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Review

miR-1296 in Human Cancers: Context-Dependent Tumor Suppressor and Oncogene Orchestrated by ceRNA Networks

Zahra Diba*

Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran

*Corresponding author: Zahra Diba, dibazarz21@gmail.com

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Abstract

Abnormal regulation of microRNA (miRNA) production is increasingly recognized as a hallmark of cancer development. Genetic alterations, disrupted transcriptional control, and deficiencies in processing machinery all contribute to changes in miRNA levels. Depending on the cellular environment, a single miRNA may act either in favor of tumor growth or as a barrier against malignancy. These small RNAs influence key oncogenic features, including uncontrolled cell division, suppression of growth-inhibitory pathways, evasion of programmed cell death, metastatic spread, and angiogenesis. Because of this broad impact, numerous studies have explored the potential of miRNAs as biomarkers for early diagnosis and prognosis, although further validation is still required before clinical translation. Among these regulators, hsa-miR-1296 has recently gained attention. Both strands of its precursor, miR-1296-5p and miR-1296-3p, are involved in modulating multiple signaling cascades across different tumor types. Depending on tissue context, miR-1296 can function as either a tumor suppressor or, less frequently, as an oncogenic factor by targeting genes central to cell-cycle progression, migration, invasion, and therapy resistance. Evidence from breast, lung, liver, colorectal, gastric, prostate, and bone cancers shows that miR-1296 interacts with networks of protein-coding genes and noncoding RNAs, shaping tumor behavior and influencing patient outcomes. Relevant studies were identified through searches in PubMed and Scopus databases up to 2025, focusing on experimental and clinical investigations of miR-1296 in human cancers and its ceRNA-mediated regulatory mechanisms. This review summarizes the current knowledge of miR-1296 biology and highlights its dual role in cancer, as well as its emerging value as a diagnostic and therapeutic candidate for precision oncology.

1. Introduction

As a major contributor to global morbidity and mortality, cancer poses persistent challenges for human well-being and healthcare systems [1]. In spite of significant advances achieved with traditional modalities including surgery, radiation therapy, and chemotherapy, as well as the advent of targeted and immune-based therapies, the overall five-year survival rate for many malignancies remains disappointingly low [2]. This unfavorable prognosis is largely attributed to late diagnosis, tumor heterogeneity, and the absence of reliable biomarkers that can detect cancer at early stages or predict treatment response with high specificity and sensitivity. Consequently, the identification of novel biomarkers and the development of more effective therapeutic strategies are urgently needed to improve patient outcomes [3].

MiRNAs are short, noncoding RNAs (~20-24 nt) that post-transcriptionally regulate gene expression by binding to complementary sites within the 3′ untranslated regions (UTRs) of target mRNAs, leading to mRNA degradation or translational repression [4,5]. Since the discovery of lin-4 in *C. elegans* in 1993, thousands of human miRNAs have been identified and curated in public repositories such as miRbase [6]. Individual miRNAs can regulate multiple target genes, while single mRNAs may be controlled by several distinct miRNAs, forming dense regulatory networks [7]. Through these networks, miRNAs influence essential cellular processes, including proliferation, differentiation, apoptosis, and stress responses [8,9]. A concise overview of canonical and non-canonical biogenesis is provided in Figure 1.

Dysregulation of miRNA expression is a hallmark of many human diseases, particularly cancer [10]. Aberrant miRNA patterns perturb signaling pathways governing cell-cycle progression, apoptosis, migration, and invasion, thereby contributing to malignant transformation and tumor progression [11]. Depending on expression context and validated targets, miRNAs may act as oncogenes (e.g., miR-21, miR-155) when upregulated or as tumor suppressors (e.g., let-7, miR-34a) when downregulated [12-14]. These dual roles underscore the promise of miRNAs as biomarkers for diagnosis, prognosis, and therapeutic stratification in oncology [15].

