Journal of Cancer Biomoleculars and Therapeutics

ETERNO PRESS

Review

The Multifaceted Role of miR-18b in Cancer: Exploring Oncogenic and Tumor-Suppressive Functions

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Article history

Received: 28 May 2024
Revised: 30 June 2024
Accepted: 1 July 2024
Published online: 4 July 2024

Keywords

miR-18b
Cancer
Oncogene
Tumor suppressor
Biomarker

Abstract

Cancer continues to pose a major global health challenge due to its high mortality rates and increasing incidence. MicroRNAs (miRNAs), which are small non-coding RNAs regulating gene expression at the post-transcriptional level, are pivotal in the development of cancer, serving either as oncogenes or tumor suppressors. miR-18b has become involved in a number of cancers and has been shown to perform both tumor-suppressive and carcinogenic activities. This review examines the biogenesis, molecular mechanisms, and functional roles of miR-18b across several cancers, including breast cancer, lung cancer, colorectal cancer, gastric cancer, and other malignancies. MiR-18b influences treatment resistance, metastasis, and cancer advancement by regulating vital pathways and interacting with circular and long non-coding RNAs. These findings emphasize the importance of miR-18b in developing cancer treatment approaches by highlighting its possible roles as a therapeutic target and diagnostic biomarker.

1. Introduction

Because of its high death rates and rising prevalence, cancer remains a major worldwide health concern [1]. Even with advancements in research on cancer, early detection, and treatment, it imposes a heavy societal and economic burden [2]. Researchers are now concentrating on finding new molecular targets for treatment and developing unique biomarkers for early diagnosis and prognosis [3]. Non-coding RNAs (ncRNAs) have become important epigenetic players in the initiation and spread of cancer. These ncRNAs include microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) [4].

Small, non-coding RNA molecules known as microRNAs (miRNAs) typically have 19–25 nucleotides and control post-transcriptional gene regulation. They are essential for several biological functions, including metabolism, apoptosis, cell division, and growth {Nemeth, 2024 #1011}[5]. Because miRNAs have diverse roles in carcinogenesis, acting as either tumor suppressors or oncogenes, they have drawn a lot of attention in the field of cancer research [6]. Recent studies have highlighted the pivotal role of microRNAs in vascular dysfunction associated with conditions such as Preeclampsia [7]. Furthermore, the promising therapeutic potential of microRNAs in clinical trials underscores their emerging importance in therapeutic strategies [8]. Therefore, when miRNAs are not working properly, they can harm several biological pathways. This can cause cells to divide without control, stop apoptosis, make new blood vessels, and spread to other parts of the body [9]. Furthermore, miRNAs have the potential to prospect as prognostic and diagnostic biomarkers due to their stability in body fluids, providing non-invasive ways to track the course of a disease and its response to treatment [10].

LncRNAs have a crucial impact on controlling transcription and other biological processes. They are over 200 nucleotides long and do not encode proteins [11]. Circular RNAs, characterized by their unique circular stability and structure, act as miRNA sponges in gene regulation and contribute to the progression of cancer [12]. By contributing as tumor suppressors or oncogenes, their dysregulation may be a factor in cancer [13].

MiR-18b has become an important performer among the several miRNAs investigated in oncology because of its diverse involvement in a range of human malignancies [14-16]. Early research revealed that the expression of miR-18b differed between tumors and nearby normal tissues, indicating that miR-18b may have a function in the development of cancer [17]. Additional investigation showed that miR-18b affects several signaling pathways, which in turn affect tumor development, metastasis, and treatment resistance [18].

The fact that miR-18b has dual roles emphasizes both its potential as a therapeutic target and its intricate regulatory involvement in the biology of cancer. Understanding the multifaceted role of miR-18b in cancer, particularly its impact on key signaling pathways, treatment resistance, and metastasis, is crucial.

This review delves into the biogenesis, molecular mechanisms, and functional roles of miR-18b across various cancers, including breast, lung, colorectal, and gastric cancers, among others. The insights gained from these findings underscore the significance of miR-18b in advancing cancer treatment strategies, highlighting its potential as both a therapeutic target and a diagnostic biomarker.

2. Basics of miRNA-18b

2.1 The Molecular Properties and Biogenesis of miR-18b

Animal cells frequently produce microRNAs as polycistronic initial transcripts, which then undergo processing into several distinct mature miRNAs. Specifically, the X chromosome harbors the miR-18b gene as a component of the miR-106a-363 cluster, comprising six distinct miRNAs [19,20]. In the nucleus, RNA polymerase II first transcribes the miR-18b gene as primary miRNAs, or pri-miRNAs. The Drosha-DGCR8 complex processes pri-miR-18b to produce pre-miR-18b, a precursor hairpin structure [21]. Following its export via Exportin-5 to the cytoplasm, this precursor is further broken by the enzyme Dicer to create the mature miR-18b molecule (Figure 1) [22].

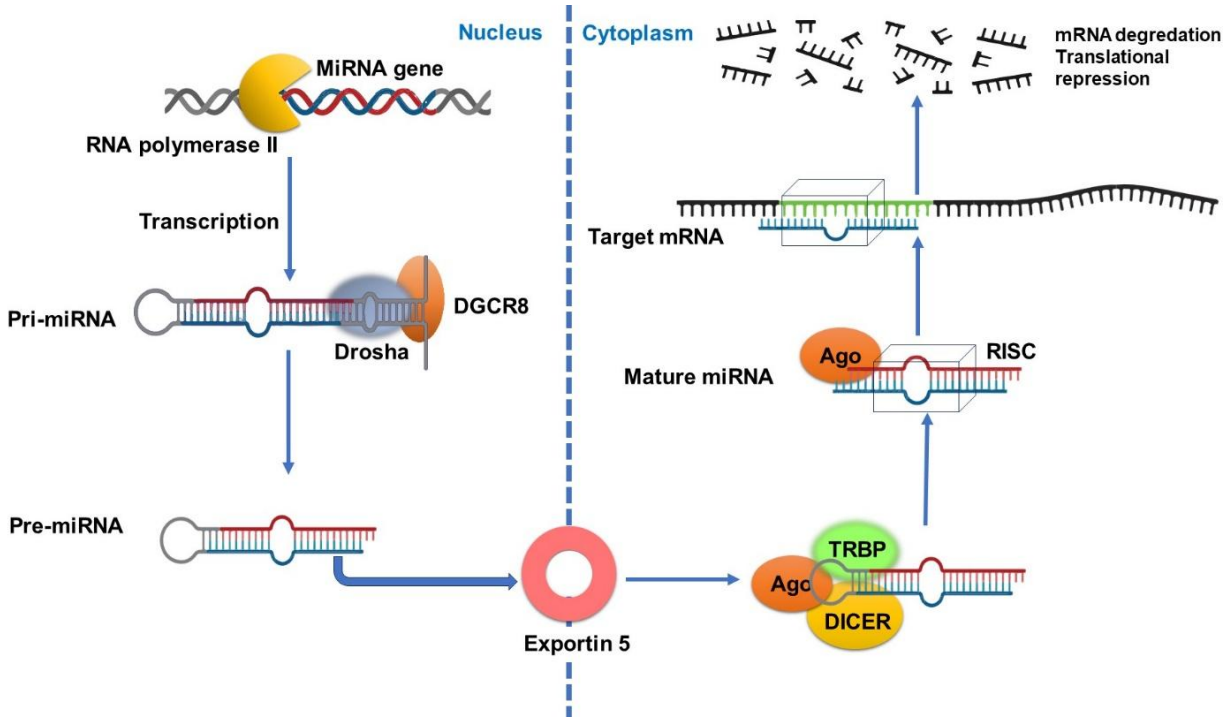

Figure 1. The process of miRNA biogenesis. Pre-miRNAs are produced after RNAPII encodes miRNA genes to pri-miRNAs, which are then produced whenever Drosha cleaves pri-miRNAs. Exportin 5 carries pre-miRNAs to the cytoplasm and nucleus, and Dicer converts them into matured miRNAs. Recombinant miRNAs and AGO2 produce RISCs, which are essential for regulating the expression of particular genes.

