncogenic reports	(39, 57, 59)
PTEN	↓ PTEN → ↑ PI3K/AKT → ↑ EMT; autophagy suppression; exosomal transfer	EMT, proliferation, invasion/migration; sorafenib resistance	HCC cell lines & tissues; sorafenib-resistant models; exosomal miR-21	(61, 69-71)
RhoB	↓ RhoB → ↑ PI3K/AKT → ↑ NF-κB → ↑ MMP-2/9	Invasion, migration; pro-metastatic traits	HCC cell lines; supportive endothelial/in vivo context for RhoB regulation	(73, 77, 80, 81)
hSulf-1	↓ hSulf-1 → ↑ MAPK/ERK → ↑ ZEB1 → ↑ EMT	Proliferation, migration, EMT	HCC models (cellular and in vivo)	(82-84, 86)
RECK	↓ RECK → ↑ MMP-14/MMP-9/MMP-2/MT1-MMP	ECM degradation, invasion/migration; prognostic implications	HCC cell studies; pathway schematic	(88, 89)
TIMP-3	↓ TIMP-3 → ↑ MMP activity; ↑ VEGF–VEGFR-2 signaling	ECM degradation, angiogenesis, metastasis	HCC cell studies; first report of miR-21→TIMP-3 in 2020	(93, 94)

Therapeutic Implications of Targeting miR-21

MiR-21 represents a promising therapeutic target in HCC because of its central role in silencing tumor suppressors (e.g., PTEN, PDCD4, TIMP-3) and promoting invasion, migration, and metastasis. Preclinical studies using antisense oligonucleotides (anti-miR-21) have shown robust suppression of HCC growth in vitro and in vivo, with increased apoptosis, reduced clonogenicity, and impaired migration[95]. Locked nucleic acid (LNA)–modified inhibitors, which exhibit high nuclease resistance and binding affinity, further enhance miR-21 knockdown efficiency[96]. Similar strategies targeting other oncogenic miRNAs, such as miR-221, have produced strong anti-tumor effects and survival benefits in HCC models[97], supporting the clinical feasibility of oligonucleotide-based therapy.

Efficient delivery remains a major challenge. Systemic administration of chemically modified antisense oligos can achieve high liver accumulation, but tumor-selective targeting is needed to reduce off-target effects [97]. Nanocarrier systems, including lipid nanoparticles, polymeric micelles, and exosome-based vehicles, have been developed to improve stability, circulation time, and tumor uptake[98]. These carriers can be engineered to release their miR-21 inhibitors in response to tumor-specific cues (e.g., acidic pH or high glutathione levels), minimizing systemic toxicity. Co-delivery approaches, demonstrated in other cancers, use sequential release of miR-21 inhibitors followed by chemotherapy to maximize therapeutic synergy [99].

Emerging technologies such as CRISPR/Cas systems offer the possibility of permanently disrupting miR-21 biogenesis, although these methods remain at an early stage and require careful safety evaluation[8]. Small-molecule modulators of miRNA processing may also provide indirect ways to downregulate miR-21[32]. Overall, combining direct miR-21 inhibition with targeted delivery and conventional therapies—such as kinase inhibitors or immune checkpoint blockade—may provide a precision medicine strategy to control HCC progression and metastasis. Further work should focus on optimizing delivery vehicles, validating long-term safety, and conducting early-phase clinical trials to translate these preclinical advances into effective patient therapies. miR-21 is widely expressed in normal tissues and participates in physiological processes such as wound healing, fibrosis, and immune regulation; therefore, its systemic inhibition carries the risk of off-target effects, including impaired tissue repair, altered immune responses, and hepatotoxicity. Moreover, partial complementarity of antisense oligonucleotides to other miRNAs or mRNAs may trigger unintended gene silencing, complicating interpretation of therapeutic outcomes. Adaptive resistance is another concern, as tumor cells may compensate for miR-21 inhibition by upregulating other oncogenic miRNAs. These issues highlight the

importance of developing tumor-selective delivery systems, conducting detailed toxicology studies, and designing combination therapies that mitigate escape mechanisms. Only through addressing these challenges can miR-21 inhibition be translated from a promising concept into a safe and effective treatment for HCC[100].

CONCLUSION

MiR-21 has emerged as a pivotal factor in the progression of HCC, influencing multiple signaling pathways that drive tumor invasion, migration, and metastasis. By targeting critical tumor suppressor proteins such as PDCD4, PTEN, KLF5, RhoB, RECK, and TIMP-3, miR-21 facilitates the activation of cell growth-inducing factors and the EMT, thereby promoting the aggressive phenotype characteristic of HCC. The intricate regulatory network orchestrated by miR-21 underscores its significance as a biomarker for HCC prognosis and potential therapeutic target. The insights gained from this review emphasize the need for continued research into miR-21's role in HCC, particularly in the context of developing targeted therapies that can effectively disrupt its oncogenic functions. Such therapeutic strategies could significantly improve clinical outcomes by inhibiting the metastatic spread of HCC and enhancing the efficacy of existing treatments. As our understanding of miR-21 and its associated pathways deepens, there is potential to translate these findings into clinical applications, offering new hope for patients with this challenging and deadly disease.

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CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

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