While several well-characterized miRNAs such as miR-21 and let-7 have been extensively studied, a growing

number of lesser-known miRNAs are now being recognized for their potential regulatory roles in specific cancers. One such emerging candidate is miR-1296, which has been implicated in modulating key oncogenic pathways including ERBB2 and mTOR [16]. Notably, initial studies have suggested that miR-1296 may function as a tumor suppressor in triple-negative breast cancer and ERBB2-positive malignancies [17]. Despite these insights, its molecular mechanisms, clinical correlations, and therapeutic implications remain largely undefined. This knowledge gap underscores the necessity for a focused investigation into miR-1296 to better understand its role in tumor biology.

One such molecule is miR-1296, which has been implicated in several malignancies. For instance, miR-1296-5p suppresses migration and invasion in breast cancer by directly targeting ERBB2 and downstream mTOR signaling, suggesting a tumor-suppressive role in this context [16]. In triple-negative breast cancer, miR-1296 also functions as a tumor suppressor by repressing CCND1 and modulating cell-cycle progression [17]. Although emerging data link its dysregulation to oncogenic signaling and potentially poor prognosis in other cancers, such as colorectal and prostate, these associations remain to be robustly validated in clinical studies. Thus, compared with classical oncomiRs or tumor-suppressive miRNAs, the biological and clinical relevance of miR-1296 remains insufficiently characterized.

Compared with extensively studied miRNAs such as miR-21, miR-155, and miR-34a-which exert broad, pleiotropic control over apoptosis and proliferation across many tumor types-miR-1296 displays a more context-dependent regulatory footprint. Current evidence links miR-1296-5p to ERBB2-mediated migration and invasion suppression in gastric cancer [18] and to tumor-suppressor activity in triple-negative breast cancer [17]. In addition, its expression appears to correlate with prognosis and to regulate ERBB2/mTOR signaling in human malignancies [19]. This distinctive profile justifies a focused review on miR-1296. This review aims to provide a comprehensive overview of miR-1296, focusing on its expression patterns, molecular functions, and emerging potential as a diagnostic, prognostic, and therapeutic biomarker across cancer types.

2. Biogenesis of microRNAs

MicroRNA biogenesis is a tightly regulated, multistep process that integrates both nuclear and cytoplasmic events to convert a noncoding transcript into a functional, mature miRNA. The most widely accepted pathway is the canonical biogenesis pathway. In this route, miRNA genes are transcribed by RNA polymerase II into long primary transcripts (pri-miRNAs), which often include 5′ caps and 3′ poly(A) tails [4,20]. These pri-miRNAs harbor one or more stem–loop hairpin structures that are recognized and cleaved in the nucleus by the microprocessor complex, composed primarily of the RNase III enzyme Drosha and its partner DGCR8 (DiGeorge syndrome critical region 8) [21]. This cleavage yields an approximately 60-70 nucleotide precursor miRNA (pre-miRNA) with a characteristic 2-nucleotide 3′ overhang [22].

Next, the pre-miRNA is exported to the cytoplasm by Exportin-5, in a Ran-GTP-dependent manner. In the cytoplasm, Dicer, another RNase III enzyme, further processes the hairpin by removing the loop, producing a ~20-24 nucleotide miRNA duplex [23]. One strand of this duplex - the guide strand - is selectively loaded into an Argonaute (AGO) protein within the RNA-induced silencing complex (RISC), while the opposite (passenger) strand is usually degraded [24]. The mature miRNA–RISC complex then binds to complementary sequences on target mRNAs (mostly in the 3′ UTR) to mediate translational repression or mRNA degradation depending on the complementarity [25].

In addition to this canonical pathway, noncanonical biogenesis pathways exist and provide alternative routes for miRNA maturation [26,27]. One well-known example is mirtrons, which are short intronic sequences that fold into hairpins after splicing and bypass the Drosha-mediated cleavage step; they are exported and processed by Dicer like canonical pre-miRNAs [24]. After Drosha cleavage in the nucleus, the hairpin is loaded directly onto AGO2 in the cytoplasm, and AGO2 cleaves the passenger-like strand to yield the mature miRNA [21]. These alternate routes highlight the versatility and adaptability of miRNA processing in different cellular contexts.