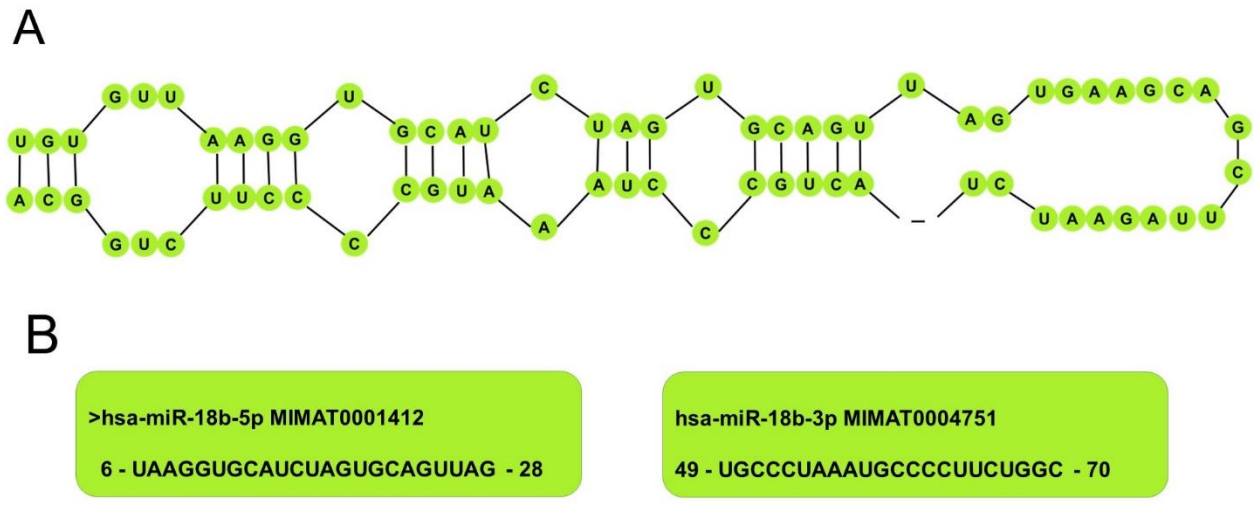

Figure 2. The mature sequences are derived from different arms of the precursor hairpin structure, with miR-18b-5p originating from the 5' arm and miR-18b-3p from the 3' arm. A. Structure of the miR-18b family sequence. B. It has two mature sequences, hsa-miR-18b-5p (MIMAT0001412, miR-18b-5p) and hsa-miR-18b-3p (MIMAT0004751, miR-18b-3p).

MiR-18b-3p and miR-18b-5p are 22 and 23 nucleotides long, respectively, when they are mature. Its unique sequence and secondary structure facilitate its ability to recognize and bind to targets [18]. Interestingly, the "seed sequence" of miR-18b—which normally extends from nucleotides 2 to 8 from its 5' end—is essential for target mRNA binding and recognition [23].

The opposing arms of the pre-miR-18b stem-loop structure give rise to the mature miRNAs miR-18b-5p and miR-18b-3p. The stability and biological role of these miRNAs vary. The miR-18b hairpin is the source of both the "guide strand" miR-18b-5p and the "passenger strand" miR-18b-3p. According to deep sequencing data, miR-18b-5p is more common than miR-18b-3p (Figure 2).

MiR-18b biogenesis is evaluated by a variety of cellular factors. For example, mutations or modifications in the Drosha or Dicer complex components can have an impact on miR-18b maturation [24]. Furthermore, extrinsic stimuli such as cellular stress or specific signaling pathways can influence miR-18b expression and maturation, highlighting the complex regulatory network that controls its biogenesis [25].

2.2 The Physiological Function of miR-18b in Cancer

Several investigations have demonstrated the important function of miR-18b in the malignant features of different types of cancer. It has been assessed that overexpression of miR-18b inhibits the growth, glycolysis, invasion, migration, and epithelial-to-mesenchymal transition of melanoma cells in vitro while upregulating apoptosis and decreasing the growth of tumor in vivo [18,26].

miR-18b plays a multifaceted and pivotal role in the progression of various cancers by modulating key signaling pathways. In breast cancer, it affects the ERα and p53/MDM2/AKT pathways [27], while in colorectal and gastric cancers, it influences cell cycle regulators and the PI3K/AKT pathway, respectively [15,28]. miR-18b also plays roles in hepatocellular carcinoma through HBV-related pathways, in lung cancer by correlating with tumor size and stage [29], and in melanoma by modulating the MDM2-p53 and glycolysis pathways [30]. In nasopharyngeal carcinoma, it promotes cell proliferation via the PI3K/AKT/C-Jun pathways [31]. These diverse roles make miR-18b a potential therapeutic target and biomarker in cancer.

MiR-18b has been proven to be an oncogene in CRC, affecting migration, proliferation, and cell cycle control [15]. According to Murakami et al., in hepatocellular carcinoma (HCC), miR-18b overexpression stimulates cell proliferation and suppresses cell adhesion [32]. Furthermore, it was shown by Fonseca-Sánchez et al. that miR-18b downregulation inhibits the migration of breast cancer cells in vitro. These results point to miR-18b's potential as a therapeutic target for a variety of malignancies by indicating that its biological roles may be tissue-specific [20].

Numerous targets of miR-18b have been found, such as trinucleotide repeat-containing 6B (TNRC6B) in HCC, cyclin-dependent kinase inhibitor 2B (CDKN2B) in colorectal cancer, and hypoxia-inducible factor 1α (HIF1α) and MDM2 in melanoma [23]. MiR-18b is linked to a poor prognosis in cases of ER-α-negative and HER2-negative breast cancer, as it negatively affects ER-α signaling in breast cancer [33]. Additionally, elevated expressions of miR-18b in the blood have been suggested as possible indicators of breast cancer [34].

Depending on the type of cancer and its environment, miR-18b can play two different functions in the disease progression: oncogene and tumor suppressor. It has been demonstrated to stimulate the growth of colorectal cancer cells while suppressing the growth of melanoma cells [14,15]. Furthermore, miR-18b affects breast cancer cell migration and is connected to the adherence of cells in hepatocellular carcinoma [20,32]. The broad-spectrum roles of miR-18b underscore its role as a beneficial target for a range of cancer types (Table 1) (Figure 3).

Table 1: Overview of miR-18b Involvement in Various Cancer Types

Type of Cancer	Target Gene	Tumor Suppressor (TS) or Oncogene (OG)	Signaling Pathway Involved	Function in Cancer	Sample Type	Ref.
Breast Cancer (BC)	ERα	OG	ERα signaling	Downregulates ERα, inhibiting estrogen-stimulated cell growth	Cell lines	[35]
	NLRP7, OLFM3, KLK3, POSTN, KIR3DL3, CEACAM5CRX, SEMG1, MAGED4B	OG	Tumor growth, cell proliferation, anoikis, apoptosis, angiogenesis, invasion, and metastasis pathways	Upregulate in BC cells and promotes migration and metastasis	Cell lines	[36]
	p53, MDM2, AKT	OG	Cell cycle control and apoptosis via pAKT/MDM2 pathways	HBXIP promotes growth by downregulating p53 via pAKT/MDM2 and miR-18b/MDM2 pathways	Cell lines	[27]
	TCEAL7	OG	NF-κB pathway	Promotes invasion, EMT, and metastasis by targeting TCEAL7, emphasizing role in tumor microenvironment and intercellular communication	Cell lines and mouse xenograft model	[37]

	ERα	OG	ERα signaling	Highly expressed in ERα-negative tissues, linked to aggressive subtypes and poor prognosis	human breast cancer sample/Tissue	[38]
	-	-	-	Identified as a circulating biomarker	Plasma and Tissue	[39]
	-	-	-	Part of a four-miRNA signature to predict survival and tumor relapse in TNBC patients	serum samples	[40]
	-	OG	-	Correlates with high inflammation in ERα-negative tumors, introducing a role in the tumor microenvironment and immune response	Tissue	[41]
	-	OG	-	Identified among six miRNAs for breast cancer subtype stratification, improving personalized treatment strategies	Tissue	[42]
Colorectal cancer (CRC)	-	TS	-	Sensitizes cells to metformin by affecting glycolysis, involvement in metabolic regulation	Cell line	[43]
	CDKN2B	OG	Cell cycle	Promotes tumor development by targeting and inhibiting CDKN2B, enhances cell proliferation and migration	Tissue and Cell line	[15]
	-	OG	-	Elevated in cancerous tissues, potentially contributing to tumor formation	Tissue	[44]
	-	OG	-	Hypermethylated in sporadic cases, subject to epigenetic regulation	Tissue	[45]
	-	OG	-	Decreased during treatment, linked to absence of lymph node metastasis post-treatment	Plasma	[46]
	-	OG	-	Consistently altered during cancer progression, crucial in several signaling pathways	Tissue	[47]
	-	OG	-	Altered expression in tumor tissues, potential to predict distant metastasis-free survival	Tissue	[48]
	-	OG	-	Increased in exosomes of plasma from patients with CRC, potential biomarker for early detection	Plasma and Tissue	[49]
	-	TS	-	Downregulated pre-treatment, potential biomarker for monitoring tumor response to CRT	Plasma	[50]
Gastric Cancer (GC)	KLF6	OG	-	Acts as an oncogene, increased significantly in cancer tissues, promotes cell proliferation and invasion	Cell line and Tissue	[51]
	Rb, PTEN	OG	PI3K/AKT signaling pathway	Markedly overexpressed in gastric cancer tissues, reduced expression of Rb and PTEN, potential diagnostic marker	Tissue	[28]
	-	OG	-	Exhibited increased methylation in gastric tumors, highlighting role in cancer progression	Tissue	[45]
	-	OG	-	Identified genetic links with SNPs in miRNA clusters, suggesting genetic variations contribute to higher risk of gastric cancer	Tissue	[52]
	FOXO3	OG	miR-18b/ FOXO3/ P53 pathway	High FOXO3 expression related to poor prognosis, affects cancer progression and immune cell infiltration	Tissue	[53]
Hepatocellular Carcinoma (HCC)	-	OG		Altered expression during acute and chronic HBV infection, suggesting role in HBV-related HCC progression	Cell line	[29]
	NUSAP1	TS	-	HBx suppresses miR-18b expression through CpG island methylation, promoting liver cancer development	Bioinformatic analysis on Cell line, tissue sample and mice models	[54]
	MACC1	OG	-	Upregulated miR-18b-5p suppressed target mRNAs, contributing to pathogenesis of HBV-associated HCC	Tissue	[55]
	-	TS	-	A new biomarker for chronic liver disorders and hepatocellular carcinoma that is decreased in either tumor and non-tumor tissues	Tissue	[56]
	-	OG	-	Higher expression in poorly differentiated HCC, related to increased cellular proliferation and lower prognosis	Tissue	[57]
Lung Cancer (LC)	-	OG	-	Upregulated in various mutational types, involved in molecular pathways of lung adenocarcinoma	Tissue	[58]

