

miR-15b-5p in Cancers: Expression Patterns and Regulatory Pathways

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Abstract

miR-15b-5p is a multifunctional microRNA (miRNA) that is highly context-dependent in cancer, acting as either an oncomiR or a tumor suppressor miRNA (TSM) depending on tumor type, molecular characteristics, and microenvironment. This review synthesizes existing evidence to outline pathway and network integration underlying the context-dependent biological roles of miR-15b-5p across different cancers. Integrated multi-omics cancer profiling demonstrates significant upregulation across several solid tumor types, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), prostate cancer (PCa), melanoma, and early-stage breast cancer. Conversely, downregulation has been observed in some malignancies, such as Hodgkin's lymphoma, renal cell carcinoma, and KRAS-mutant CRC. This indicates the dual roles of miR-15b-5p. Upstream, miR-15b-5p is regulated by multiple lncRNA-miRNA-mRNA axes, which affect key targets such as *CHRM3*, *PPM1D*, *CCND1*, *CDC42*, *CA2*, and *CCNE2*, which are involved in oncogenic pathways such as PI3K/Akt, NF-κB, p53, MAPK/ERK, Wnt/β-catenin, TGF-β, and VEGF signaling. In our analysis, the PI3K/Akt network and its interaction with p53 and mTOR appear to be prominently affected signaling pathways, although other regulators such as *PAQR3*, *AXIN2*, and *ACVR2A* may contribute to broader tumor-specific phenotypes. By systematically integrating evidence across diverse malignancies and distinguishing experimentally validated targets from predicted interactions, this study provides a consolidated and mechanistically grounded framework positioning miR-15b-5p as a context-dependent therapeutic, prognostic, and diagnostic candidate. While current evidence remains largely preclinical, our synthesis clarifies inconsistencies in the literature and establishes a structured foundation for future clinical validation.

Keywords: miRNA, miR-15b-5p, Profiling, OncomiR, Tumor suppressor miRNA, Pathways, Cancers

Introduction

MicroRNAs (miRNAs) are 19-25-nucleotide non-coding RNAs that function as regulators of gene expression, primarily at the post-transcriptional level [1,2]. miRNA biogenesis begins with the transcription of pri-miRNAs by RNA polymerases II/III, then processed by the Drosha-DGCR8 complex into hairpin-structured pre-miRNAs. These pre-miRNAs are then exported to the cytoplasm via Exportin-5 and subsequently cleaved by Dicer to generate mature

miRNAs, then loaded into Argonaute (AGO) proteins to mediate gene regulation [2–4]. The first miRNA, lin-4 and lin-7, initially discovered in *Caenorhabditis elegans*, were thought to be small RNAs without biological function, but their conservation across species later revealed essential regulatory roles. It is known that more than 1,000 human miRNAs regulate over 30% of mammalian genes, underscoring their importance as key components of gene-expression control [1–3].

miRNAs regulate gene expression by binding to the 3'UTR of target mRNAs, where the degree of complementarity determines whether regulation proceeds through mRNA degradation or translational repression. Because a single miRNA can regulate multiple transcripts, and each mRNA can be targeted by several miRNAs, target identification requires integrating bioinformatic predictions with experimental validation [2,5,6]. In cancer, miRNAs modulate genes involved in essential cellular processes such as proliferation, apoptosis, differentiation, metabolism, metastasis, and immune response [7–10].

Dysregulation of miRNA expression disrupts molecular homeostasis and drives tumor initiation, progression, and heterogeneity, ultimately shaping their potential as diagnostic, prognostic, and therapeutic-stratification biomarkers [1,4,11]. Notably, the miR-15 family targets several oncogenes, including *BCL2*, *Cyclin D1*, and *MCL1*, as well as key cell cycle-related genes such as *cyclin B*, *cyclin D1*, *cyclin D3*, and *cyclin E*, thereby suppressing cancer cell proliferation. The miR-15 family can partially compensate for p53 loss and is regulated by epigenetic mechanisms. Therefore, epigenetic modulators that restore miR-15 expression represent a promising strategy for miRNA-based anticancer therapy. Thus, the miR-15 family emerges as a tumor suppressor in cancer [12].

miR-15b-5p belongs to the miR-15 family encoded by the *MIR15B* gene, which is located on chromosome 3q25.33 [13,14]. miR-15b-5p is upregulated in NSCLC [15], gastric cancer [16], and PCa [17] compared to healthy controls. Meanwhile, it has also been found to be downregulated in KRAS-mutated CRC compared to non-mutated samples [18] and classical Hodgkin lymphoma (cHL) compared to reactive lymphadenopathy samples [19]. Previous studies suggest that miR-15b-5p has a context-dependent dual function, acting either as an oncomiR or TSM, reflecting its complexity and tissue-specific regulatory roles in cancer [14].

Unlike previous reviews that primarily summarized individual targets, this review proposes a pathway-integrated conceptual framework by explaining how miR-15b-5p exerts context-dependent dual roles across cancers. Rather than acting through a single linear lncRNA-miRNA-mRNA axis, miR-15b-5p functions as a regulatory node within interconnected

signaling networks, coordinately modulating multiple downstream pathways and contributing to its context-dependent effects across various cancers. This network-oriented perspective may help reconcile conflicting reports, which describe it as either oncogenic or tumor-suppressive and provide a conceptual basis for future mechanistic and translational studies.

Materials and methods

This study utilized narrative approaches to conduct a comprehensive review analysis. Relevant literature was searched using the PubMed database with the keywords “miR-15b-5p; AND cancer” within the search section. In addition to PubMed, we searched on Google Scholar using the same keywords to support relevant literature.

The initial screening was performed based on titles and abstracts. The inclusion criteria for the literature comprised original research articles and review papers published in English between 2015 and 2025. Articles identified during the initial screening were further assessed through full-text review to determine their relevance to the scope of this review. Non-English publications, lacking cancer-related studies, and non-human biological samples, such as animal cancer cell line models, were excluded from the analysis. To improve interpretability, this review differentiates between predicted and experimentally validated miR-15b-5p target genes. Predicted targets were derived from bioinformatic and expression profiling studies, whereas validated targets were supported by in vitro and in vivo studies.

To ensure systematic evaluation, selected studies were organized using a structured Excel-based checklist, which included information on miRNA type, associated lncRNAs, target genes, major findings, experimental methods, sample type (e.g., plasma, tissue, FFPE), study population, and DOI. This structured evaluation facilitated the identification of studies that were sufficiently relevant and informative to serve as the primary sources for this review.

The extracted data then categorized into 4 main areas:

- 1) The dual roles of miR-15b-5p in cancers, including its oncogenic and tumor-suppressive functions through profiling studies.
- 2) Upstream regulatory mechanisms influencing miR-15b-5p.
- 3) Experimentally validated and predicted target genes of miR-15b-5p and their involvement in key signaling pathways.
- 4) The potential clinical implications of miR-15b-5p, including its therapeutic relevance in reducing cancer aggressiveness and improving treatment outcomes.

