Review

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Review

Dual Roles of miR-10a and miR-10b as Tumor Suppressors and Oncogenes in Diverse Cancers

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Abstract: Cancer is a complex genetic disorder characterized by abnormalities in both coding and regulatory non-coding RNAs. microRNAs (miRNAs) are key regulatory non-coding RNAs that modulate cancer development, functioning as both tumor suppressors and oncogenes. miRNAs play critical roles in cancer progression, influencing key processes such as initiation, promotion, and metastasis. They exert their effects by targeting tumor suppressor genes, thereby facilitating cancer progression, while also inhibiting oncogenes to prevent further disease advancement. The miR-10 family, particularly miR-10a and miR-10b (miR-10a/b), is notably involved in cancer progression. Intriguingly, their functions can differ across different cancers, sometimes promoting and at other times suppressing tumor growth depending on the cancer type and molecular environment. This review explores the dual roles of miR-10a/b as tumor suppressor miRNAs (TSmiRs) or oncogenic miRNAs (oncomiRs) in various cancers by examining their molecular and cellular mechanisms and their impact on the tumor microenvironment. Furthermore, we discuss the potential of miR-10a/b as therapeutic targets, emphasizing miRNA-based strategies for cancer treatment. Insights discussed in this review aim to advance our understanding of miR-10a/b's roles in tumor biology and their application in developing innovative cancer therapies.

Keywords: microRNAs; cancer; tumor suppressor; oncogene; mechanisms; miRNA therapeutics

1. Introduction

Cancer is a complex genetic disorder marked by abnormalities in the expression of both coding and non-coding transcripts [1,2]. microRNAs (miRNA) are small non-coding RNAs, typically 20 to 25 nucleotides in length, that play pivotal roles in cellular processes by binding to specific coding mRNAs and regulating their translation into proteins. The discovery of miRNAs has revolutionized research, revealing their critical functions not only in organismal development but also in disease mechanisms, particularly cancer [3,4]. Emerging evidence highlights the dysregulation of miRNAs in cancer development and progression [5,6].

miRNAs exhibit dual functionality in cancer, acting as both tumor suppressors (TSmiRs) and oncogenes (oncomiRs) [5]. Their regulatory roles span key cellular processes such as proliferation, differentiation, and apoptosis, with defects in these pathways contributing to oncogenesis [7,8]. Recent studies have shed light on the miR-10 family (miR-10a-5p and miR-10b-5p), demonstrating their therapeutic potential in conditions like diabetes and gastrointestinal (GI) motility disorders, where they restore insulin-secreting pancreatic β cells and GI pacemaker cells, the interstitial cells of Cajal [9–13].

In cancer, miR-10a/b-5p exhibit bifunctional roles, acting as TSmiRs in some contexts and as oncomiRs in others, depending on their target genes and the cellular environment [14–18]. For instance, the downregulation of miR-10a/b-5p in some cancers suppresses tumor growth and metastasis [17,19–21], whereas their overexpression has been implicated in enhancing proliferation, migration, and invasion in malignancies in other cancers [17,22,23]. These dual roles are particularly

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evident in cancers such as gastric, colorectal, breast, and gynecological cancers, highlighting their complex regulatory functions in cancer biology [15,16,24,25]. Notably, the role of a miRNA, whether tumor-suppressive or oncogenic, can vary even within a single cancer type, highlighting their context-dependent functionality [16,24,25].

This functional dichotomy is closely linked to their targets, including Hox transcripts and Krüppel-like factor 11 (KLF11). Both Hox genes and KLF11 exhibit dual roles, acting as tumor suppressors or oncogenes depending on cellular context and oncogenic signals in various cancers [14,26,27]. The dual roles of miR-10a/b-5p in tumorigenesis underscore their complex and context-dependent regulatory mechanisms, highlighting their potential as both biomarkers and therapeutic targets in cancer.

This review provides a comprehensive overview of the dual roles of miR-10a/b-5p in cancer biology and their prospective applications in developing innovative cancer therapies.

Dual Roles of miR-10a/b as Tumor Suppressors (TSmiRs) and Oncogenes (oncomiRs)

Figure 1 provides an overview of the dual roles of miR-10a/b, functioning as both TSmiRs and oncomiRs across various cancers and even within the same cancer type (Tables 1 and 2).