	-	TS	-	Downregulated in NSCLC, correlated with larger tumor sizes, smoking status, advanced tumor stages, higher proliferation indices	Tissue	[59]
	-	TS	-	Downregulated in serum of NSCLC patients, potential utility in early detection and prognosis prediction	Serum samples	[60]
Melanoma	MDM2-p53	TS	MDM2-p53 signaling pathway	Acts as a tumor suppressor via modulating the MDM2-p53 signaling pathway, downregulation associated with melanoma progression	Nevi and melanoma samples, melanoma cell lines, normal melanocytes	[14]
	HIF-1alpha	TS	Glycolysis/HIF1a pathway	Inhibits growth by targeting HIF-1alpha, reduces glycolysis in melanoma cell lines	Melanoma cell lines	[61]
	IGF1	TS	IGF signaling pathway	Downregulation cisplatin sensitized cells in Melanoma via adjusting the miR-18b/IGF1 axis	Melanoma tissues, cisplatin-resistant melanoma cells	[62]
	MDM2-p53	TS	MDM2-p53 signaling pathway	Regulates the MDM2-p53 pathway, crucial for cell cycle control and apoptosis	Melanoma samples	[30]
Nasopharyngeal Carcinoma (NPC)	CTGF	OG	PI3K/AKT/C-Jun pathways	Elevates miR-18b expression by promoting cell proliferation via C-Mycand PI3K/AKT/C-Jun pathways	Tissue	[31]
	-	OG	Cell cycle signaling	Regulates genes participated in cancer pathways and cell cycle signaling	Tissue	[63]
Ovarian Cancer (OC)	PTEN	OG	PI3K/AKT signaling pathway	Increased in ovarian cancer tissues and cells, enhances the migration and invasion of cancer cells via targeting PTEN	Tissue, cell lines	[64]
	-	OG	-	Possible diagnostic and prognostic biomarkers	Tissue	[65]
	-	OG	-	Identified as a biomarker for metastasis in endometrioid endometrial cancer	Tissue	[66]
	-	OG	Inflammatory pathways and metabolic complications	Differentially expressed in non-obese women with PCOS compared to controls, linked to inflammatory pathways and metabolic complications	Tissue	[67]
Esophageal Squamous Cell Carcinoma (ESCC)	-	OG	-	Regulates various signaling pathways and target genes affecting cell proliferation, invasion, migration, and fatty acid metabolism; implicated in radioresistance	ESCC cell line	[68]
	FBP1	OG	The metabolism of fatty acids signaling pathway	Loss regulates the metabolism of fatty acids to stimulate invasion, migration, and proliferation	ESCC cell line	[69]
	-	OG		Increased plasma levels observed in ESCC patients but not statistically significant as a diagnostic biomarker	Plasma samples	[70]
Prostate Cancer (PC)	-	OG	-	potential diagnostic and prognostic marker	Serum samples	[71]
	-	OG	-	Regulation by DNA methylation, potential therapeutic target	Tissue	[72]
Thyroid Carcinoma (TC)	NUSAP1	OG	-	Associated with shorter overall survival, lymph node metastasis, and higher immune checkpoint inhibitor scores	Tissue	[73]
Basal Cell Carcinoma (BCC)	-	OG	MAPK/ERK and Hedgehog	Involved in pathways including MAPK/ERK and Hedgehog	Tissue	[74]
Mantle Cell Lymphoma (MCL)	-	OG	-	Overexpression predicts high risk and poor prognosis, reduces proliferation rate of MCL cells	Tissue	[75]
Osteosarcoma (OS)	PHF2	OG	-	Promotes cellular proliferation and metastasis via inhibiting tumor suppressor gene PHF2	Tissues and cell lines	[76]
Canine Mammary Tumor (CMT)	ESR1	OG	-	Associated with decreased ESR1 expression and increased tumor cell proliferation	Tissue	[77]
Head and Neck Squamous Cell Carcinoma (HNSCC)	-	TS	-	Downregulation suggests a role in inhibiting tumorigenesis	Tissue	[78]

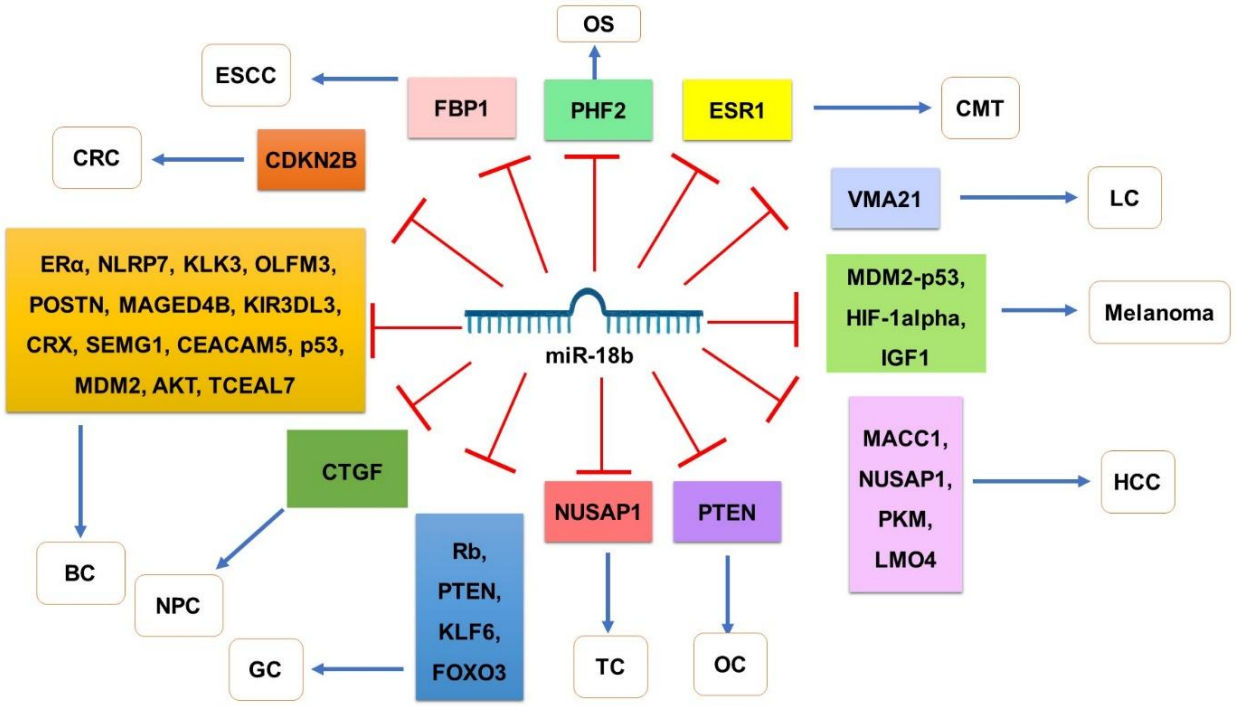

Figure 3. A thorough depiction of the relationships between miR-18b and its principal target genes in various cancers.

2.2.1 Breast Cancer (BC)

Globally, breast cancer is the greatest frequent cancer in women [79,80]. Currently available treatment options include targeted therapy, radiation therapy, chemotherapy, endocrine therapy, and surgical removal [81]. Breast tumors are remain the principal cause of cancer-related death in women, in spite of increasing prognoses [79].