To guide the analysis, several research questions were addressed, including how miR-15b-5p exhibits dual roles in cancer through profiling studies and how its upstream regulators influence its expression in different tumor contexts. We also examined how miR-15b-5p regulates multiple signaling pathways through its predicted and experimentally validated target genes. Finally, we discussed the broader implications of miR-15b-5p in cancer biology, including its potential therapeutic relevance in attenuating tumor aggressiveness and improving treatment outcomes.

Results and discussions

Profiling miR-15b-5p and its dual roles in cancer

Profiling studies consistently show that miR-15b-5p is dysregulated in various cancer types. This dysregulation has been detected using quantitative Real-Time Reverse Transcription PCR (qRT-PCR) [15,20–22], droplet digital Reverse Transcription PCR (dd-RT-PCR) [23], next-generation sequencing (NGS) [24,25], microarray [16,26], NanoString [27,28], and miRNA-seq [15,29].

miR-15b-5p is commonly upregulated, particularly in solid tumors. In NSCLC, miR-15b-5p is significantly upregulated in serum, plasma, and tumor-derived exosomes, whereas in CRC, it is upregulated in both systemic and tumor tissues. PCa similarly shows robust upregulation in serum and at the transcriptomic

level, both in single-cell and bulk RNA-seq datasets [17,30]. This consistent upregulation suggests that miR-15b-5p may function as a conserved oncogenic factor in various malignancies.

Moreover, miR-15b-5p has also been reported to be downregulated in several types of cancer, such as cHL [19], renal cell carcinoma [31], Erdheim-Chester disease (ECD) [27], and specific gastrointestinal cancer [29]. In CRC, however, its expression appears to be compartment-specific (**Table 1**). miR-15b-5p is upregulated in CRC serum compared with healthy controls [32], whereas miR-15b-5p is significantly downregulated in KRAS-mutated tissues compared to wild-type counterparts [18]. Interestingly, plasma samples from KRAS-mutated CRC have shown increased miR-15b-5p levels [23]. This apparent discrepancy may reflect differences between intracellular and circulating miRNA dynamics. While miR-15b-5p appears to be downregulated in KRAS-mutated tumor tissues, tumor cells may actively release miRNAs into the circulation through extracellular vesicles (EV) [33] or RNA-binding protein complexes [34]. In addition, evidence suggests that miRNA loading into EV is not a passive process but may involve selective sorting mechanisms. Consistent with this, several diseases, including cancer, exhibit dysregulated EV-miRNA profiles, suggesting selective miRNA packaging into extracellular vesicles during pathogenesis [34]. This may contribute to the elevated circulating levels observed in plasma or serum. However, this relationship needs further investigation, particularly regarding the correlation between miR-15b-5p expression in tumor tissues and plasma. Studies analyzing paired tissue and plasma samples collected at the same time point would be important to better elucidate this relationship in CRC. Furthermore, given that KRAS mutations drive constitutive activation of the EGFR downstream signaling cascade, miR-15b-5p may participate in KRAS-dependent transcriptional and post-transcriptional networks, potentially functioning within a dynamic feedback regulatory loop.

However, variations in sample types (e.g., tissue vs plasma or serum), patient characteristics, and experimental methodologies across studies may also contribute to these discrepancies. Furthermore, many mechanistic insights into miRNA secretion are derived from preclinical models, and their relevance in clinical

settings remains to be fully elucidated. Collectively, these contrasting patterns suggest that miR-15b-5p regulation is highly context-dependent and influenced by tumor origin, microenvironment, and molecular characteristics.

Table 1 Summary of studies investigating the profile of miR-15b-5p in human cancer. The table shows that miR-15b-5p exhibits differential expression, either upregulated or downregulated, depending on the type of cancer.

Cancer type	Sample types	Methods	Pattern of expression	Cancer stage	Population	Citation
NSCLC	- Serum (n = 94 training cohort, n = 70 validation) - HC (n = 58 TC, n = 54 validation)	- qRT-PCR - Fluorescence quantum dots - liquid bead array	Upregulated	Stage I, IIa-IIIb	China	[20]
NSCLC	- Serum-derived exosomes from NSCLC patients EGFR-mutant (n = 32) - EGFR-WT (n = 32) - HC (n = 20)	qRT-PCR	Upregulated	Stage II-IV	China	[21]
NSCLC	- Plasma-derived tumor exosomes (n = 46) - HC (n = 42)	- miRNA-seq - qRT-PCR	Upregulated	Stage I	China	[35]
Lung Cancer	- Plasma samples from LC (n = 68), TB (n = 38) - HC (n = 41)	qRT-PCR	Upregulated	Stage I	Kazakhstan	[36]
CRC	- Serum of CRC (n = 59) - Serum from AA (n = 74) - HC (n = 80)	qRT-PCR	Upregulated in CRC and AA vs HC (not significant)	Stage I, II, III, IV	Barcelona, Spain	[32]
CRC	- Tumoral (n = 26, 11 <i>KRAS</i> -mutated, 15 WT: Non-mutated <i>KRAS</i>) - Peritumoral (n = 13) tissues	qRT-PCR	Downregulated in <i>KRAS</i> -mutated vs WT	Unspecified	Romania	[18]
CRC	- Plasma (n = 35) - Plasma from <i>KRAS</i> -WT (n = 11) - Plasma from <i>KRAS</i> -mutated (n = 16)	dd-RT-PCR	Upregulated in <i>KRAS</i> -mutated vs WT (borderline <i>p</i> -value)	Primary CRC	Italy	[23]
CRC	Human colorectal adenoma (n = 15), intramucosal cancer (n = 8), and invasive CRC (n = 19) with MSS phenotype	- miRNA microarray - qRT-PCR	Upregulated	Stage I, II, III, IV	Japan	[26]
PCa	- Serum from PCa patients (n = 112) - HC (n = 112)	qRT-PCR	Upregulated	≤ T2 and ≥ T2	China	[17]
PCa	- scRNA-seq and buRNA-seq data of primary PCa from GEO and TGCA - Fibroblast cell lines	- Single-cell RNA sequencing - Bulk RNA sequencing	Upregulated in PCa tissues vs HC	Unspecified	Unspecified	[30]