Figure 1

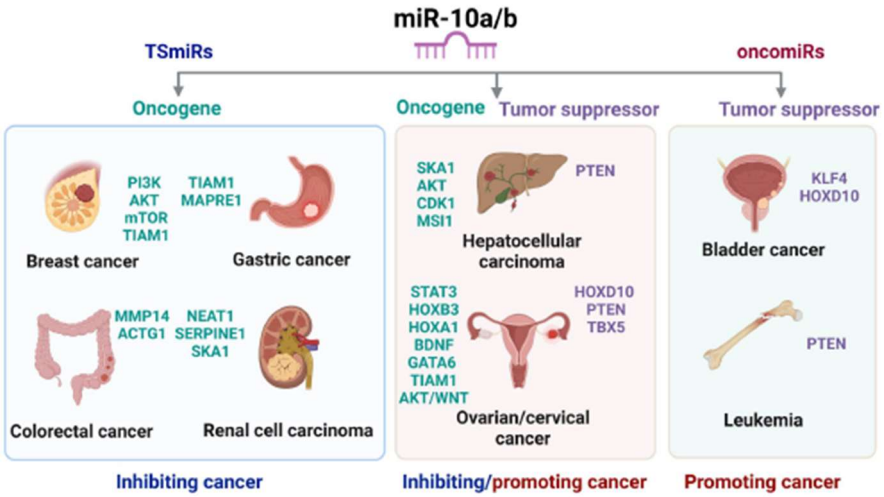

Figure 1. Dual roles of miR-10a and miR-10b as TSmiRs and/or oncomiRs in various cancers.

Table 1. Roles and target genes of miR-10a and miR-10b as tumor supressor miRNAs in human cancers and mouse models.

miRNA		Taget gene	Cancer	Human			Mouse	Reference (PMID)
Name	Role			Tissue (n)	Cell (n)	Bood (n)		
miR-10a-5p	TSmiRs	PI3K/Akt/mTOR	Breast cancer (BC)		BC (2)			29113237
miR-10a-5p	TSmiRs	BDNF	Cervical cancer (CC)		CC (5)			29285171
miR-10a-5p	TSmiRs	USF2	Chronic myeloid leukemia (CML)	CML (6) Bone marrow (85)	CML (5)			19074828
miR-10a-5p	TSmiRs	MMP14/ACTG1	Colorectal cancer (CRC)	CRC (26)	CRC (2)			28383561

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miR-10a-5p	TSmiRs	Lpo/KLF4	Colorectal cancer (CRC)	CRC (16)			CRC (Apc) mice mir-10a KO mice	24204315
miR-10a-5p	TSmiRs	Tiam1	Esophageal squamous cell carcinoma (ESCC)	ESCC (54)	ESCC (2)		ESCC xenograft mice Pulmonary metastasis mice	30426564
miR-10a-5p	TSmiRs	SKA1	Hepatocellular carcinoma (HCC)	HCC (30)	HCC (4)	Plasma (32)		34002462
miR-10a-5p	TSmiRs	HOXA1	Ovarian cancer (OC)	OC (56)	OC (4)			33332731
miR-10a-5p	TSmiRs	GATA6	Ovarian cancer (OC)	OC (376)	OC (2)		OC xenograft mice	37768544
miR-10b-5p	TSmiRs		Bladder cancer (BlC)	BlC (77)				22704449
miR-10b-5p	TSmiRs	Tiam1	Breast cancer (BC)		BC (4)			20444703
miR-10b-5p	TSmiRs	HOXA1	Cervical cancer (CC)	CC (40)	CC (2)			27296950
miR-10b-5p	TSmiRs	IGF-1R	Cervical cancer (CC)	CC (46)	CC (5)			28599502
miR-10b-5p	TSmiRs	TFAP2A/Tiam1	Cervical cancer (CC)	CC (70)	CC (3)			30504727
miR-10b-5p	TSmiRs		Clear cell renal cell carcinoma (ccRCC)	ccRCC (250)				28360191
miR-10b-5p	TSmiRs		Endometrial serous adenocarcinoma (ENC)	ESA (21)	ESA (1)			19891660
miR-10b-5p	TSmiRs		Endometrioid endometrial carcinoma (EEC)	EEC (28)		Plasma (12)		24491411
miR-10b-5p	TSmiRs	Tiam1	Gastric cancer (GC)	GC (12)	GC (3)		GC xenograft mice	34487733
miR-10b-5p	TSmiRs	TIAM1	Gastric cancer (GC)	GC (19)	GC (4)			31934163
miR-10b-5p	TSmiRs	Tiam1	Gastric cancer (GC)	GC (100)	GC (4)			24481854
miR-10b-5p	TSmiRs	MAPRE1	Gastric cancer (GC)	GC (32)	GC (11)			21562367
miR-10b-5p	TSmiRs	CREB1	Renal cancer (RC)	RC (35)	RC (4)			26796749
miR-10b-5p	TSmiRs		Small cell cervical carcinoma (SCCC)	SCCC (44)				22438992
miR-10b-5p	TSmiRs		Cervical cancer (CC)	CC (44)				30711417

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*TSmiRs, Tumor suppressor miRNAs; n, number; KO, knockout.