Regulation of miRNA biogenesis occurs at multiple levels. Transcriptional control is mediated by transcription factors and epigenetic modifiers that influence pri-miRNA transcription. Post-transcriptionally, RNA-binding proteins (e.g., Lin28, hnRNPs) can modulate Drosha or Dicer processing efficiency for specific miRNAs. Disruption to the core machinery (mutations or altered expression of Drosha, DGCR8, Dicer, or AGO proteins) has been implicated in various pathologies, especially cancers [28]. For instance, reduced Dicer expression has been correlated with poorer prognosis in several tumor types, and aberrant activity of AGO2 is associated with tumor progression and metastasis (Figure 1) [29].

Overall, miRNA biogenesis is a well-coordinated and evolutionarily conserved process. Disturbances anywhere along this pathway can lead to dysregulation of miRNA expression, which in turn may contribute to the initiation and progression of malignant phenotypes. Understanding this machinery is crucial when investigating the role of any specific miRNA - such as miR-1296 - in cancer.

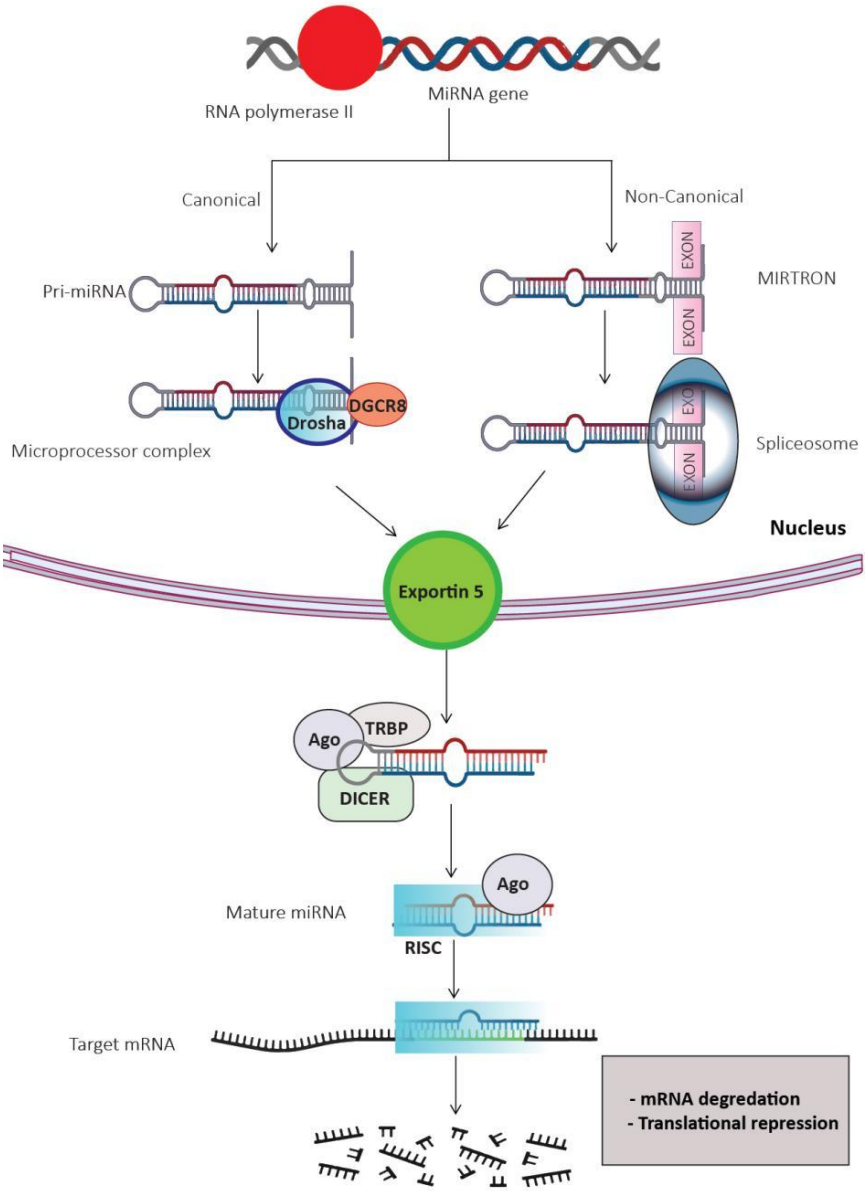

Figure 1. Canonical and non-canonical pathways of miRNA biogenesis. In the canonical pathway, pri-miRNAs transcribed by RNA polymerase II are processed by the Microprocessor complex (Drosha and DGCR8) into pre-miRNAs, which are exported from the nucleus via Exportin-5 and subsequently cleaved by Dicer to produce mature miRNA duplexes. In the non-canonical (mirtron) pathway, splicing directly generates short hairpin precursors that bypass Drosha processing. Mature miRNAs are loaded into the RISC complex, containing Argonaute (Ago) and TRBP, to mediate mRNA degradation or translational repression.