Cancer type	Sample types	Methods	Pattern of expression	Cancer stage	Population	Citation
	- Mouse xenograft model	- qRT-PCR - <i>in vitro</i> - <i>in vivo</i> - Western blot				
Melanoma	- Plasma from melanoma patients (n = 30) - HC (n = 32)	qRT-PCR	Upregulated	Stage I, II, III, IV	Italy	[37]
Melanoma	FFPE from cutaneous melanoma with 3 cohort (training, validation, and independent) (n = 92, n = 119, n = 45)	- Microarray - qRT-PCR - CD45 IHC	Upregulated	Stage I, II, III, IV	USA	[38]
ESCC	- ESCC tissue stage I (n = 27), stage II (n = 74), stage III (n = 60) - Normal esophageal mucosa tissues (n = 11) from TCGA - ESCC tissues for validation (n = 51) and self-paired normal tissues (n = 51)	- Integrative bioinformatics analysis (TCGA) - qRT-PCR	Upregulated	Stage I, II, III, IV	China	[39]
ECD	- Plasma and tissue biopsies of ECD (n = 32), LCH patients (n = 7) - HC (n = 15)	- NanoString - qRT-PCR	Downregulated in ECD vs HC Upregulated in LCH vs ECD	Unspecified	Israel, USA, France	[27]
Laryngeal Cancer	Plasma and exosome from pre- and post-therapy of laryngeal cancer patients (n = 30)	qRT-PCR	Upregulated	Stage I, II, III, IV	Romania	[22]
HPV-associated Penile Squamous Cell Carcinoma	- Fresh penile cancer tissue (HPV-positive) (n = 22) - Adjacent non-tumor tissue (n = 5)	Nanostring	Upregulated	Stage I, II, III	Brazil	[40]
Early-stage Breast Cancer	- Plasma from women with BI-RADS category 4 breast lesions malignant (n = 27) - Benign (n = 86)	- NGS - qRT-PCR	Upregulated	DCIS, Stage I & III	United States	[24]
cHL	- FFPE tissue from cHL (n = 32) - Reactive lymphadenopathy (n = 60)	qRT-PCR	Downregulated	Early vs late stage	Turkey	[19]
Gastric Cancer	Three different SNU-5 subtypes (cell line) (CD44+ CSCs, CD90+ CSCs, and CD44- CD90- (control))	- miRNA microarray - qRT-PCR	Upregulated in CD44+ CSCs vs control	Unspecified	Unspecified	[16]
Oral Cancer	Public datasets from GEO (GSE28100: oral cancer (n = 17) vs normal tissues (n = 3); GSE23558: oral cancer (n = 27) vs normal tissues (n = 5))	Bioinformatics (GEO2R, DAVID, STRING, Cytoscape, and miRDIP databases)	Upregulated	Unspecified	Unspecified	[41]

Cancer type	Sample types	Methods	Pattern of expression	Cancer stage	Population	Citation
Bladder Cancer	Matched samples of FFPE, urine exosomes, plasma (n = 16) and white blood cells (WBCs) (n = 11)	- NanoString nCounter - miRNA assay - ddPCR	Upregulated	Unspecified	USA	[28]
Primary CNS Lymphoma (CNS DLBCL)	- CSF and brain tumor biopsies (n = 19) - Non-malignant brain lesions (n = 22)	- NGS - qRT-PCR	Upregulated	Unspecified	Poland	[25]
TNBC	- TCGA dataset (n = 173)	- Bioinformatics (TCGA analysis, Cox regression, GO/KEGG, ceRNA network) - qRT-PCR	Upregulated	Unspecified	China	[42]
ccRCC	- Urine specimens (n = 28) - HC (n = 28)	qRT-PCR	Upregulated	T1, T2, T3, T4, M0, M1, N0, N1	Italy	[43]
Gastrointestinal Cancer	- Plasma and muscle biopsies (rectus abdominis) (n = 25) - Non-malignant (n = 15)	- qRT-PCR - sRNA-seq	Downregulated	Stage I, II, III, IV	Italy	[29]
HCV-induced HCC	- Blood from HCV patients without cirrhosis (n = 100) - HCV with cirrhosis (n = 100) - HCC and HCV patients (n = 100) - HC (n = 100)	qRT-PCR	Upregulated	Unspecified	Egypt	[44]
Renal cell carcinoma	- Tumorous specimens (n = 20) - Adjacent normal kidney tissues (n = 20)	qRT-PCR	Downregulated	Stage I & III	Hungary	[31]
PDAC	- PDAC tumor tissues (n = 30) - Non-tumoral pancreatic tissues (n = 16)	qRT-PCR	Upregulated	Stage IA/IB/IIA/IIB/III/IV	Romania	[45]

miR-15b-5p is also frequently upregulated in early-stage tumors. This indicates that miR-15b-5p is likely involved in the initiation and early development of cancer. Elevated levels have been reported in the early stages of NSCLC [15,20,36], melanoma [37], CRC and advanced adenomas [32], as well as early breast lesions such as ductal carcinoma in situ (DCIS) and stage I breast cancer [24]. Therefore, miR-15b-5p can be developed as a promising non-invasive biomarker for early cancer detection.

miR-15b-5p exhibits a broad and reproducible deregulation profile across various malignancies. Its frequent upregulation, detectability in early disease

stages, and robust cross-platform consistency underscore its potential as a clinically relevant biomarker for cancer detection and monitoring [14]. Conversely, miR-15b-5p downregulation in specific tumor types reflects the complexity of its biological mechanisms, suggesting that it may act as an oncomiR or a TSM depending on the molecular context. These dual roles highlight the importance of evaluating miR-15b-5p within the unique biological framework of each tumor type when interpreting its mechanistic role and potential clinical applications.

Upstream regulation of miR-15b-5p

Genetic variation of miRNA

Several studies have demonstrated that mutations in miRNA sequences can disrupt their biogenesis. Research by Duan *et al.* [46] showed that a Single Nucleotide Polymorphism (SNP) of miR-125a sequence in Human HEK293 cell lines decreases the processing of pri-miRNA to pre-miRNA, thereby reducing the miRNA's ability to regulate its target genes. Similar findings were reported for the SNP of miR-126 in chronic lymphocytic leukemia (CLL) patient samples, diminishing the activity of the Drosha-DGCR8 complex in cleaving its pri-miRNA [47]. Sun *et al.* [48] also provided evidence of polymorphism-induced effects on miR-15b-5p. Although conducted in porcine, the study demonstrated that mutations within miR-15b host gene can disrupt the transition from pri- to pre-miRNA and alter strand selection, shifting the dominant mature miRNA from miR-15b-5p to miR-15b-3p loaded onto AGO. Collectively, these findings underscore that polymorphisms of miRNA genes may substantially disrupt their biogenesis and alter mature miRNA expression. Additionally, it suggests a potential impact

on the regulation of downstream targets that still requires further study.

Long non-coding RNA

Long non-coding RNAs (lncRNAs), which are transcripts longer than 200 nucleotides, represent key regulatory molecules that modulate miRNA activity through multiple interconnected molecular mechanisms [49]. The well-established function of lncRNA is to act as competing endogenous RNAs (ceRNAs) by sponging miRNA through complementary base pairing of miRNA recognition elements (MREs), thereby preventing miRNA interaction with its target mRNAs [50,51]. Moreover, lncRNA also influences transcriptional and post-transcriptional miRNA biogenesis, including epigenetic regulation, miRNA maturation, and miRNA stability [49,52]. In the case of miR-15b-5p, the biological consequences are highly contextual, depending on its function as a tumor suppressor miR (TSM) or as an oncomiR. Consequently, the biological outcomes of lncRNA can function either as oncogenic or tumor-suppressive lncRNA, depending on the genes targeted by miRNA, as shown in **Table 2**.