Table 2. Roles and target genes of miR-10a and miR-10b as oncogenic miRNAs in human cancers and mouse models.

miRNA		Taget gene	Cancer	Human		Mouse	Reference (PMID)
Name	Role			Tissue (n)	Cell (n)		
miR-10a-5p	oncomiRs	Akt	Cholangiocarcinoma (CCA)		CCA (3)	CCA xenograft mice	30410355
miR-10a-5p	oncomiRs	PTEN/Akt/Wnt	Granulosa cell tumor (GCT)		Granulosa cells (2)	mir-10a KO mice GCTxenograft mice	30348959
miR-10a-5p	oncomiRs	PTEN	Hepatocellular carcinoma (HCC)	HCC (30)	HCC (1)		31396320
miR-10b-5p	oncomiRs	STAT3	Ovarian cancer (OC)	OC (6)	OC (3)		32901049
miR-10b-5p	oncomiRs	HOXD10	Ovarian cancer (OC)	OC (68)	OC (3)		23670532
miR-10a-5p	oncomiRs	PTEN	Acute myeloid leukemia (AML)	AML (60)	AML (1)		32319862
miR-10a-5p	oncomiRs	TBX5	Cervical squamous cell carcinoma (CSCC)	CSCC (60)	CSCC (2)	GSCC xenograft mice	33235271
miR-10a-5p	oncomiRs	PTEN	Cervical cancer (CC)	CC (40)	CC (2)		25018014
miR-10b-5p	oncomiRs	E-cadherin	Breast cancer (BC)	BC (45)	BC (2)	BC xenograft mice	32305959
miR-10b-5p	oncomiRs	IQGAP2	Triple-negative breast cancer (TNBC)	TNBC (42)	TNBC (3)		33248413
miR-10b-5p	oncomiRs	Twist	Breast cancer (BC)	BC (18)	BC (6)		17898713
miR-10b-5p	oncomiRs	E-cadherin	Breast cancer (BC)	BC (44)	BC (1)		22847191
miR-10b-5p	oncomiRs	HOXD10	Gastric cancer (GC)	GC (436)	GC (7)		26311318
miR-10b-5p	oncomiRs	p21 and p53	Colorectal cancer (CRC)	CRC (63)	CRC (5)	CRC xenograft mice	31595500
miR-10b-5p	oncomiRs	FGF13	Colorectal cancer (CRC)	CRC (28)	CRC (5)		33495804
miR-10b-5p	oncomiRs	HOXD10	Colorectal cancer (CRC)	CRC (70)			25606801
miR-10b-5p	oncomiRs	TWIST-1 and E-cadherin	Colorectal cancer (CRC)	CRC (50)	CRC (1)		28345456

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miR-10b-5p	oncomiRs		Colorectal cancer (CRC)	CRC (246)		2759 2860
miR-10b-5p	oncomiRs	GSK3β	Prostate cancer (PC)		PC (2)	3084 4757
miR-10b-5p	oncomiRs	TGF-β1	Glioblastoma	GBM (15)	Glioma (2)	2839 3237
miR-10b-5p	oncomiRs	HOXD10	Glioma	Glioma (22)	Glioma (4)	2141 9107
miR-10b-5p	oncomiRs	Sirt1	Glioma		Glioma (2	3188 9362
miR-10b-5p	oncomiRs	HOXB3	Endometrial cancer (EC)	EC (20)		2744 7302
miR-10b-5p	oncomiRs	KLF4/HOXD10	Bladder cancer	Bladder cancer (20)	Bladder cancer (6)	2457 3354

*oncomiRs, oncogenic miRNAs; n, number; KO, knockout.

miR-10a/b as TSmiRs

Chronic Myeloid Leukemia

miR-10a functions as a TSmiR and regulates the expression of upstream stimulatory factor 2 (USF2) in chronic myeloid leukemia (CML) [28]. This study revealed reduced miR-10a levels in $CD34^+$ cells from CML patients. The downregulation of miR-10a led to the overexpression of USF2, a transcription factor that promotes cell growth. Restoring miR-10a levels in these cells decreased USF2 expression, reduced cell proliferation, and enhanced apoptosis, thereby confirming the tumor-suppressive role of miR-10a in CML.

Esophageal Squamous Cell Carcinoma

miR-10a functions as a TSmiR and inhibits cell proliferation and metastasis in esophageal squamous cell carcinoma (ESCC). Reduced levels of miR-10a were observed in ESCC tissues and cell lines [29]. Overexpression of miR-10a suppresses ESCC cell proliferation, migration, and invasion, both in vitro and in vivo. Mechanistically, miR-10a directly targets Tiam1, a gene associated with tumor progression, leading to its downregulation. This interaction subsequently inhibits the Rac1 signaling pathway, which is crucial for cytoskeletal reorganization and cell motility. Restoring miR-10a expression in ESCC cells inhibits tumor growth and metastasis [29].