The MIR1296 gene is annotated under the HGNC symbol MIR1296 and is located on chromosome 10 (chr10: 63,372,957-63,373,048, minus strand, GRCh38) [19,30-32]. Its precursor hairpin is recorded in miRBase under accession number MI0003780 and classified within the mir-1296 family (RF01921). The canonical stem-loop transcript (pre-miR-1296) is approximately 92 nucleotides in length and adopts a stable secondary structure with the typical stem-loop configuration necessary for Drosha and Dicer processing [30-33].

From this precursor, two mature strands are generated: hsa-miR-1296-5p (MIMAT0005794; sequence: 5′-UUAGGGCCCUGGCUCCAUCUCC-3′) and hsa-miR-1296-3p (MIMAT0026637; sequence: 5′-GAGUGGGGCUUCGACCCUAACC-3′) [31]. As with other miRNAs, one strand usually serves as the guide strand incorporated into the RISC, while the complementary passenger strand is degraded. Both strands of miR-1296 have been detected in sequencing datasets, suggesting potential biological relevance for each, although current evidence indicates that miR-1296-5p has been more frequently investigated in the context of cancer.

The predicted secondary structure of pre-miR-1296 (Figure 2A) displays extended paired regions with small internal loops and bulges, typical of pre-miRNA substrates for Dicer cleavage. After nuclear processing and cytoplasmic maturation, the resulting duplex gives rise to two functionally distinct mature forms. As illustrated in Figure 2B, the miR-1296 hairpin yields the guide strand miR-1296-5p and the passenger strand miR-1296-3p, each with the potential to regulate different sets of cancer-associated targets.