In cell culture studies, Leivonen et al. found that miR-18b downregulates estrogen receptor-alpha (ERα) in breast cancer cells, significantly inhibiting estrogen-stimulated cell growth. This highlights miR-18b's regulatory role in ERα signaling pathways, crucial for breast cancer progression [35]. Fonseca-Sánchez et al. displayed that miR-18b is upregulated in breast cancer and promotes cell migration, indicating its role in metastasis. Their findings showed that knocking down miR-18b in BC cells significantly reduced migration, with the study identifying key target genes such as OLFM3, KLK3, POSTN, CEACAM5, MAGED4B, SEMG1, KIR3DL3, CRX, and NLRP7. Inhibition of miR-18b modulates genes involved in crucial cancer-related pathways, including tumor growth (CHRM2 and POSTN), cell proliferation (NLRP7 and CHMR2), anoikis (OLFM3), apoptosis (REG1B, SCN3B, and POSTN), angiogenesis (KLK3, CHRM2, and POSTN), and invasion and metastasis (KIR3DL3, NLRP7, KLK3, OLFM3, SEMG1, CRX, POSTN, and CEACAM5) [36].

Li et al., showed that the oncoprotein HBXIP encourages BC growth via decreasing p53 through the miR-18b/MDM2 and pAKT/MDM2 axes, revealing a critical oncogenic mechanism of miR-18b. They found miR-18b is involved in the regulation of the p53 pathway via MDM2 and the pAKT/MDM2 pathways, both of which are crucial for cell cycle control and apoptosis [27]. Yan et al. demonstrated that exosomal miR-18b produced from cancer-associated fibroblasts stimulates metastasis and invasion of BC cells by binding to TCEAL7, emphasizing miR-18b's role in the tumor microenvironment and intercellular communication. Restoring miR-18b expression in xenografted mice inhibits HBV-related tumor development and reduces metastasis. The miR-18b-TCEAL7 pathway promotes nuclear snail ectopic activation by activating the nuclear factor-kappa B (NF-κB) pathway [37]. Further expanding on miR-18b's role, Wang et al. found that lncRNA AC073284.4 inhibits EMT via sponging miR-18b-5p in paclitaxel-resistant BC cells, highlighting a crucial role for miR-18b-5p in drug resistance and metastasis [82]. Kang et al. revealed that lncRNA SNHG1 promotes TERT expression in breast cancer through sponging miR-18b-5p, showing that miR-18b-5p acts as a tumor repressor, and targeting this pathway could offer new therapeutic options [83]. This aligns with Fu et al. discussed how lncRNA LOXL1-AS1 sponges miR-18b-5p, promoting various cancer cell processes, including proliferation and migration, indicating miR-18b-5p's involvement in multiple malignancies [84].

In human breast cancer sample studies, Yoshimoto et al. reported that miR-18b is highly expressed in ERα-negative breast cancer tissues, linking its expression to aggressive breast cancer subtypes. Their analysis showed higher miR-18b expression in ERα-negative tumors in comparison with ERα-positive tumors and found it related to estrogen receptor signaling. This association implies miR-18b's role in the aggressiveness and poor prognosis of ERα-negative breast cancers. It

highlights miR-18b's potential for stratifying patients for tailored therapies [38]. Cookson et al., identified miR-18b as a circulating biomarker, with higher plasma levels in patients, suggesting its potential for the detection of non-invasive breast cancer [39]. This complements the findings of Kleivi Sahlberg et al., who established a four-miRNA signature, including miR-18b, to predict tumor relapse and survival in TNBC patients, reinforcing miR-18b's prognostic value [40]. Additionally, Egeland et al. observed that miR-18b correlates with high inflammation in ERα-negative breast tumors, introducing its role in the tumor microenvironment and immune response [41]. MotieGhader et al. found that miR-18b was one of six miRNAs that were important for figuring out the subtypes of breast cancer. This shows that miR-18b has diagnostic potential and may help figure out the subtypes of breast cancer, which can lead to more personalized treatment plans [42].

Together, these studies illustrate the complex and multifaceted roles of miR-18b in breast cancer progression. miR-18b's involvement in regulating key pathways and its potential as a biomarker and therapeutic target highlight its significance in cancer research and clinical applications.

2.2.2 Colorectal Cancer (CRC)

Colon cancer (CRC) is the second most common cause of cancer-related death and the third most common type of cancer to be diagnosed [85]. In CRC, miR-18b is generally upregulated and acts primarily as an oncogene, promoting tumor growth and progression. It targets and inhibits tumor suppressor genes such as CDKN2B [15]. While it may have tumor-suppressive properties in certain contexts, miR-18b's role in CRC is predominantly oncogenic.

In cell culture studies, Li et al. showed that miR-18b upregulation in colorectal cancer promotes tumor development by targeting and inhibiting CDKN2B. They demonstrated that miR-18b enhances cell proliferation and migration, underscoring its oncogenic role in colorectal cancer. The findings suggest that targeting miR-18b or its downstream pathways could offer new therapeutic approaches for treating colorectal cancer and preventing tumor growth and spread [15]. Orang et al. identified miRNAs that influence metabolism in colorectal cancer cells and found that miR-18b-5p sensitizes these cells to metformin by affecting glycolysis. This role highlights miR-18b-5p's involvement in metabolic regulation and its potential to boost the anti-proliferative effects of metformin. The study suggests novel therapeutic approaches that combine miR-18b-5p modulation with metabolic treatments to improve colorectal cancer therapy efficacy [43]. Xu et al. investigated the role of exosomal circ-FBXW7 in colorectal cancer and found that it mitigates chemoresistance to oxaliplatin by sponging miR-18b-5p. This interaction suggests that miR-18b-5p is participated in the mechanisms of chemoresistance, and targeting this pathway could improve chemotherapy effectiveness. The study offers insights into potential strategies for overcoming chemoresistance in colorectal cancer, enhancing treatment outcomes [86]. Zhou et al. demonstrated that the transcription factor SOX9 promotes CRC growth and metastasis via activating the lncRNA FARSA-AS1, which in turn upregulates SOX9 and FARSA by sequestering miR-18b-5p. This creates a feedback loop that enhances tumorigenesis and metastasis. The study reveals the SOX9-FARSA-AS1-miR-18b-5p regulatory axis as a critical pathway in colorectal cancer, offering potential targets for therapeutic intervention [87].

In human sample studies, Wang et al. explored miRNA expression profiles in colonic cancer lacking lymph node metastasis and discovered that miR-18b was elevated in cancerous tissues in comparison with adjacent non-cancerous tissues. This elevation suggests miR-18b's function in colon cancer development, potentially involving tumor formation. The study offers new perspectives on how miRNAs influence colorectal cancer progression and highlights miR-18b as a potential focal point for further investigation into colorectal cancer diagnostics and development [44]. Pavicic et al. examined the methylation patterns of miRNAs in various cancers, including colorectal cancer, and identified that miR-18b was hypermethylated, particularly in sporadic colorectal cancer cases. This hypermethylation indicates that miR-18b may be subject to epigenetic regulation, affecting its expression and role in tumor suppression and progression. The study emphasizes the importance of miRNA methylation in cancer development and suggests that targeting these epigenetic changes could be a therapeutic strategy [45].

Azizian et al. analyzed miRNA expression in rectal cancer patients undergoing chemoradiotherapy (CRT) and found that miR-18b levels decreased during treatment. This reduction was significantly linked to the absence of lymph node metastasis post-treatment, suggesting miR-18b could be a useful biomarker for evaluating lymph node status and response to CRT. The findings imply that miR-18b might help tailor treatment strategies and improve outcomes for rectal cancer patients [46]. Yin et al. conducted a comprehensive analysis of key miRNAs involved in colorectal tumorigenesis and identified miR-18b as consistently altered during cancer progression. They found that miR-18b plays an important function in several signaling pathways related to colorectal cancer development, highlighting its importance in the molecular mechanisms of the disease. The study suggests that miR-18b could act as a target for therapeutic interventions as well as a biomarker for monitoring disease progression and treatment response in colorectal cancer [47].

Bobowicz et al. investigated the prognostic implications of miRNAs in stage T2-T3N0 colon cancer and found that miR-18b had altered expression in tumor tissues. Their results indicate that miR-18b could be utilized to predict distant metastasis-free survival in early-stage colon cancer, assisting in patient management and treatment decisions. The study underscores the potential

of miR-18b to enhance prognostic assessments and guide therapy in early-stage colon cancer [48].

Zhang et al. created a diagnostic panel of miRNAs for colorectal cancer, identifying miR-18b-5p as significantly higher in CRC patients' plasma exosomes than in healthy controls. This elevation suggests that miR-18b-5p could be an important biomarker for the early recognition of CRC, improving diagnostic accuracy. The study highlights the potential of miR-18b-5p in non-invasive diagnostic methods and early intervention strategies for colorectal cancer [49].