Renal Cell Carcinoma

miR-10b functions as a TSmiR, with its expression progressively reduced from normal kidney tissue to primary metastatic renal cell carcinoma (RCC) and further diminished in metastatic RCC [30]. This downregulation is associated with disease progression and poorer patient outcomes. Mechanistically, the loss of miR-10b-5p leads to the upregulation of cAMP-responsive element binding protein 1 (CREB1), an oncogene implicated in RCC pathogenesis [31]. These findings highlight the tumor-suppressive role of miR-10b in RCC and suggest that restoring its expression could serve as a potential therapeutic strategy.

miR-10a/b as oncomiRs

Cholangiocarcinoma

miR-10a functions as an oncomiR, as it is upregulated and promotes tumor growth by activating the Akt signaling pathway in cholangiocarcinoma (CCA) [19]. Inhibition of miR-10a-5p in vitro and in vivo suppresses proliferation and induces apoptosis, thereby inhibiting CAA growth [19]

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Granulosa Cell Tumors

miR-10a functions as an oncomiR and promotes tumor development in granulosa cell tumors (GCT) by regulating the Akt and Wnt pathways. One study showed that miR-10a is significantly upregulated in malignant GCT tissues [23]. Functional analyses revealed that miR-10a enhances GCT progression by targeting the tumor suppressor PTEN, thereby activating the Akt and Wnt signaling pathways. In vivo experiments using GCT xenograft mice showed that miR-10a overexpression accelerates tumor growth, while *mir-10a* knockout results in a less aggressive tumor phenotype, further supporting the oncogenic role of miR-10a [23].

Acute Myeloid Leukemia

miR-10a functions as an oncomiR and promotes cell proliferation in acute myeloid leukemia (AML) by downregulating the tumor suppressor gene PTEN. miR-10a is upregulated in AML cells, leading to a decrease in PTEN expression [32]. This reduction in PTEN activates the PI3K/AKT signaling pathway, thereby enhancing AML cell proliferation.

Prostate Cancer

miR-10b acts as an oncomiR by promoting cell proliferation and epithelial-mesenchymal transition (EMT) by regulating key signaling pathways in prostate cancer [33]. miR-10b is upregulated by the long non-coding RNA CHRF in PC3 prostate cancer cells, which enhances aggressive tumor behavior [33]. Mechanistically, miR-10b activates the GSK3β/AKT and NF-κB signaling pathways, both of which are critical for tumor cell survival, proliferation, and EMT. These findings highlight the oncogenic role of miR-10b in prostate cancer by modulating pathways that drive tumor progression and metastasis.

Glioblastoma

miR-10b functions as an oncomiR and promotes proliferation, migration, invasion, and EMT in glioblastoma (GBM) [34]. TGF-β1, a critical regulator of GBM progression, upregulates miR-10b expression, which targets key tumor suppressors like E-cadherin, Apaf-1, and PTEN, thereby enhancing tumor aggressiveness. Inhibition of miR-10b with antagomir-10b suppresses tumor growth in xenograft models [34]. Moreover, miR-10b promotes glioma cell invasion by downregulating HOXD10 and upregulating invasion factors such as MMP-14 and uPAR, highlighting the miR-10b/HOXD10/MMP-14/uPAR axis as a key driver of glioma malignancy [35]. Additionally, the long non-coding RNA GAS5 inhibits glioma progression by suppressing miR-10b, indirectly affecting the Sirt1/PTEN/PI3K/AKT and MEK/ERK pathways [36]. GAS5-induced apoptosis and reduced motility are reversed by miR-10b overexpression, further demonstrating the oncogenic role of miR-10b in sustaining glioma growth and invasion [36]. These studies emphasize miR-10b as a critical therapeutic target and its oncogenic role in GBM and glioma.

miR-10a/b as both TSmiRs and oncomiRs

Breast Cancer

miR-10a/b play dual roles as TSmiRs and oncomiRs in breast cancer. As a tumor suppressor, miR-10a inhibits tumor progression by targeting the PI3K/Akt/mTOR pathway, thereby reducing cell proliferation and invasion [25]. Similarly, miR-10b suppresses breast cancer cell migration by downregulating Tiam1, a guanine nucleotide exchange factor for Rac1, leading to decreased Rac activation and reduced motility [37].

In contrast, miR-10b also functions as an oncomiR in breast cancer. It promotes metastasis by targeting HOXD10 and upregulating RHOC, a gene critical for cell migration and invasion [38]. Elevated miR-10b expression is associated with increased aggressiveness and metastatic potential in breast cancer tissues [39].

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Additionally, miR-10b enhances EMT and invasiveness by modulating TGF-β signaling [40,41]. Further evidence highlights miR-10b's role in driving proliferation and invasion by suppressing tumor suppressor genes and activating oncogenic pathways [42]. Collectively, these findings underscore miR-10b as a pivotal oncogene in breast cancer, promoting EMT, invasion, and metastasis.

Bladder Cancer

miR-10b exhibits dual roles as both a TSmiR and an oncomiR in bladder cancer. Its expression is significantly downregulated in bladder cancer tissues compared to adjacent normal urothelium, indicating a tumor-suppressive function [43]. This downregulation enhances tumor cell proliferation, migration, and invasion, whereas restoring miR-10b levels in bladder cancer cells inhibits these oncogenic behaviors [43].