Table 2 lncRNA/miR-15b-5p regulatory interactions and associated biological activities. This highlights the involvement of lncRNA/miR-15b-5p interactions in regulating cancer progression, including proliferation, migration, invasion, and apoptosis.

	Cancer type	lncRNA	Target gene(s)	Biological activity	Citation
Oncogenic Activity	PCa	TTN-AS1, TRPM2-AS, and AFAP-AS1	<i>CHRM3</i>	↑ cell proliferation and aggressiveness	[53]
	Hypopharyngeal Squamous Cell Carcinoma (HPSCC)	Linc00662	Not mentioned	↑ cell proliferation, invasion, and migration ↓ cell apoptosis	[35]
	Osteosarcoma	TRPM2-AS	<i>PPM1D</i>	↑ cell viability, proliferation, and migration ↓ cell apoptosis	[54]
	CRC	CERS6-AS1	<i>SPTBN2</i>	↑ cell proliferation, invasion, migration, EMT process, and stemness	[55]

	Cancer type	lncRNA	Target gene(s)	Biological activity	Citation
Tumor Suppressive Activity	Hepatocellular Carcinoma (HCC)	H19	<i>CDC42</i>	↑ proliferation, invasion, and migration ↓ apoptosis	[56]
	Breast Cancer (BC)	MEG3 and FAM66E	<i>PIK3R1</i> and <i>JUN</i>	↑ proliferation ↓ apoptosis	[42]
	Osteosarcoma	PVT1	<i>CCND1</i>	↑ cell proliferation and chemotherapy resistance	[57]
	Bladder Cancer	MAGI2-AS3	<i>CCDC-19</i>	↓ cell proliferation, colony formation, migration, and invasion	[51,58]
	HBV-induced Hepatocellular Carcinoma	SSTR5-AS1 and FAM138B	<i>CA2</i> and <i>CCNE2</i>	↑ cell proliferation	[50]
	Cervical Cancer (CC)	FENDRR	<i>TUBA1A</i>	↓ cell viability, proliferation, invasion, and migration ↑ cell apoptosis	[59]

Recent studies consistently demonstrate that lncRNA/miR-15b-5p interactions regulate the expression of target genes involved in major oncogenic pathways. In prostate cancer, the lncRNA AFAP-AS1 decreases miR-15b-5p activity through sequence-specific interactions, resulting in overexpression of *CHRM3* and activating the Hippo-YAP pathway, thereby promoting tumor proliferation, cell viability, and aggressiveness [53]. A similar upstream interaction is observed in HNSCC, where Linc00662 suppresses miR-15b-5p activity and supports cancer stem cell-like phenotypes [35]. In triple-negative breast cancer (TNBC), TCGA-based bioinformatic analyses suggest that MEG3 and FAM66E are significant upstream regulators of miR-15b-5p. Both lncRNAs show strong statistical associations with altered expression of *PI3KR1* and *JUN*, key components of PI3K/Akt and AP-1 signalling, respectively. Contributing to the heterogeneity of proliferative and stress-response pathways characteristic of TNBC [42].

A more complex pattern is observed in osteosarcoma, where 2 different lncRNAs, TRPM2-AS and PVT1, simultaneously suppress the tumor-suppressive activity of miR-15b-5p [54,57]. TRPM2-AS upregulates *PPMID*, a negative regulator of p53-mediated apoptosis, thus promoting proliferation and

survival [54]. Whereas PVT1 derepresses *CCND1*, enhancing the G1/S transition and accelerating cell proliferation [57]. Furthermore, in HCC, miR-15b-5p demonstrates opposing biological roles depending on its specific target genes, which influence the functional activity of the lncRNA involved. H19 acts as an oncogenic lncRNA that suppresses miR-15b-5p and activates the CDC42/PAK1 axis to promote tumor proliferation, invasion, and migration [56]. Whereas SSTR5-AS1 and FAM138B exert the opposite effect by neutralizing the oncomiR activity of miR-15b-5p, maintaining *CA2* and *CCNE2* expression and ultimately promoting tumor suppressive signaling [50].

Overall, although lncRNAs exhibit diverse regulatory activities, available experimental evidence consistently indicates that most lncRNA/miR-15b-5p interactions occur via sponging or ceRNA mechanisms, thereby preserving the expression of target mRNAs. This predominance pattern suggests that downstream regulatory changes are driven not only by alterations in miR-15b-5p expression levels, but also by lncRNA-mediated inhibition of its biological activity. Moreover, cross-malignancy findings show that the final biological outcome is determined not solely by the presence of sponging interactions, but also by the functional context of miR-15b-5p and its target genes in each cancer type.

Downstream regulation of miR-15b-5p

miR-15b-5p targets genes across multiple signaling pathways, leading to context-dependent biological effects across various cancer types. Its predicted (bioinformatic and expression profiling) and validated (*in vitro* and *in vivo*) targets are distributed across major oncogenic networks, as illustrated in **Figure 1** and summarized in **Table 3**. Because each target gene contributes to a distinct signaling cascade, miR-15b-5p repression results in pathway-specific

effects that influence the proliferation, survival, inflammation, or migration of cancer cells. Consequently, the functional role of miR-15b-5p, whether TSM or oncomiR, is determined by which signaling pathway is predominantly affected in a given cancer type. The following section provides an integrated overview of these signaling mechanisms by illustrating the relationships between miRNA target genes and their positions within each pathway.