Jo et al. analyzed miRNA levels in the plasma of rectal cancer patients undergoing chemoradiotherapy (CRT) and found that miR-18b, along with other miRNAs, was significantly downregulated pre-treatment. This downregulation was further validated post-treatment, suggesting that miR-18b levels could serve as biomarkers for monitoring tumor response to CRT. The study emphasizes the need for further validation in prospective studies to confirm the utility of these miRNAs as non-invasive biomarkers [50].

2.2.3 Gastric Cancer (GC)

Nowadays, gastric cancer ranks second globally in terms of cause of death and continues to be one of the more common cancers [88]. Research has shown that miR-18b is significantly overexpressed in GC tissues, with its increased levels being associated with reduced target gene expression like Rb and PTEN, genetic variations in miRNA clusters, and epigenetic regulation through methylation, contributing to higher cancer risk, poor prognosis, and enhanced cellular proliferation and invasion [28].

Luo et al. showed that miR-18b performs as an oncogene in GC, being significantly upregulated in cancer tissues and promoting cellular proliferation and invasion via targeting KLF6 in the cell line of GC, emphasizing miR-18b's vital role in the progression of cancer and its potential as a therapeutic target [51].

Guo et al. discovered that miR-18b was markedly overexpressed in GC tissues in comparison with nearby non-cancerous tissues, indicating its potential as a diagnostic marker and its involvement in gastric cancer development. They also observed a reduction in the expression of target genes like Rb and PTEN in the cancerous tissues [28]. Similarly, Pavicic et al. found that miR-18b exhibited increased methylation in gastric tumors, particularly in sporadic cases. This suggests an epigenetic regulation mechanism for miR-18b, highlighting its role in gastric cancer progression [45]. Espinosa-Parrilla et al. examined the genetic links between miRNA clusters and gastric cancer, identifying significant associations with SNPs in clusters that include miR-18b. Their results suggest that genetic variations in miR-18b may involve a higher risk of GC, especially noncardia types [52].

Zhong et al. noted that high FOXO3 expression in gastric cancer tissues, regulated by miR-18b-5p, was linked to a poor prognosis. It is also significantly associated with the TP53 mutation in gastric cancer. They proposed that miR-18b-5p could affect cancer progression and immune cell infiltration, highlighting its importance in cancer prognosis [53].

2.2.4 Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma, which mostly affects liver cells, is the sixth most prevalent and fourth deadliest cancer worldwide [89]. Zhang et al. investigated miRNA expression changes during acute and chronic HBV infection in relation to HCC. They identified miR-18b as one of the miRNAs with changed expression, suggesting its role in the progression of HBV-related HCC. This study indicates that miR-18b, along with other miRNAs, may contribute to the genesis of HCC from HBV infection [29]. The study examined the ways in which the Hepatitis B virus X protein (HBx) amplifies the process of hepatocarcinogenesis by influencing the miR-18b-mediated targeting of NUSAP1 mRNA. There was a lower amount of miR-18b in HBV-positive liver cancer tissues after HBx stopped its expression by methylating a CpG island in its promoter. miR-18b normally acts as a tumor suppressor by targeting NUSAP1 mRNA, inhibiting hepatoma cell proliferation. However, HBx upregulates NUSAP1 by depressing miR-18b, thus promoting liver cancer development. This study offers new understandings into the impact of HBx on liver cancer progression through miR-18b modulation [61]. Ji et al. investigated exosomal ZFPM2-AS1's function in HCC and how it interacted with miR-18b-5p. It was demonstrated that ZFPM2-AS1, which is abundant in exosomes produced from HCC, promotes tumor development and metastasis via sponging miR-18b-5p, which controls the expression of PKM. The findings of this work indicate that miR-18b-5p, a key participant in the exosomal modulation of HCC growth, offers therapeutic potential as a target [90]. Moreover, Chen and associates looked into the role of long noncoding RNA, also known as SNHG15, in liver cancer and its interactions with miR-18b-5p and LIM-only 4 (LMO4). They found that SNHG15 and LMO4 are overexpressed while miR-18b-5p is downregulated in cancerous liver tissues and cells. An aggressive tumor profile and a worse prognosis were associated with SNHG15 overexpression. SNHG15 knockdown or miR-18b-5p restoration decreased the proliferation, migration, and invasion of liver cancer cells both in vitro and in vivo. The study demonstrated that SNHG15 promotes the growth of liver cancer via affecting the miR-18b-5p/LMO4 axis, suggesting the potential for therapy by focusing on this axis [91].

Cui et al. identified differentially expressed miRNAs and mRNAs in HBV-associated HCC using PCR microarrays. They found that upregulated miR-18b-5p suppressed target mRNAs, including MACC1. The study suggests that the dysregulation of miR-18b-5p contributes to the pathogenesis of HCC through its interaction with specific mRNAs, highlighting its role in cancer development [55]. Additionally, Katayama et al. performed miRNA expression profiling on tumor and non-tumor tissues from patients with HCC who had different clinical characteristics. Regardless of the

presence of a viral infection, they exposed that miR-18b was dysregulated in both tumor and non-tumor tissues, signifying that it may be a unique biomarker for chronic liver disorders and HCC [56]. Murakami et al. also investigated the miRNA expression profiles in 110 HCC cases with distinct morphological differentiations. They found that, in weakly differentiated HCC cases as opposed to well-differentiated instances, miR-18b expression was considerably higher. Higher levels of miR-18b were linked to poor prognosis and increased cell proliferation in HCC, suggesting that it functions as an oncogene and may be a prognostic marker [57].

Overall, miR-18b has an important oncogenic role in HCC. It is upregulated in poorly differentiated HCC, enhancing cellular proliferation and invasion via targeting tumor suppressor genes such as PTEN. Studies have shown altered expression in HBV-related HCC, indicating its involvement in disease progression. Exosomal lncRNAs also regulate miR-18b, contributing to tumor growth and metastasis These results imply that miR-18b may be an important biomarker and potential target for treatment for HCC.

2.2.5 Lung Cancer (LC)

Lung cancer is a highly common cancer in the world that causes a significant portion of cancer-related death [92]. Histologically, lung carcinoma is primarily classified as small cell (SCLC) and non-small cell (NSCLC). Approximately 85% of instances of lung cancer are NSCLC [93].

In cell culture studies, Xue et al. displayed the role of the lncRNA ZFPM2-AS1 in lung adenocarcinoma and discovered that it promotes cell proliferation by regulating the miR-18b-5p/VMA21 axis. They found that ZFPM2-AS1 binds to and negatively regulates miR-18b-5p, controlling the expression of VMA21. This interaction suggests that miR-18b-5p plays a crucial role in controlling gene expression involved in lung adenocarcinoma proliferation, positioning it as a potential target for therapeutic strategies [94].

Dacic et al. studied miRNA expression in LC with different mutations, including EGFR and KRAS mutations. They discovered that various mutational types upregulated miR-18b and other miRNAs. This suggests miR-18b's involvement in the molecular pathways of lung adenocarcinoma, although specific target genes for miR-18b were not detailed in this study. The results show that miR-18b might play a function in the carcinogenesis pathways influenced by different oncogenic mutations [58].

Sun et al. examined miRNA expression in NSCLC and found that miR-18b-5p was significantly downregulated in tumor tissues. This downregulation correlated with larger tumor sizes, smoking status, advanced tumor stages, and higher proliferation indices marked by Ki-67 positivity. Although miR-18b-5p was studied alongside other miRNAs, its specific targets in NSCLC were not identified in this research. The findings highlight the potential role of miR-18b-5p in tumor growth and progression [59].

Zhou et al. developed a miRNA-based molecular signature for NSCLC diagnosis and prognosis, identifying miR-18b as one of the top ten downregulated circulating miRNAs. The reduced levels of miR-18b in the serum of NSCLC patients indicate its potential utility in early detection and prognosis prediction. Although specific target genes were not mentioned, the downregulation of miR-18b suggests its involvement in the molecular mechanisms underlying NSCLC and its progression [60].

Taken together, miR-18b displays elevated expression in lung adenocarcinoma, correlating with various oncogenic mutations. Tumor proliferation links this upregulation, as evidenced by its regulation through the lncRNA ZFPM2-AS1 and its impact on target genes like VMA21.However, in non-small cell lung carcinoma (NSCLC), miR-18b-5p is significantly downregulated, associated with larger tumor size, smoking status, and advanced stages, indicating a complex role in different lung cancer subtypes and contexts.

2.2.6 Melanoma

The most lethal type of skin cancer, melanoma, has become more common over the last thirty years and is the main cause of skin cancer-associated fatalities globally [95]. Recent epidemiological studies rank melanoma as the fifth most common cancer in males and the sixth in females among all human malignancies [96].