Conversely, miR-10b also functions as an oncomiR in bladder cancer [44]. Elevated miR-10b expression has been observed in bladder cancer cell lines and metastatic tissues, where it enhances cell migration and invasion [44]. Inhibition of miR-10b reduces these aggressive phenotypes [44] . Mechanistically, miR-10b promotes metastasis by targeting tumor suppressor genes such as KLF4 and HOXD10, leading to the upregulation of invasion-related factors like MMP14 [44].

Endometrial Cancer

miR-10b exhibits dual roles in endometrial serous adenocarcinoma, acting as both a TSmiR and an oncomiR. As a TSmiR, decreased miR-10b expression is associated with vascular invasion, advanced tumor stage, and poor overall survival [45,46]. Its downregulation correlates with increased tumor aggressiveness and metastatic potential, likely by disrupting pathways that regulate cell proliferation and invasion. The loss of miR-10b contributes to endometrial cancer development, underscoring its tumor-suppressive role in maintaining normal cellular regulation and its potential as a prognostic marker for disease severity and progression.

Conversely, miR-10b also functions as an oncomiR by promoting tumor progression. It enhances cell proliferation, migration, and invasion and suppresses apoptosis by regulating Homeobox B3 (HOXB3) [47]. miR-10b is upregulated in endometrial cancer tissues, coinciding with reduced HOXB3 expression [47]. Silencing the miR-10b increases apoptosis and inhibits endometrial cancer cell proliferation, migration, and invasion. Mechanistically, miR-10b targets HOXB3, as confirmed by dual-luciferase reporter assays. Overexpression of HOXB3 counteracted these oncogenic effects by promoting apoptosis and suppressing tumor growth and metastasis [47].

Cervical Cancer

miR-10b/b exhibits dual roles as both TSmiRs and oncomiRs in cervical cancer. miR-10a/b act as tumor suppressors in cervical cancer by targeting key oncogenes and signaling pathways. miR-10a suppresses cancer cell proliferation by directly targeting brain-derived neurotrophic factor, thereby inhibiting tumor progression [48]. Similarly, miR-10b, often downregulated in cervical cancer tissues, inhibits cell proliferation, migration, and invasion by targeting insulin-like growth factor-1 receptor [21,49]. In HPV-positive cervical cancer, miR-10b downregulation—mediated by DNA methylation—further reduces tumor aggressiveness by targeting Tiam1 [50]. Additionally, miR-10a inhibits cervical cancer progression by downregulating transcription factor AP-2 alpha [50]. In small-cell cervical carcinoma, reduced miR-10b expression correlates with advanced tumor stages, lymph node metastasis, and decreased survival [51]. Notably, miR-10b also targets HPV16/18-E6 mRNA, potentially inhibiting viral oncogene expression and subsequent tumorigenesis in high-grade squamous intraepithelial lesions [52]. These findings highlight the tumor-suppressive roles of miR-10a and miR-10b in regulating oncogenic targets and pathways.

Conversely, miR-10a can function as an oncomiR, promoting metastasis, angiogenesis, and tumor progression in cervical cancer. Elevated miR-10a expression is associated with lymph node metastasis in primary tumor tissues [53]. miR-10a mimics promote cancer cell migration and invasion

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by targeting the tumor suppressor PTEN, contributing to metastatic progression [53]. Furthermore, cancer-associated fibroblasts (CAFs) secrete extracellular vesicle (EV)-encapsulated miR-10a-5p, which is upregulated in cervical cancer tissues. miR-10a-5p promotes tumor growth and angiogenesis by activating Hedgehog signaling through the downregulation of TBX5 [54]. Inhibition of miR-10a-5p in CAF-EVs effectively suppresses tumor growth and angiogenesis.

Ovarian Cancer

miR-10a/b play dual roles as TSmiRs and oncomiRs in ovarian cancer. As a TSmiR, miR-10a-5p targets oncogenes such as HOXA1 and GATA6, reducing cell proliferation, migration, and invasion, thereby inhibiting tumor progression [55,56].

Conversely, miR-10b acts as an oncomiR. Its overexpression in ovarian cancer tissues and cell lines downregulates the tumor suppressor gene HOXD10, promoting enhanced migration and invasion of ovarian cancer cells and driving tumor progression [57].

Gastric Cancer

miR-10b exerts dual roles as both a TSmiR and an oncomiR in gastric cancer. As a tumor suppressor, miR-10b targets the oncogenic proteins TIAM1 and MAPRE1 in gastric cancer cells [58–60]. Its downregulation in gastric cancer tissues leads to increased expression of TIAM1 and MAPRE1. Overexpression of miR-10b inhibits cell proliferation, migration, and invasion while inducing apoptosis. Additionally, miR-10b suppresses tumor growth in gastric cancer xenograft models by downregulating TIAM1 [61]. The CBFβ/RUNX3-miR-10b-TIAM1 molecular axis further inhibits gastric cancer cell proliferation, migration, and invasion [59]. miR-10b also epigenetically regulates MAPRE1, reinforcing its tumor-suppressive role in gastric cancer [58].