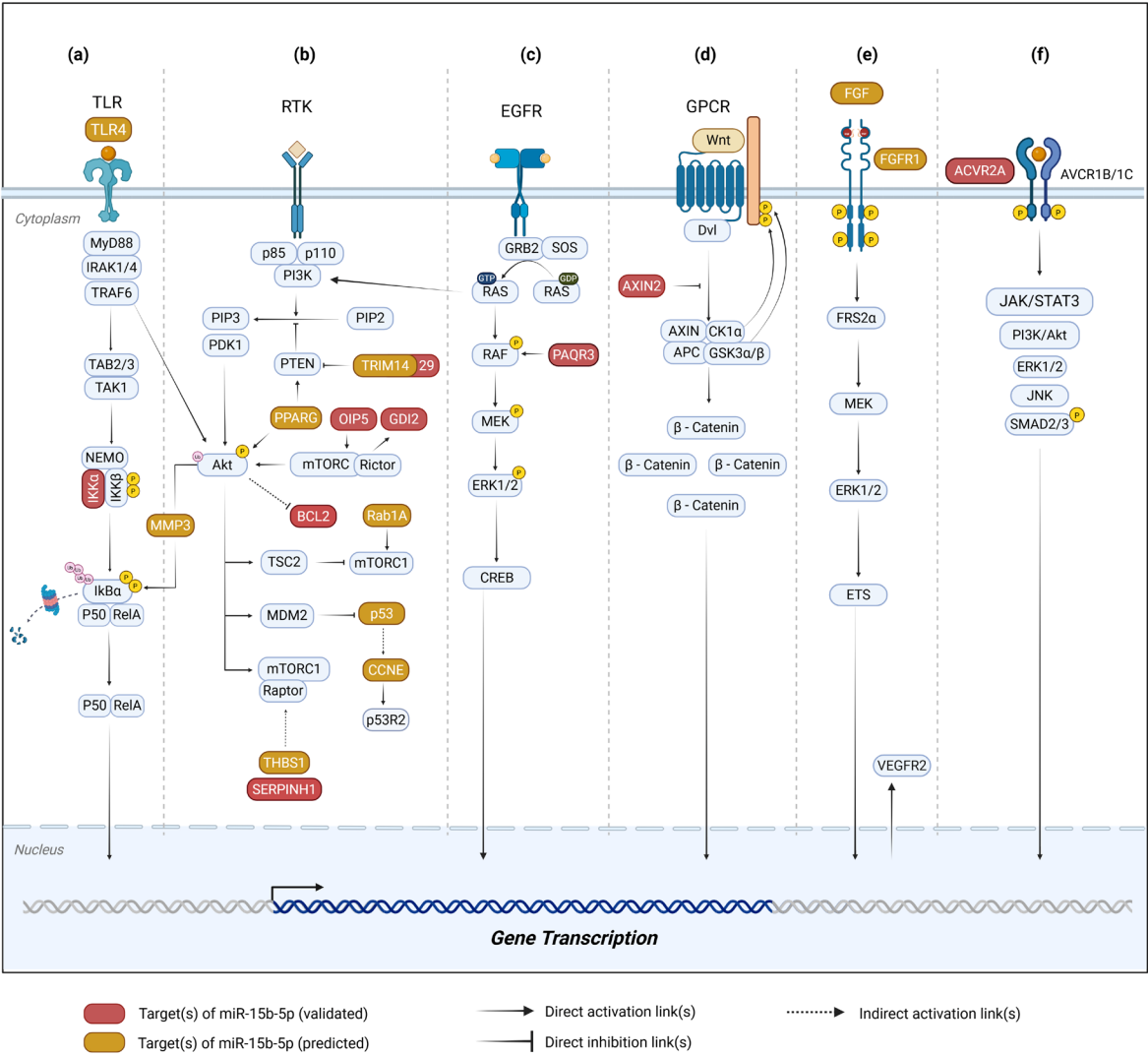


Figure 1 Downstream signaling pathways modulated by miR-15b-5p across multiple cancer-related molecular networks. (a) NF-κB pathway, (b) PI3K/Akt signaling with downstream crosstalk to the p53 regulatory axis, (c) MAPK/ERK pathway, (d) Wnt/β-catenin pathway, (e) VEGF signaling pathway, and (f) TGF-β/SMAD pathway. Created in BioRender. Dewi, D. (2025) <https://BioRender.com/eernija>.

Table 3 Summary of pathways involved in miR-15b-5p regulation. This highlights the target genes and signaling pathways associated with *miR-15b-5p*. In addition, *miR-15b-5p* may function as either an oncogenic miRNA or tumor suppressor depending on the molecular context.

Cancer type	Sample type	Methods	Target genes	Pathway	Validation Status	Potential role of miRNA	Citation
PCa	- Human prostate epithelial cell lines - LNCaP (ATCC, CRL-1740) - PC3 cells	- qRT-PCR - In cell Western	<i>ACVRA2</i>	TGF- β	Validated	oncomiR $\downarrow$ miR-15b-5p in LNCaP cells vs HC $\downarrow$ miR-15b-5p $\uparrow$ <i>ACVRA2</i> cell cycle arrest occurred	[60]
PCa	Data sets of mRNA and miRNA expression and clinical information from the University of California Santa Cruz Xena database	Bioinformatics	<i>NUSAPI</i> and <i>AURKB</i>	- Sphingosine 1-phosphate - Liver Kinase B1 signaling - TRAIL signaling pathway - ErbB receptor signaling network - IFN-gamma pathway - Alpha9 beta1 integrin signaling	Predicted	oncomiR $\uparrow$ miR-15b-5p poor prognosis	[61]
PCa	- PCa cell lines (22RV1, PC3) - PCa tissues - Adjacent normal tissues (TCGA data) - Xenograft mouse model	- qRT-PCR - Western blot - Dual-luciferase reporter assay - <i>In vitro</i> - <i>In vivo</i>	<i>RECK</i>	RECK/ MMP	Validated	oncomiR $\downarrow$ miR-15b-5p $\rightarrow$ <i>RECK</i> $\uparrow$ cell growth $\uparrow$ invasiveness $\uparrow$ tumor recurrence	[8]
HCC	- HepG2, Hep3B, SKHEP-1, Alexander cells, Chang liver, THLE2, Huh7, HLK2, HKK2, HLK4, HLK1, HLK5, HKK1, HLK6, HLK3, SH-J1 cell lines - BALB/c nude mice (BALB/cByJ-Hfh11 ^{nu})	- <i>In vitro</i> - <i>In vivo</i> - qRT-PCR - Dual-luciferase assay - IHC - Immunoblotting	<i>OIP5</i>	AKT/mTORC1 and β -catenin	Validated	TSM $\uparrow$ miR-15b-5p $\downarrow$ <i>OIP5</i> $\downarrow$ tumor growth $\downarrow$ metastasis	[62]
HCC	- Liver cancer tissues (n = 69) - Adjacent non-cancerous tissues	- qRT-PCR - Western blot - Dual-luciferase reporter assay - <i>In vitro</i> - <i>In vivo</i>	<i>Axin2</i>	Wnt/ β -catenin	Validated	oncomiR $\uparrow$ miR-15b-5p $\downarrow$ <i>Axin2</i> $\uparrow$ proliferation $\uparrow$ invasion $\uparrow$ TNM stage	[7]