Using nevi, melanoma tissues, melanoma cell lines, and normal melanocytes, Dar et al. investigated the expression of miR-18b. Their results demonstrated that miR-18b acts as a tumor suppressor in melanoma by modulating the MDM2-p53 signaling pathway. The study establishes a connection between the progression of melanoma and the downregulation of miR-18b, highlighting the latter's potential as a therapeutic target [14]. Consistent with this study, Jazirehi et al. explored the role of the miR-18b/MDM2/p53 circuitry in melanoma progression. Their study highlights how miR-18b regulates the MDM2-p53 pathway, which is crucial for cell cycle control and apoptosis [30]. Another study found that miR-18b targets HIF-1alpha, a crucial regulator of glycolysis, to prevent the growth of malignant melanoma. Overexpression of miR-18b reduced glycolysis in melanoma cell lines A375 and B16, demonstrating its role in metabolic regulation and tumor suppression. This study suggests that miR-18b could be a potential therapeutic target in melanoma by inhibiting HIF-1alpha-mediated pathways [61]. According to An et al., melanoma cells are more vulnerable to cisplatin when lncRNA H19 is downregulated, which is achieved through modulation of the miR-18b/IGF1 axis. LncRNA H19 was shown to be upregulated and miR-18b to be downregulated in melanoma tumors and cisplatin-resistant melanoma cells. This relationship suggests that cisplatin treatment for melanoma may be more effective if the lncRNA H19/miR-18b/IGF1 axis is modulated, offering a novel therapeutic approach [62].

As a result, miR-18b acts as a tumor suppressor in melanoma by modulating critical pathways like MDM2-p53 and targeting HIF-1alpha, which reduces glycolysis and tumor proliferation. It shows significant potential as a diagnostic and therapeutic marker, with its upregulation sensitizing melanoma cells to treatments like cisplatin. These findings underscore miR-18b's importance in melanoma progression and therapy.

2.2.7 Nasopharyngeal Carcinoma (NPC)

One prevalent cancer in Southeast Asia, particularly in Southern China, is nasopharyngeal carcinoma (NPC), with significantly higher incidence rates compared to other regions. NPC is known for its tendency to cause distant metastasis and its association with a poor prognosis [97]. MiR-18b has an important role in NPC progression by promoting cell proliferation and tumor growth. It has a function in the regulation of key pathways, including the PI3K/AKT/C-Jun and C-Myc signaling pathways, which contribute to NPC development and metastasis. Yu et al. investigated the role of connective tissue growth factor (CTGF) in NPC and found that its downregulation is associated with poor prognosis. They discovered that reduced CTGF levels elevate miR-18b expression, promoting cell proliferation through the PI3K/AKT/C-Jun and C-Myc pathways. miR-18b directly suppresses CTGF, creating a feedback loop that enhances tumor growth. This study highlights miR-18b as an oncomir that contributes to NPC progression by regulating CTGF [31]. Liu et al. used microarray expression profiling to find important miRNAs and the genes they target in NPC. Between NPC and normal tissues, they found 982 differentially expressed mRNAs and 27 differentially expressed miRNAs. Among these, hsa-miR-18b had a major impact on the regulation of genes related to cell cycle signaling and cancer pathways. Their findings suggest that miR-18b is very important in the development of NPC because it negatively regulates target genes that are needed for tumor growth and development [63].

2.2.8 Ovarian Cancer (OC)

Ovarian cancer ranks as the fifth most prevalent malignant cancer in women globally. Every year, there are about 239,000 instances of OC reported, and the condition has been linked to 152,000 deaths [98]. Kim and colleagues discovered that there were five miRNAs that were expressed differently in malignant ovarian tumors as opposed to borderline and benign ovarian tumors: miR-519a, miR-153, miR-18b, miR-511, and miR-485-5p. In particular, there was an upregulation of miR-519a and miR-18b and a downregulation of miR-485-5p, miR-153, and miR-511. The observed variation in expression raises the possibility that these miRNAs have a function in the development and identification of ovarian cancer. This implies that they may serve as biomarkers for diagnosis and prognosis in ovarian cancer. The research demonstrated that several miRNAs, among them miR-18b, may be candidates for medicinal intervention [65]. In line with these findings, Han et al. displayed that miR-18b is significantly upregulated in ovarian cancer tissues and cells. This upregulation enhances cell migration and invasion through targeting PTEN, a well-known tumor suppressor gene. The study proposes that miR-18b functions as an oncogene in ovarian cancer [64].

Furthermore, Xue et al. discovered that OC tissues exhibit a substantial upregulation of LOXL1-AS1. This lncRNA regulates VMA21 and sponging miR-18b-5p to increase the proliferation, migration, and invasion of cancer cells. The findings provide credence to the idea that LOXL1-AS1 represents a potential target for ovarian cancer therapeutic intervention. Through miR-18b-5p modification, LOXL1-AS1 affects important pathways in the development of cancer [99].

Furthermore, Wilczynski et al. found five miRNAs during the screening stage of their investigation into endometrioid endometrial cancer: miR-424, miR-18b, miR-204, miR-129-1-3p, and miR-148a-5p. According to this study, these miRNAs may serve as metastatic biomarkers [66]. Furthermore, Butler et al. showed that miR-1260a, miR-18b-5p, miR-424-5p, and, miR let-7b-3p are expressed differentially in non-obese women with polycystic ovary syndrome (PCOS) in comparison with controls. The study links these miRNAs to inflammatory pathways and potential metabolic complications. This finding supports the relevance of miR-18b-5p found in other studies, indicating its broad impact. miR-18b-5p’s involvement in PCOS suggests it could be a target for therapeutic strategies [67].

Overall, miR-18b has emerged as a significant factor in ovarian cancer, predominantly acting as an oncogene. By targeting the tumor suppressor gene PTEN, it increases cell migration and invasion in ovarian cancer tissues and cells, because its expression is markedly overexpressed. This increased expression of miR-18b is linked to lymph node metastases and advanced tumor grades, suggesting that it plays a role in accelerating the spread and metastasis of cancer. As a result, miR-18b is a viable target for medical treatment as well as a potential biomarker for ovarian cancer detection and prognosis.

2.2.9 Esophageal Squamous Cell Carcinoma (ESCC)

Roughly 90% of esophageal cancer cases worldwide are caused by esophageal squamous cell carcinoma (ESCC), one of the most prevalent forms of the disease [100]. These areas have much higher incidence rates because of risk factors such as heavy alcohol intake, smoking, poor diet, and persistent esophageal irritation. Because of its aggressive tumor activity and late-stage diagnosis, ESCC continues to have a dismal prognosis even with advancements in treatment [101]. MiR-18b regulates many signaling pathways and target genes, which is linked to the development and radioresistance of ESCC. It has an impact on fatty acid metabolism, invasion, migration, and proliferation of cells, underscoring its part in the development of ESCC and resistance to treatment. MiRNAs implicated in esophageal cancer cells' radioresistance were discovered by Su et al. They discovered that in radioresistant esophagus cell lines, miR-18b was significantly downregulated. This downregulation, which affects genes linked to apoptosis,

cell cycle, and DNA damage repair, will aid future research on miR-18b's function in ESCC and contribute to radioresistance [68]. He and colleagues showed that, through controlling fatty acid metabolism, FBP1 depletion stimulates ESCC proliferation, migration, and invasion. They discovered that miR-18b-5p targets FBP1 and that inhibiting it reverses the consequences of FBP1 loss. This suggests that miR-18b-5p regulates metabolism to contribute to the advancement of ESCC [69]. In a different study looking at how lncRNA ZNF667-AS1 is regulated in ESCC, it was found to competitively bind to miR-18b-5p, which enhances RASA1 transcription and inhibits ESCC cell invasion and proliferation. ZNF667-AS1/miR-18b-5p/RASA1 axis in ESCC is important since overexpressing miR-18b-5p or silencing RASA1 reversed these inhibitory effects [102]. Furthermore, Si et al. discovered that circ_ZNF778_006 increases HIF-1α expression through sponging miR-18b-5p, hence promoting the advancement of ESCC. According to their research, circ_ZNF778_006 promotes ESCC cell proliferation, invasion, and migration as well as accelerates tumor growth in vivo. This suggests that addressing the circRNA-miRNA axis could be a viable ESCC treatment approach [103].

Moreover, Kahng et al. investigated the expression of plasma microRNAs in ESCC patients. They found that while plasma miR-18b levels increased in ESCC patients, the difference was not statistically significant. Their study suggests that other miRNAs, such as miR-21, miR-31, and miR-375, show more promise as diagnostic biomarkers for ESCC [70].