Conversely, miR-10b acts as an oncomiR by promoting cell migration and invasion. Its upregulation in gastric cancer tissues and cell lines leads to the suppression of HOXD10, a tumor suppressor gene, resulting in increased expression of RHOC, a gene linked to enhanced metastatic potential [62]. Overexpression of miR-10b facilitates the aggressive behavior of gastric cancer cells, highlighting its oncogenic role in tumor progression [62].

Colorectal Cancer

miR-10a/b exhibits dual roles as TSmiRs and oncomiRs in colorectal cancer (CRC). As a TSmiR, miR-10a regulates key processes involved in metastasis and epithelial integrity in CRC [24]. miR-10a inhibits CRC metastasis by suppressing EMT and anoikis resistance by downregulating MMP14 and ACTG1 [24]. Additionally, the loss of miR-10a activates lipocalin 2 and Wnt signaling, driving intestinal neoplasia in female mice, emphasizing its role in maintaining epithelial stability and preventing tumor progression [63].

Conversely, miR-10b acts as an oncomiR in CRC, promoting tumor progression and metastasis through multiple mechanisms [64–66]. Its upregulation in CRC tissues and cell lines enhances migration and invasion by targeting the tumor suppressor HOXD10, leading to increased RHOC expression [64]. Elevated miR-10b levels are also associated with increased TWIST-1 expression and reduced E-cadherin levels, facilitating EMT and driving tumor progression [65]. Furthermore, miR-10b promotes CRC growth and metastasis by modulating the PI3K/Akt signaling pathway [66]. Clinically, high miR-10b expression correlates with advanced-stage disease, liver metastasis, and aggressive tumor behavior in CRC patients [67].

Hepatocellular Carcinoma

miR-10a exhibits dual roles as a TSmiR and an oncomiR in hepatocellular carcinoma (HCC). As a TSmiR, miR-10a inhibits cell metastasis by targeting spindle and kinetochore-associated protein 1 (SKA1) in HCC tissues and cell lines [20]. Its expression is downregulated in HCC tissues and cell lines, and overexpression of miR-10a suppresses HCC cell migration and invasion, both in vitro and in vivo [20]. Mechanistically, miR-10a-5p binds to the 3′ untranslated region of SKA1 mRNA,

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promoting its degradation and reducing SKA1 protein levels, thereby inhibiting the EMT process critical for cancer metastasis. Restoring miR-10a expression in HCC cells effectively impedes tumor growth and metastasis [20].

Conversely, miR-10a also functions as an oncomiR in HCC. It facilitates metastasis by downregulating PTEN and activating the PI3K/AKT/MMP-2/MMP-9 signaling axis [68]. Overexpression of miR-10a in HCC tissues suppresses PTEN, leading to activation of the AKT pathway. This activation increases the levels of matrix metalloproteinases MMP-2 and MMP-9, which degrade the extracellular matrix and enhance tumor invasiveness [68].

The paradoxical dual roles of miR-10a/b in cancer highlight the complexity of miRNA-mediated regulation in tumor biology. These miRNAs demonstrate context-dependent functions, acting as TSmiRs by targeting oncogenes and inhibiting critical pathways such as EMT and metastasis while also functioning as oncomiRs by repressing tumor suppressor genes and activating oncogenic signaling pathways, including PI3K/Akt and Wnt. Their roles vary significantly across cancer types, including breast, bladder, endometrial, cervical, ovarian, gastric, colorectal, and hepatocellular cancers, depending on the molecular context and specific gene targets within the tumor microenvironment.

This dual functionality underscores the importance of precision medicine, which considers the unique tumor microenvironment and regulatory networks of miR-10a/b in each cancer type. Future therapeutic strategies should focus on restoring their tumor-suppressive functions or inhibiting their oncogenic effects, paving the way for tailored and effective cancer treatments.

miR10a/b in the Regulation of Key Cancer Pathways

miR-10a/b plays pivotal roles in regulating cancer-related signaling pathways, exhibiting both tumor-suppressive and oncogenic functions. This summary highlights the key pathways influenced by miR-10a/b, emphasizing their dual roles in cancer suppression and progression (Figure 2).