Cancer type	Sample type	Methods	Target genes	Pathway	Validation Status	Potential role of miRNA	Citation
	- Cell lines (HepG2, Huh7, Hep3B, HCCLM3)					↑ tumor capsular infiltration ↓ overall survival	
CRC	- CRC cell lines (SW620, HCT116, DLD1, SW1116, NCM460) - CRC tissues and adjacent normal mucosa (23 pairs) - CRC patient tissues (TCGA data) - CAC and xenograft mouse model	- qRT-PCR - Western blot - Dual-luciferase reporter assay - ChIP - IHC - <i>In vitro</i> - <i>In vivo</i>	<i>NF-KB1</i> , <i>IKK-α</i>	NF-KB/XIAP	Validated	TSM ↑ miR-15b-5p ↓ <i>NF-KB1</i> ↓ <i>IKK-α</i> ↑ miR-15b-5p → 5-FU resistance ↓ tumor progression	[63]
CRC	- CRC tissues (n = 94) HCT116, SW480, - SW620, LoVo, Caco-2, HT-29 cell lines - Xenograft mouse model	- qRT-PCR - Western blot - Luciferase reporter assay - IHC - <i>In vitro</i> - <i>In vivo</i>	<i>ACOX1</i>	Peroxisomal β-oxidation	Validated	oncomiR ↑ miR-15b-5p → <i>ACOX1</i> ↑ metastasis	[9]
Microsatellite Stable Colorectal Cancer (MSS CRC)	- MSS CRC tissues (human, n = 160 - 261) - MSS CRC cell lines (CT26, MC38, SW1116, HT29, SW480, SW620); Colitis-Associated Cancer (CAC) - Murine models; Syngeneic subcutaneous CT26 - MC38 tumor-bearing mice	- qRT-PCR - Luciferase reporter assay - Western blot - ChIP - IHC - <i>In vitro</i> - <i>In vivo</i>	<i>PD-L1</i>	Immune Response Checkpoint (PD1-PDL1)	Validated	TSM ↑ miR-15b-5p ↓ <i>PD-L1</i> ↑ IL-17A ↑ p65 / NRF1 activation ↓ miR-15b-5p ↑ PD-L1 expression ↑ anti-PD-1 resistance IL-17A blockade ↓ p65 / NRF1 signaling ↑ miR-15b-5p ↓ PD-L1 expression ↑ anti-PD-1 efficacy	[64]
NB	- SK-N-AS, NB-19, and SK-N-BE, NB975, K562.mbIL21.4-1BBL cell lines co-cultured with CD8+T cell and NK cells - C57/BL6 mice	- <i>In vitro</i> - <i>In vivo</i> - Western blot - qRT-PCR - Luciferase reporter assay - IHC	<i>PD-L1</i>	Immune Response Checkpoint (PD1-PDL1)	Validated	TSM ↓ miR-15b-5p ↑ <i>PD-L1</i> ↑ TIL exhaustion in NB patients and PDX tumors	[65]

Cancer type	Sample type	Methods	Target genes	Pathway	Validation Status	Potential role of miRNA	Citation
NB	- NB patient-derived xenografts - NB cell lines (SK-N-BE (2), NB-19, CHLA-136, SH-EP Tet21N) - Xenograft model in NSG mice	- qRT-PCR - Western blot - Luciferase reporter assay - <i>In vitro</i> - <i>In vivo</i>	<i>MYCN</i>	Post-transcriptional repression (RISC/Ago2/3'UTR) of MYCN	Validated	TSM ↑ miR-15b-5p ↓ <i>MYCN</i> ↓ proliferation ↓ migration ↓ invasion ↓ colony formation ↓ tumorigenesis	[66]
NPC	- 5-8F, 6-10B, S-18, S-26, CNE1, CNE2 and SUNE2 cell lines - Fresh NPC tissues (n = 25), - HC tissues (n = 17) - FFPE of primary NPC tissues (n = 69)	- qRT-PCR - Western blot - IHC - <i>In vitro</i> - <i>In vivo</i> - Luciferase reporter assay	<i>TRIM29</i>	PTEN/AKT/mTOR OR	Validated	TSM ↓ miR-15b-5p ↑ <i>TRIM29</i> ↑ proliferation ↑ EMT ↑ metastasis	[67]
LGG	- Glioma tissues (n = 5) - Normal cerebral tissues (n = 3)	- Bioinformatics - Western blot	<i>SPTBN2</i>	- Neuroactive ligand-receptor interaction - Cytokine-cytokine receptor interaction - Calcium signaling pathway - cAMP signaling pathway	Predicted	oncomiR ↑ miR-15b-5p ↓ <i>SPTBN2</i> poor prognosis	[68]

NF- κ B pathway

NF- κ B is a central transcription factor complex that maintains cellular homeostasis by regulating inflammation, survival, and immune responses. Its dimer remains inactive by binding to I κ B until upstream signals trigger I κ B phosphorylation and degradation, enabling NF- κ B nuclear translocation and promoting gene transcription [69]. Within the NF- κ B axis, miR-15b-5p modulates several key components across different cancer types. In HCV-induced hepatocellular carcinoma, miR-15b-5p is predicted to target *TLR4*, suggesting a potential regulation in inflammatory signaling based on bioinformatic [44]. In colorectal cancer, its downregulation leads to upregulation of *IKK α* expression, thereby decreasing sensitivity to 5-fluorouracil chemotherapy [63]. Whereas in oral cancer, miR-15b-5p is predicted to target *MMP3* and its overexpression enhances cell proliferation, migration and epithelial-mesenchymal transition (EMT) in vitro [41,70].

PI3K/Akt pathway

The PI3K/Akt pathway is one of the major regulators that plays a crucial role in cell survival, proliferation, and metabolism. Activated primarily through receptor tyrosine kinases (RTKs) or G-protein coupled receptors (GPCRs). PI3K activation generates PIP3, which recruits and activates Akt, enabling downstream regulation of targets involved in cell-cycle progression, apoptosis suppression, and motility. Dysregulation of these pathways is common in cancer and frequently associated with enhanced tumor growth and therapeutic resistance [71].

In head and neck squamous cell carcinoma (HNSCC), miR-15b-5p downregulation contributes to the upregulation of *TRIM14* and *Rab1A*. TRIM14 suppresses PTEN, thereby enhancing PI3K/Akt activity and promoting tumor progression. Whereas *Rab1A* amplification further strengthens proliferative signaling [72]. In nasopharyngeal carcinoma (NPC), elevated *TRIM29* similarly promotes proliferation and

metastasis by inhibiting PTEN, reinforcing sustained Akt activation [67,73]. In oral cancer, bioinformatic analyses predict that miR-15b-5p targets *PPARG* [41], a transcription factor that exerts dual effects on Akt signalling, particularly in HNSCC [74]. *PPARG* is typically elevated in stromal or tumor-adjacent normal cells within the tumor microenvironment (TME), where it can activate PTEN to enhance apoptosis, yet simultaneously stimulates Akt as part of anti-inflammatory and tissue-repair responses. In certain contexts, *PPARG* can increase chemosensitivity rather than promote tumor growth [74]. More broadly, bioinformatic studies in oral cancer indicate miR-15b-5p is predicted to target *SERPINH1* [41]. Furthermore, evidence from colorectal cancer, however, confirms *SERPINH1* as a direct miR-15b-5p target, which is associated with advanced T stage, lymph node involvement, distant metastasis, and poor overall survival [75].