2.2.10 Prostate Cancer (PC)

Prostate cancer ranks sixth globally in terms of death from cancer in males and is the second most common type of cancer in men [104]. Prostate cancer primarily arises due to dysregulation of androgen signaling, which plays a crucial role in the development and progression of the disease. Non-coding RNAs, including miR-18b, have been shown to impact androgen signaling pathways significantly. miR-18b targets and downregulates AR co-activators, leading to reduced AR signaling and decreased tumor cell proliferation [104]. Recent studies have shown that alterations in ncRNA expression can be associated with prostate cancer progression and response to treatment [105]. Cochetti et al. evaluated serum miRNA levels in prostate cancer and benign prostatic hyperplasia, finding that miR-18b exhibited differential expression between the two conditions. Their study suggests that miR-18b could serve as a diagnostic and prognostic marker for prostate cancer, aiding in distinguishing it from benign conditions and assessing disease progression [71].

In prostate cancer, Formosa et al. identified miR-132 silencing through promoter CpG island methylation. While miR-132 was the primary focus, this study highlights that similar epigenetic mechanisms can impact other miRNAs, like miR-18b. The regulation of miR-18b by DNA methylation could influence prostate carcinogenesis, underscoring its potential role as a therapeutic target [72].

Lakshmanan et al. reviewed advances in personalized medicine for prostate cancer, emphasizing the role of microRNAs, including miR-18b. The review highlighted how discoveries from microarray and next-generation sequencing (NGS) technologies have identified miR-18b as a significant biomarker. miR-18b's involvement in diagnosis, prognosis, and therapy underscores its potential to improve personalized treatment strategies for prostate cancer [106].

2.2.11 Thyroid Carcinoma (TC)

The most common endocrine cancer, thyroid cancer, has increased in prevalence over the past few decades throughout the world. Because of improved detection techniques, it primarily affects women more than males and is being identified at a rising rate [107]. miR-18b plays a critical role in thyroid cancer by regulating gene expression involved in the cell cycle and immune-related pathways, contributing to tumor progression and metastasis. Its interaction within ceRNA networks highlights its potential as a diagnostic marker and therapeutic target.

In their assessment of NUSAP1's diagnostic and prognostic utility in papillary thyroid cancer (PTC), Gao et al. Higher NUSAP1 expression was discovered to be a distinct prognostic risk factor that corresponds with a shorter overall survival. NUSAP1 expression in PTC tissues was significantly enhanced, which was associated with the pathogenic form of PTC, lymph node metastases, lower progression-free survival, and greater efficacy for immunity checkpoint inhibitor treatment. The study revealed a network of genes, immune-related and engaged in the cell cycle, including miR-18b-5p, underscoring the significance of miR-18b-5p in the tumor microenvironment. This emphasizes NUSAP1's potential for use in PTC therapy [73].

In PTC, Wang et al. investigated the molecular mechanism by which circRNA controls immune-related mRNA by means of sponge miRNA. By identifying mRNAs, miRNAs, and circRNAs with differential expression, they were able to build a ceRNA regulation network. The study identified the hsa_circ_0082182-hsa-miR-18b-5p-FGF1/PDGFC axis as a critical regulatory pathway in PTC. Functional evaluations revealed a substantial difference in immune cell infiltration between the PTC and control groups. These findings provide potential markers for diagnosis and therapy targets by highlighting the crucial roles that miR-18b-5p and the associated ceRNA axis play in the onset and progression of PTC [108].

2.2.12 Other Cancers

Sand et al. conducted a study to identify differentially expressed miRNAs in basal cell carcinoma (BCC) by profiling miRNA expression in tumor and adjacent nonlesional skin biopsies from seven patients. They identified 16 significantly upregulated miRNAs, including hsa-miR-18b, and 10 significantly

downregulated miRNAs in BCC. The findings suggest that these miRNAs are involved in tumor-promoting pathways such as Hedgehog and MAPK/ERK. The validation of these miRNAs was done using quantitative real-time PCR. This study highlights the potential role of specific miRNAs in the molecular pathogenesis of BCC [74].

Using diagnostic samples taken from the Nordic MCL2 and MCL3 trials, Husby et al. performed genome-wide miRNA profiling to investigate the function of miR-18b in mantle cell lymphoma (MCL). They discovered that those with poor outcomes had considerably higher expression levels of miR-92a, miR-18b, and miR-378d. Since miR-18b was the best indicator of high risk, a new prognostic score that combined miR-18b levels with MIPI-B data was created. The recognition of high-risk patients in terms of overall survival free of progression was enhanced by this new score. Functional investigations revealed that overexpression of miR-18b lowered the rate of MCL cell proliferation, indicating a chemoresistance mechanism [75].

According to Luo et al.'s investigation into the function of miR-18b-5p in osteosarcoma (OS), OS tissues and cell lines exhibit a considerable overexpression of this miRNA. They showed that upregulating miR-18b-5p stimulates OS cell proliferation and metastasis and that high levels of the protein are linked to a poor prognosis. The tumor suppressor gene PHF2 is inhibited mechanistically by miR-18b-5p, and in hypoxic environments, HIF-1α mediates its transcriptional expression. MiR-18b-5p may be a useful prognostic biomarker and therapeutic target for OS, according to this study [76].

In their investigation of miR-18b's function in canine mammary tumors (CMTs), Abbate et al. discovered that malignant CMTs had higher levels of this gene. Reduced ERα immunoexpression and decreased expression of the ESR1 gene, which codes for the estrogen receptor alpha (ERα), are linked to this upregulation. According to the Ki67 index, the study showed that miR-18b is associated with enhanced tumor cell proliferation and negatively correlates with ESR1 mRNA levels. Because miR-18b is involved in both tumor aggressiveness and ERα downregulation, these results imply that miR-18b may function as a prognostic biomarker in CMTs, suggesting a poor prognosis [77].

MiR-18b and miR-145 expression in tissue samples from patients with head and neck squamous cell carcinoma (HNSCC) was examined by Yadav et al. When compared to nearby control tissues, they discovered a notable downregulation of miR-18b and miR-145 in HNSCC patients. Due to their downregulation, miR-18b and miR-145 may serve as carcinogenesis inhibitors and thus be useful biomarkers for HNSCC early detection and prognosis. The work emphasizes the significance of miR-18b in the pathophysiology of HNSCC and its possible application in treatment approaches in the future [78].

The function of Circular-CDC like kinase 1 (circ-CLK1) in oral squamous cell cancer (OSCC) was examined by Guo et al. They discovered that OSCC tissues and cell lines exhibit a marked overexpression of circ-CLK1. The knockdown of circ-CLK1 led to an increase in apoptosis and a decrease in the survival and proliferation of OSCC cells Subsequent investigation showed that circ-CLK1 acts via the miR-18b-5p/Y-box protein 2 (YBX2) axis; circ-CLK1 knockdown was reversed by blocking miR-18b-5p or overexpressing YBX2. This study highlights the potential of circ-CLK1 as a therapeutic target for OSCC by indicating that it reduces cell apoptosis via the miR-18b-5p/YBX2 pathway [109]. By suppressing miR-18b-5p epigenetically through DNA methylation, Jin et al. found that the lncRNA PVT1 stimulates the proliferation of gallbladder cancer (GBC) cells. MiR-18b-5p functions as a tumor suppressor, as evidenced by this suppression, and PVT1's downregulation of it promotes the spread of cancer. The study points to the PVT1/miR-18b-5p/HIF1A axis as a possible target for treating gallbladder cancer. This means that there are more treatment options (Figure 4) (Table 2) [110].

Table 2: LncRNAs sponge miR-18b in various cancers

lncRNA	Cancer Type	Target	Tumor Suppressor or Oncogene	Function in Cancer	Ref.
AC073284.4	BC	miR-18b-5p	TS	Suppresses EMT via targeting miR-18b-5p in paclitaxel-resistant cells	[82]
SNHG1	BC	miR-18b-5p	TS	Promotes TERT expression via targeting miR-18b-5p	[83]
FARSA-AS1	CRC	miR-18b-5p	TS	Activates SOX9 and FARSA by targeting miR-18b-5p	[87]
ZFPM2-AS1	HCC	miR-18b-5p, PKM	OG	Enhances metastasis and tumor growth via targeting miR-18b-5p, which regulates PKM expression	[90]
SNHG15	HCC	miR-18b-5p, LMO4	TS	Therapeutic potency of SNHG15/miR-18b-5p/LMO4 axis	[91]
ZFPM2-AS1	LC	miR-18b-5p, VMA21	OG	Promotes cell proliferation by interacting with the VMA21 axis	[94]
LOXL1-AS1	OC	miR-18b-5p, VMA21	OG	Promotes cancer cellular growth and invasion by targeting miR-18b-5p and regulating VMA21	[99]
ZNF667-AS1	ESCC	miR-18b-5p, RASA1	TS	Suppresses ESCC cell proliferation and invasion by promoting RASA1 transcription through competitive binding to miR-18b-5p	[102]
PVT1	GBC	miR-18b-5p	OG	Promotes cell proliferation via epigenetically repressing miR-18b-5p through DNA methylation	[110]