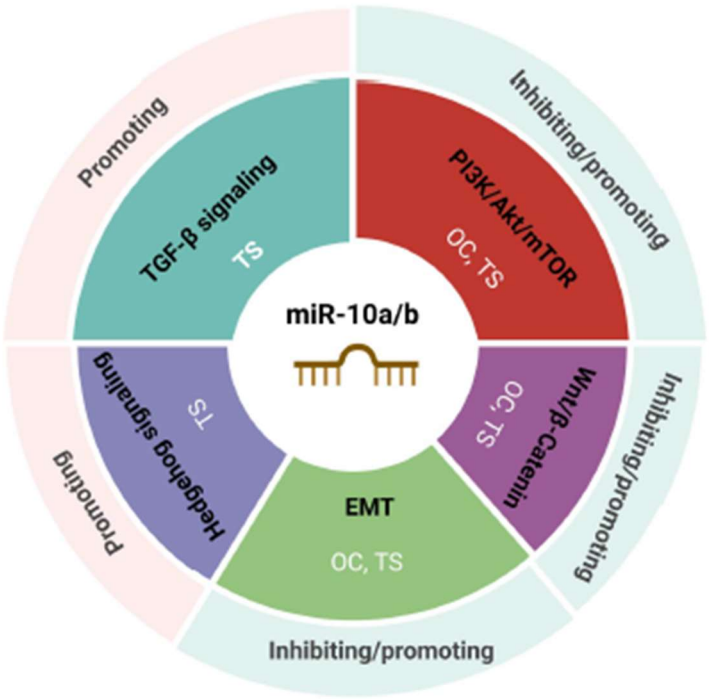

Figure 2. miR-10a and miR-10b mediated cancer pathways.

PI3K/Akt/mTOR: The PI3K/Akt/mTOR pathway is essential for cell growth, proliferation, and survival, with its dysregulation often associated with oncogenesis [69,70]. In glioblastoma, miR-10a

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suppresses tumor growth by targeting components of the PI3K/Akt pathway, resulting in reduced cell proliferation and increased apoptosis [71]. In contrast, in HCC, miR-10a acts as an oncomiR by downregulating PTEN, thereby activating the PI3K/Akt pathway and promoting metastasis [68].

Wnt/β-Catenin: The Wnt/β-catenin pathway regulates cell fate determination, proliferation, and migration [72], with its aberrant activation linked to various cancers [73]. In colorectal cancer, miR-10a suppresses metastasis by inhibiting EMT and anoikis resistance, primarily through downregulating MMP14 and ACTG1, which are key components of the Wnt/β-catenin pathway [24]. In glioma, miR-10a promotes tumorigenesis by targeting myotubularin-related protein 3 (MTMR3) and modulating the Wnt/β-catenin signaling pathway, leading to increased cell proliferation and invasion [74].

***Epithelial-Mesenchymal Transition (EMT)*:** EMT is a process by which epithelial cells acquire mesenchymal properties, enhancing their migratory capacity and invasiveness, thereby contributing to metastasis [75]. In gastric cancer, miR-10b functions as a TSmiR by targeting oncogenic proteins such as TIAM1 and MAPRE1 [58,61]. Overexpression of miR-10b inhibits proliferation, migration, and invasion while inducing apoptosis, thereby modulating the tumor microenvironment to suppress tumor progression. In breast cancer, however, miR-10b promotes EMT by targeting HOXD10, increasing cell migration and invasion [38].

Hedgehog signaling: The Hedgehog pathway is essential for cancer as well as embryonic development and tissue regeneration [76]. In cervical cancer, miR-10a-5p promotes angiogenesis and tumor progression by activating Hedgehog signaling through the downregulation of TBX5 [54].

TGF-β signaling: The TGF-β pathway regulates cell growth, differentiation, and apoptosis [77,78]. TGF-β suppresses tumor growth in early stages but promotes metastasis in advanced stages [78]. TGF-β1 upregulates miR-10b expression, which downregulates the tumor suppressors E-cadherin, Apaf-1, and PTEN, thereby enhancing tumor aggressiveness in GBM [34]. In breast cancer, miR-10b enhances invasiveness through modulation of TGF-β signaling, contributing to EMT and metastasis [41].

miR-10a/b and Tumor Microenvironment

miR-10a/b play a pivotal role in modulating the tumor microenvironment (TME) by regulating cellular functions within the tumor niche [79–82]. Extracellular miRNAs facilitate intercellular communication, interacting with stromal cells and extracellular matrix components to establish a microenvironment that supports tumor growth and immune evasion [83]. Among these, miR-10a and miR-10b have emerged as critical regulators in various cancers. In HCC, miR-10a inhibits cell metastasis by targeting SKA1 and suppressing the EMT process, a key driver of metastasis, thereby reducing the metastatic potential within the TME [20]. Conversely, in breast cancer, miR-10b promotes metastasis by targeting HOXD10, which leads to RHOC upregulation—a gene crucial for cell migration and invasion—altering the TME to favor metastatic dissemination [38]. In gastric cancer, miR-10b targets oncogenic proteins such as Tiam1 and MAPRE1, and its overexpression inhibits proliferation, migration, and invasion while inducing apoptosis, effectively modulating the TME to suppress tumor progression [58,60,61]. In CRC, miR-10b is upregulated, enhancing cell migration and invasion by targeting the tumor suppressor gene HOXD10 and increasing RHOC expression, thereby supporting tumor aggressiveness [64].