In hepatocellular carcinoma (HCC), miR-15b-5p is linked to OIP5-driven Akt activation and increased migration. Thus, suggesting a direct regulatory axis that enhances metastatic behavior through augmented Akt signaling [62]. Moreover, miR-15b-5p directly targets *GDI2* in thyroid cancer. Increased *GDI2* furthermore induces *MMP2/9*, leading to enhanced proliferation and invasion [76]. In lung cancer, miR-15b-5p directly represses *BCL2* expression, thereby reducing apoptosis and promoting cell viability, migration, and EMT, driven by survival signaling [77]. Collectively, these findings indicate that the PI3K/Akt pathway is more frequently implicated across various cancer types, suggesting its prominent role compared with other signaling pathways.

p53 pathway

The Tumor Protein p53 (p53) axis integrates stress responses to regulate apoptosis, cell-cycle arrest, and DNA repair, and miR-15b-5p intersects with this pathway primarily through genes that regulate proliferation and apoptosis properties [78]. In penile cancer and glioblastoma, profiling data show that tumor protein p53 (*TP53*), the gene encoding p53, is directly suppressed by miR-15b-5p. This downregulation of p53 leads to reduced apoptosis and enhanced proliferative capacity [40,79]. In HBV-induced HCC, miR-15b-5p represses *CCNE*, a key regulator of the G1/S transition. This reduced *CCNE* expression paradoxically associated with a poorer prognosis, reflecting a complex interplay among viral oncogenesis, disrupted p53 signaling, and compensatory alterations in cell-cycle regulators [50].

MAPK pathway

Mitogen-activated protein kinase (MAPK) regulates various cellular processes, including proliferation, differentiation, apoptosis, and stress responses [80]. miR-15b-5p functions as an oncomiR in gastric cancer (GC). Overexpression of miR-15b-5p in GC cells promotes proliferation, migration, invasion, and epithelial-mesenchymal transition (EMT) through direct repression of progesterin and adiponectin receptor family member 3 (*PAQR3*) [13]. *PAQR3* functions as a tumor suppressor that constrains cellular proliferation, migration, tumorigenicity, epithelial-mesenchymal transition (EMT), and metastatic progression [13,81]. By binding to Raf-1 and sequestering it within the Golgi apparatus, *PAQR3* prevents its translocation to the cytoplasm and thereby blocks the activation of downstream effectors, ultimately suppressing MAPK pathway signaling [82].

Wnt/ β -catenin pathway

In the Wnt/ β -Catenin pathway, dysregulation of the transcription factor β -catenin significantly contributes to the initiation and progression of cancer [83–85]. miR-15b-5p is known to regulate the Wnt/ β -Catenin pathway. Dong *et al.* [7] reported that miR-

15b-5p was overexpressed in liver cancer tissue compared with normal and was validated to target the axis formation inhibitor 2 (*Axin2*). *Axin2* functions as a TSG that attenuates Wnt/ β -catenin signaling activity [7,86]. *Axin2* serves as a scaffold component of the β -catenin destruction complex under both Wnt-active and Wnt-inactive conditions. Notably, *Axin2* is a direct transcriptional target of β -catenin, such that activation of the Wnt/ β -catenin cascade leads to a concurrent rise in *Axin2* expression. This induction establishes a negative feedback loop that restrains excessive activation of the Wnt/ β -catenin pathway [87], positioning *Axin2* as a key negative regulator of the pathway. In this context, the downregulation of *Axin2* by miR-15b-5p in liver cancer supports its oncomiR role, as suppression of *Axin2* facilitates sustained Wnt/ β -catenin activation, thereby enhancing tumor cell proliferation and invasion.

VEGF pathway

The VEGF signaling cascade is a principal regulator of tumor angiogenesis via VEGFR2-dependent activation of the PI3K/AKT, Ras-Raf-MEK-ERK, and PLC γ /PKC pathways, promoting endothelial proliferation, migration, and survival [88]. Hypoxia-induced stabilization of HIF-1 α further enhances VEGF-A transcription, sustaining pathological angiogenesis, while crosstalk with fibroblast growth factor (*FGF*) signaling amplifies the angiogenic response [89,90]. In renal cell carcinoma, miR-15b-5p is markedly downregulated and inversely associated with tumor grade, indicating a tumor-suppressive and anti-angiogenic function [31]. Mechanistically, miR-15b-5p has been reported to target *FGF* ligands and *FGFR1/2*, which are central upstream regulators of the Fibroblast Growth Factor-Fibroblast Growth Factor Receptor (*FGF-FGFR*) axis responsible for activating Ras-Raf-MAPK, PI3K-AKT, and PLC γ signaling pathways essential for angiogenesis and endothelial activation. Downregulation of miR-15b-5p may therefore release *FGF/FGFR* signaling from post-transcriptional repression, consequently amplifying VEGF-mediated

angiogenesis through synergistic pathway activation [91].

TGF- β pathway

The TGF- β pathway is initiated when active TGF- β binds to type II receptors, leading to recruitment and phosphorylation of type I receptors and subsequent activation of the canonical SMAD2/3-SMAD4 complex, which translocates to the nucleus to regulate genes controlling proliferation, differentiation, and tissue homeostasis [92,93]. In canonical pathway, TGF- β activates several non-SMAD pathways including MAPK, PI3K/AKT, and Rho GTPase signaling, which control cell migration, epithelial-mesenchymal transition (EMT), and tumor progression. Within the activin subfamily of TGF- β ligands, activin binds to type II receptors such as *ACVR2A* (Activin A Receptor Type 2A), which subsequently recruit type I receptors (e.g., *ACVR1B*) to initiate both SMAD-dependent and SMAD-independent signaling cascades [93]. Activin A has been shown to downregulate miR-15b-5p and increases *ACVR2A* expression in prostate cancer cells, suggesting an inverse regulatory relationship [60]. Upregulation of *ACVR2A* may therefore enhance activin/TGF- β signaling by phosphorylating SMAD2/3 and activating non-SMAD pathways, promoting proliferation, EMT, apoptosis resistance, and tumor aggressiveness [94].

Future prospect of miR-15b-5p in cancer studies

Defining molecular heterogeneity and the dual roles

Literature profiling reveals the unique behavior of miR-15b-5p, which exhibits a dual role expression pattern determined by tumor origin, molecular subtype, and microenvironment. Although its differential expression has been well documented across various tissues, the specific molecular factors underlying this heterogeneity remain incompletely understood. Research must now focus on identifying the regulatory factors causing this variation, particularly upstream transcription regulators,

epigenetic modifications, and non-coding RNA networks (such as the lncRNA-miRNA-mRNA axis). It is also important to conduct pan-cancer and cross-tissue analyses to determine whether this dual role stems from distinct biological programs or from shared regulatory motifs. Limited pan-cancer miRNA analyses have been reported, mainly to identify miRNAs that are consistently upregulated or downregulated across multiple tumor types compared to normal tissues [95]. This study has highlighted miRNAs that act as broad tumor suppressors or oncogenic regulators in either cancer-type-specific or pan-cancer contexts. However, miR-15b-5p has rarely been a primary focus in these investigations and has been only incidentally included in a limited number of studies. Given that miR-15b-5p shows context-dependent expression patterns across different cancers, dedicated pan-cancer and integrated multi-omics analyses centered on this miRNA remain largely unexplored and represent an important direction for future research. Discovering these mechanisms is key to establishing miR-15b-5p as a promising and context-specific biomarker for diagnosis and prognosis.