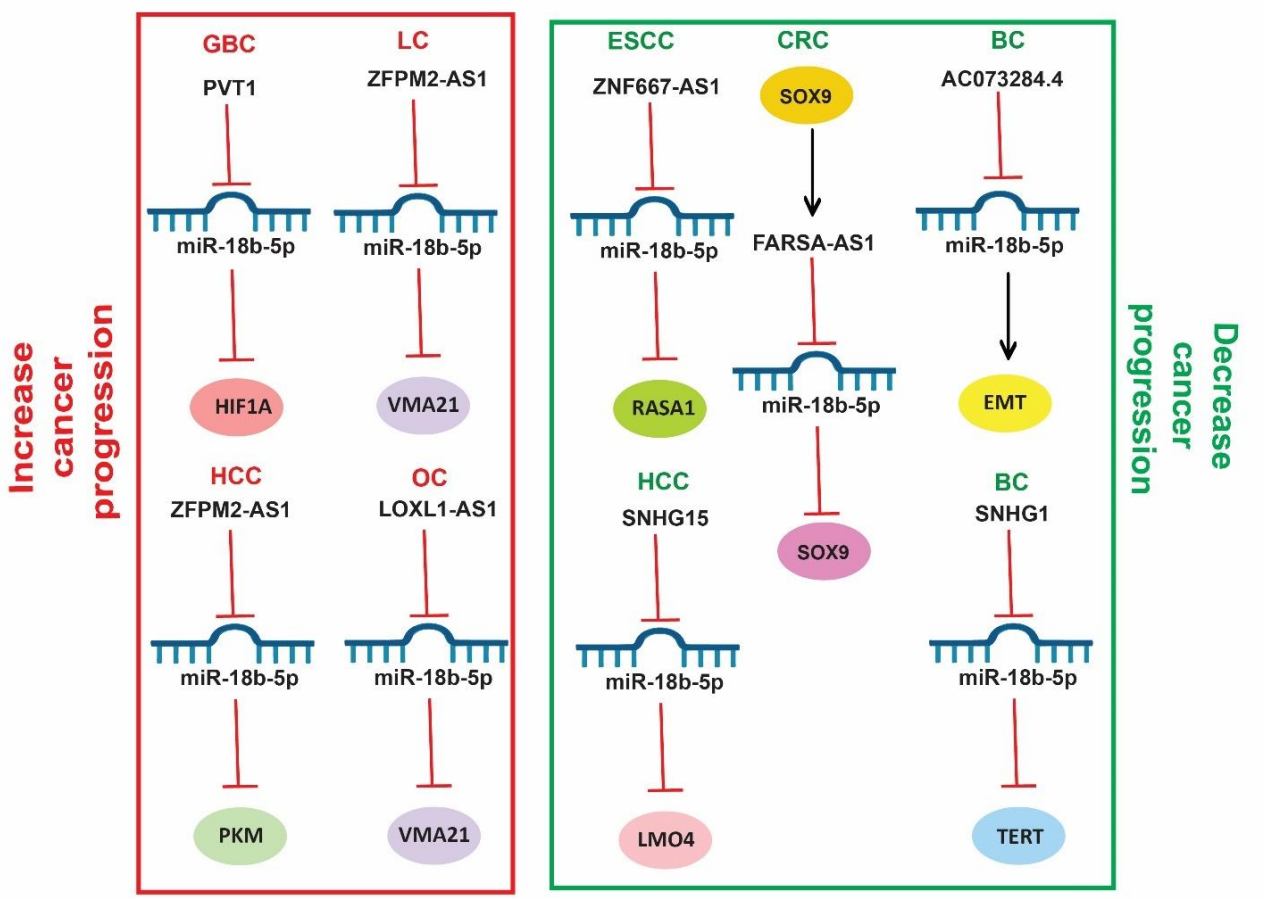

Figure 4. The relation of LncRNAs and miR-18b in various cancers

2.3 Therapeutic Potential of Targeting miR-18b

Modulating miR-18b expression in cancer cells presents a range of therapeutic strategies, given its critical role in cancer progression and metastasis. For instance, miR-18b downregulates ERα in breast cancer cells, inhibiting estrogen-stimulated cell growth. Therapeutic approaches that inhibit miR-18b could restore ERα signaling and reduce tumor proliferation [35]. In colorectal cancer, targeting miR-18b could inhibit cell cycle progression by modulating CDKN2B, thereby suppressing tumor growth and migration [23].

In hepatocellular carcinoma, miR-18b acts as a tumor suppressor by targeting NUSAP1, with its suppression promoting liver cancer development. Restoring miR-18b expression could inhibit HBV-related tumor development [54]. In non-small cell lung cancer (NSCLC), miR-18b is downregulated, correlating with larger tumor sizes and advanced stages. Therapeutic strategies aimed at restoring miR-18b levels could suppress tumor progression and improve patient outcomes [59].

Moreover, miR-18b functions as a tumor suppressor in melanoma by modulating the MDM2-p53 and glycolysis/HIF-1alpha pathways [14]. Targeting miR-18b in melanoma could inhibit tumor growth and glycolysis. In nasopharyngeal carcinoma, miR-18b promotes cell proliferation via the PI3K/AKT/C-Jun pathways, and its inhibition could suppress tumor growth [31]. Additionally, miR-18b modulation has the potential to enhance chemosensitivity in various cancers, providing a promising avenue for combination therapies.

These insights collectively demonstrate a diverse landscape of therapeutic strategies centered on miR-18b modulation, ranging from restoring tumor suppressor functions to inhibiting oncogenic pathways and enhancing chemosensitivity. This multifaceted approach offers significant promise for advancing cancer treatment strategies and improving patient outcomes.

3. Conclusion

MiR-18b plays diverse and significant roles in various human cancers, acting as both an oncogene and a tumor suppressor, depending on the context. It controls important signaling pathways, interacts with other non-coding RNAs, and changes how tumors behave, all of which show how complicated and important it is. It's clear that MiR-18b could be used as a diagnostic and prognostic biomarker because its expression changes in many types of cancer. This gives doctors a way to check on the progress of the disease and see how well treatment is working without having to do any invasive tests. MiR-18b's involvement in various molecular mechanisms underscores its relevance as a target for therapeutic interventions, providing new avenues for improving cancer diagnosis and treatment.

Abbreviations

miR-18b (microRNA-18b), miRNA (microRNA), RNA (Ribonucleic Acid), DGCR8 (DiGeorge Syndrome Critical Region 8), Exportin-5, Dicer, ERα (Estrogen Receptor Alpha), HER2 (Human Epidermal growth factor Receptor 2), TNRC6B (Trinucleotide Repeat Containing 6B), CDKN2B (Cyclin Dependent Kinase Inhibitor 2B), HIF1α (Hypoxia-Inducible Factor 1 Alpha), MDM2 (Mouse Double Minute 2 homolog), HBXIP (Hepatitis B X-interacting protein), p53 (Tumor protein p53), MDM2 (Mouse Double Minute 2 homolog), pAKT (Phosphorylated Protein Kinase B), HCC (Hepatocellular Carcinoma), ERα (Estrogen Receptor Alpha), miRNA (microRNA), lncRNA (Long Non-Coding RNA), ceRNA (Competing Endogenous RNA), SNHG15 (Small Nucleolar RNA Host Gene 15), LMO4 (LIM Only Domain 4), PI3K (Phosphoinositide 3-Kinase), AKT (Protein Kinase B), C-Jun (c-Jun N-terminal kinasemiR-18b-5p (microRNA-18b-5p), (Platelet Derived Growth Factor C), FGF1 (Fibroblast Growth Factor 1), HNSCC (Head and Neck Squamous Cell Carcinoma), VMA21 (Vacuolar ATPase Assembly Factor 21), CRC (Colorectal Cancer), BC (Breast Cancer), PCOS (Polycystic Ovary Syndrome), ERα (Estrogen Receptor Alpha), NSCLC (Non-Small Cell Lung Carcinoma), SCLC (Small Cell Lung Carcinoma), CDKN2B (Cyclin Dependent Kinase Inhibitor 2B), HCC (Hepatocellular Carcinoma), ESCC (Esophageal Squamous Cell Carcinoma), PC (Prostate Cancer), BCC (Basal Cell Carcinoma), MCL (Mantle Cell Lymphoma), OSCC (Oral Squamous Cell Carcinoma), GBC (Gallbladder Cancer), NPC (Nasopharyngeal Carcinoma), OC (Ovarian Cancer), TC (Thyroid Carcinoma).TS(Tumor Suppressor), OG (OncoGenes)

Competing Interests

The authors declare no competing interests

Authors' Contributions

F.S. and Z.R. contributed to the conceptualization, writing the original draft, review, and editing. All authors read and approved the final manuscript.

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