These findings highlight the dual roles of miR-10a/b in shaping the TME across different cancer types. By modulating key signaling pathways and gene expressions, these miRNAs influence tumor progression, metastasis, and the behavior of the tumor niche. Further research is needed to unravel their precise molecular mechanisms and functions within the TME. Such insights could pave the way for novel therapeutic strategies targeting miR-10a/b to modulate the tumor microenvironment effectively.

miRNA Therapeutic Targets in Cancer

miR-10a/b have emerged as pivotal regulators in cancer biology, demonstrating dual roles as TSmiRs and oncomiRs. This dual functionality positions them as promising therapeutic targets. The

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capacity of miRNAs to modulate multiple genes within the same pathway further underscores their therapeutic potential [84,85]. These multifaceted roles make them attractive candidates for novel cancer therapies.

Preclinical and in vitro studies have shown that inhibiting oncomiRs or reintroducing tumor-suppressive miRNAs can effectively suppress cell migration and proliferation or induce apoptosis [13,86,87]. These findings suggest that miRNAs, whether functioning as oncomiRs or TSmiRs, could serve as therapeutic agents or targets. Unlike traditional gene-targeting therapies, modulating miRNA expression offers the advantage of simultaneously influencing multiple genes and pathways [88].

In cancers where miR-10a/b act as oncomiRs, miRNA inhibitors can restore the synthesis of target tumor-suppressor proteins, thereby inhibiting tumor growth (Figure 3) [89,90]. For instance, in metastatic breast cancer, miR-10b inhibitors significantly reduced miR-10b expression, leading to decreased cell migration and invasion, highlighting their potential for treating aggressive cancers [91]. This approach highlights the potential of miR-10b inhibitors in treating aggressive cancers.

Conversely, in cancers where miR-10a/b function as TsmiRs, mimics can be used to inhibit target oncogenes and suppress tumor progression (Figure 3). In cervical cancer, cancer-associated fibroblasts (CAFs) secrete extracellular vesicles (EVs) containing miR-10a, which promotes angiogenesis and tumor growth. Targeting this pathway with miR-10a mimics has shown promise in reducing tumor growth and angiogenesis, suggesting a viable therapeutic strategy for cervical cancer [54].

Figure 3

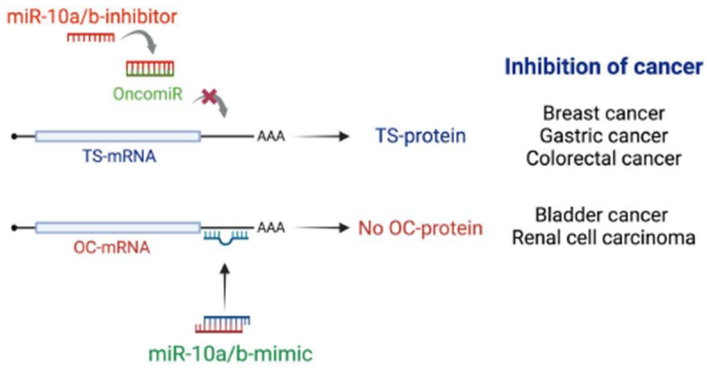

Figure 3. miR10a and miR-10b therapeutic approach in inhibition of cancer.

Advancements in miRNA delivery systems and an enhanced understanding of their regulatory networks are crucial to fully realize their therapeutic potential. By modulating entire biological pathways, miRNA-based therapies represent a novel and highly promising class of cancer treatment, offering improved efficacy and specificity.

Conclusion and Future Prospectives

Cancer is a multifaceted genetic disorder involving alterations in both coding and non-coding transcripts. Emerging evidence underscores the pivotal role of miR-10a/b dysregulation in cancer development and progression. These miRNAs, particularly miR-10a/b-5p, exhibit dual roles in oncogenesis, functioning as either TSmiRs or oncomiRs depending on the cellular context and the genes or pathways they regulate.

The downregulation of miR-10a/b-5p is implicated in various cancers, including breast, colorectal, and gastric cancers. In these contexts, miR-10a/b mimics demonstrate therapeutic potential by targeting and inhibiting oncogenic factors such as PI3K, AKT, TIAM1, MMP14, mTOR, and MAPRE1, thereby suppressing tumorigenicity. Conversely, the overexpression of miR-10a/b-5p is

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linked to cancers such as bladder cancer, leukemia, and renal cell carcinoma. In these cases, miR-10a/b inhibitors may restore tumor suppressor pathways by modulating targets like KLF4, HOXD10, and PTEN, thereby inhibiting tumor growth.

These findings highlight the promise of miR-10a/b-based therapeutics, including mimics and inhibitors, for clinical applications. However, their successful translation into clinical use necessitates interdisciplinary efforts to enhance specificity, safety, and delivery mechanisms, particularly for cancer-specific targeting.

Further research is essential to elucidate the dual roles of miR-10a/b—tumor-suppressive or oncogenic—within individual cancer types. For example, in hepatocellular carcinoma and ovarian or cervical cancers, their function may vary depending on the stage of disease progression. Understanding these mechanisms is crucial for leveraging miR-10a/b in precision oncology.

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