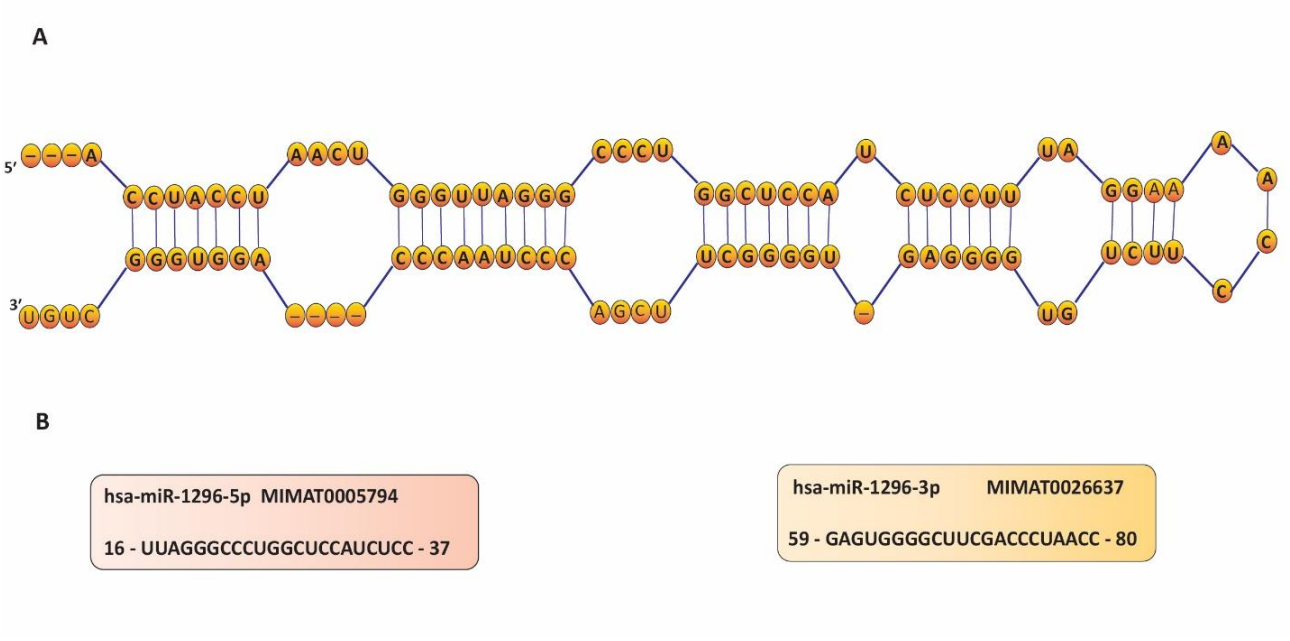

Figure 2. Molecular information for hsa-miR-1296. (A) Predicted secondary structure of the human miR-1296 precursor hairpin (pre-miR-1296), illustrating the typical stem–loop configuration of canonical miRNAs. The structure was generated based on sequence data retrieved from the miRBase database (https://www.mirbase.org; accession MI0003780). (B) Two mature strands are derived from this precursor: hsa-miR-1296-5p (MIMAT0005794; nucleotides 16-37, shown in orange) and hsa-miR-1296-3p (MIMAT0026637; nucleotides 59-80, shown in yellow). Color coding indicates strand orientation and arm origin (5′ vs. 3′), corresponding to the highlighted regions within the predicted hairpin.

3. Biological Functions of miR-1296 in Human Cancers

MicroRNAs play essential roles in a wide range of physiological processes, including development, differentiation, proliferation, apoptosis, and metabolism. In cancer, however, aberrant expression of specific miRNAs contributes to almost every hallmark of tumorigenesis, influencing initiation, progression, and metastatic spread [34]. Depending on their expression profile and validated targets, miRNAs may act as oncomiRs or tumor suppressors [35,36].

OncomiRs are frequently overexpressed in tumors, where they downregulate tumor suppressor genes or pro-apoptotic factors, thereby promoting uncontrolled proliferation and survival. For example, miR-21, one of the most studied oncomiRs, is upregulated in breast, colorectal, and lung cancers and suppresses PTEN and PDCD4, two critical tumor suppressors [37]. Similarly, the miR-17-92 cluster is known to enhance tumor growth by modulating cell cycle regulators and apoptotic pathways [38].

By contrast, tumor suppressor miRNAs are commonly downregulated in cancers. Their loss leads to the repression of oncogenes and enhanced malignant transformation. A well-characterized example is the let-7 family, which normally inhibits RAS and HMGA2; reduced let-7 expression is associated with increased tumor aggressiveness and poor prognosis [39]. Another key tumor suppressor miRNA, miR-34a, directly regulated by p53, induces cell cycle arrest and apoptosis through inhibition of CDK4/6 and BCL2 [40].

Beyond growth and apoptosis, miRNAs also play critical roles in regulating epithelial–mesenchymal transition (EMT), invasion, and metastasis. The miR-200 family (miR-200a/b/c, miR-141, and miR-429) maintains the epithelial phenotype by targeting transcriptional repressors of E-cadherin such as ZEB1 and ZEB2. Downregulation of this family facilitates EMT, enabling tumor cells to acquire invasive and metastatic properties [41]. In contrast, miR-10b has been shown to promote invasion and metastasis, particularly in breast cancer, by targeting HOXD10 and enhancing RhoC activation [42].