Clarifying mechanistic networks and pathway intersections

Our pathway-based analysis indicates that miR-15b-5p is involved in multiple cancer processes, from proliferation to apoptosis. Most of these effects converge on the PI3K/Akt pathway, a central hub for cell survival, which interacts extensively with the p53 signaling axis to control the cell cycle. In addition to direct mRNA targeting, miR-15b-5p activity is likely shaped by multilayered regulation involving lncRNA-mediated sponging and epigenetic modulation, which may shift pathway dominance across different tumor contexts and contribute to its context-dependent dual role. Based on the literature we reviewed, upstream lncRNA regulators of miR-15b-5p remain limited and are not yet well characterized, indicating an important gap for further investigation.

While many targets cluster within the PI3K/Akt network, we also identified predicted and validated targets like PAQR3, AXIN2, and ACVR2A. These genes may have had a significant effect because they became key nodes with other major oncogenic pathways, including Wnt/ β -catenin, MAPK/ERK, and TGF- β /SMAD. It's likely to act as context-dependent modulators, broadening the functional impact of miR-15b-5p on specific tumor phenotypes. To validate these connections, future work must prioritize gain- and loss-of-function studies and luciferase reporter assays to verify direct miRNA-mRNA binding. Furthermore, using *in vivo* models is essential to confirm their physiological relevance. Further understanding of this deeper mechanistic insight would properly evaluate miR-15b-5p's potential as a candidate for pathway-guided therapy.

Driving translational applications and therapeutic strategies

It is important to distinguish between experimentally validated findings and emerging hypotheses when considering the translational potential of miR-15b-5p. Due to the large number of targets that have not been experimentally validated yet, the interpretation bioinformatics predictions require careful consideration when discussing therapeutic implications. The initial discovery-driven phase should be followed by a more rigorous and systematic validation. Using human miRNA mimics and *in vivo* xenograft models may serve as a practical starting point for confirming target interactions. This step is essential, particularly for assessing toxicity and bioavailability before any therapy can move toward human clinical trials.

One of the most likely directions of translation at this stage is the potential role of miR-15b-5p in modulating therapeutic resistance. Preclinical evidence indicates that miR-15b-5p may reverse or modulate 5-fluorouracil resistance by disrupting the NF- κ B/IKK α /XIAP axis. Some predicted targets, such as *PPARG*, may also influence the tumor microenvironment, potentially affecting treatment

response, although these indirect effects remain to be experimentally confirmed. Taken together, these findings suggest potential directions for future clinical translation, in which modulation of miR-15b-5p could be explored as a potential chemosensitizing strategy to enhance the effectiveness of standard treatment regimens, although current evidence remains largely preclinical.

The potential of miR-15b-5p in immunotherapy is also becoming an increasingly interesting area of exploration. Several reports suggest that this miRNA modulates *PD-L1* expression in neuroblastoma and CRC, suggesting a potential immunoregulatory role in specific experimental contexts. In limited preclinical models, delivery of miR-15b-5p mimics has been associated with increased responsiveness to anti-PD-1 therapy by lowering the threshold for immune activation. Even so, the effectiveness of this approach still depends heavily on how the molecule is delivered. This is why the development of nanoparticle- or exosome-based carriers that can protect and safely transport RNA remains a key requirement for advancing miRNA-based immunotherapy toward clinical use.

Overall, these results suggest that miR-15b-5p may be useful for more than just regulating a single pathway, especially in approaches aimed at overcoming treatment resistance. MiR-15b-5p may function as a context-dependent regulator of pathways associated with treatment resistance and immune modulation, as it controls NF- κ B signaling, which is involved in chemotherapy resistance to agents such as 5-fluorouracil, and modulates immune-related pathways, including PD-L1 expression and T cell responses [65,96]. These characteristics raise the possibility that miR-15b-5p-targeted approaches could be investigated in combination with immunotherapeutic modalities, including cell-based strategies; Such applications remain theoretical and require substantial preclinical validation. In addition, because RNA molecules are naturally unstable and context-dependent, delivery issues still limit the therapeutic application of miRNAs. Although there

are still significant challenges related to safety, specificity, and scalability, delivery platforms such as exosomes or nanoparticle-based carriers have been proposed to improve stability and targeting accuracy. Importantly, any combination strategy requires spatial and temporal control to minimize off-target or oncogenic effects due to the dual nature and context-dependent behavior of miR-15b-5p. This perspective highlights the potential significance of miR-15b-5p in influencing intrinsic tumor signaling and the tumor immune microenvironment, although further mechanistic and translational studies are required.

Conclusions

The context-dependent nature and regulatory complexity of miR-15b-5p across various cancer types indicate that its oncogenic or tumor-suppressive functions are dictated by tumor-specific molecular features and microenvironmental cues. miR-15b-5p biogenesis is also influenced by upstream regulators such as genetic polymorphisms, thereby reshaping mature miRNA expression and potentially conferring downstream regulatory consequences. The role of miR-15b-5p in cancer is further shaped by lncRNAs acting as upstream regulators, whose cancer-specific regulatory patterns govern the context-dependent functions of miR-15b-5p across malignancies. By targeting genes within distinct signaling pathways, miR-15b-5p exerts pathway-specific effects that ultimately determine its tumor-suppressive or oncogenic role in a cancer type-dependent manner. It should also be noted that existing studies exhibit substantial heterogeneity in sample sources, experimental platforms, and patient populations, which may contribute to the inconsistent expression patterns reported across various cancers. Furthermore, many mechanistic insights are derived from preclinical models, highlighting the need for further validation in well-characterized clinical cohorts. Overall, miR-15b-5p is a promising candidate for a non-invasive biomarker and therapeutic target in cancer. However, further integrative and mechanistic studies are essential in order to define the determinants

of its divergent roles and advance its use in precision oncology.

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Declaration of Generative AI in Scientific Writing

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CRedit Author Statement

Kharisma Arethusa Maisaroh, Putri Rohmatul Laili, Reza Adhi Pratama, and Auraga Dewantoro: Contributed equally to this work: Conceptualization; writing the original draft; visualization. **Dyah Laksmi Dewi:** Conceptualization; writing; review and editing; supervision; funding acquisition. **Teguh Aryandono:** Supervision; review and editing. **Irianiwati Widodo:** Supervision; review and editing; funding acquisition.

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