Another crucial aspect of miRNA function in cancer involves drug resistance and therapy response. Dysregulated miRNAs can alter sensitivity to chemotherapy, radiotherapy, and targeted therapies. For instance, elevated miR-155 contributes to resistance against chemotherapeutic agents in hematological malignancies, whereas miR-125b and miR-221/222 have been implicated in endocrine resistance in breast cancer [43,44]. Conversely, restoration of tumor suppressor miRNAs such as miR-34a has been explored as a therapeutic strategy to sensitize cancer cells to treatment [45].

Within this broad framework, miR-1296 has emerged as a relatively underexplored candidate. Early evidence suggests that miR-1296 may influence tumor-related processes such as proliferation, invasion, and therapy resistance. In the following sections, we will summarize the current knowledge regarding the expression patterns, molecular targets, and functional roles of miR-1296 across different human cancers (Figure 3).

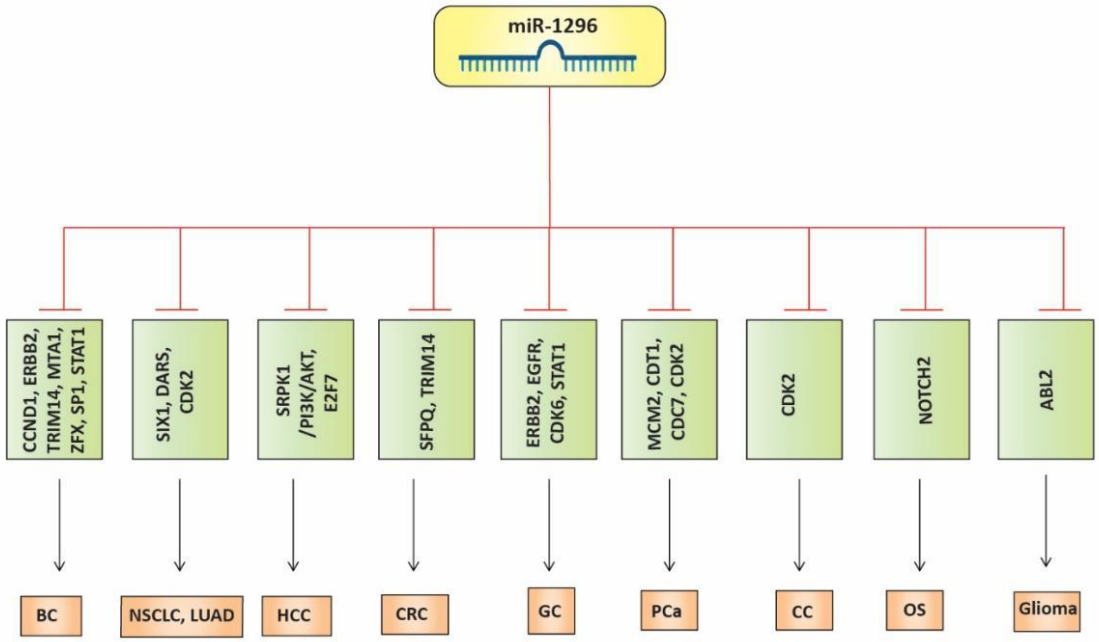

Figure 3. Regulatory network of miR-1296 across human cancers, summarized based on experimentally validated data from published studies. Green boxes represent confirmed target genes, and orange boxes indicate the corresponding cancer types.

3.1 Breast Cancer

Breast cancer (BC) is the leading malignancy among women worldwide and continues to be the most common cause of cancer-related mortality [46]. It accounts for more than two million new cases annually and represents a major global health burden. Current standard therapies for BC include surgical excision, chemotherapy, radiotherapy, endocrine therapy, and targeted therapies such as trastuzumab for HER2-positive tumors [47]. Despite these therapeutic advances, breast cancer remains clinically challenging due to recurrence, metastatic dissemination, and the development of therapy resistance, particularly in aggressive subtypes such as HER2-positive and triple-negative breast cancer (TNBC) [48]. Therefore, the identification of novel molecular biomarkers and regulatory pathways is essential to improve diagnosis, prognostic assessment, and treatment outcomes in BC.

Important studies in TNBC demonstrated that miR-1296 functions as a tumor suppressor by directly targeting Cyclin D1 (CCND1). Restoration of miR-1296 expression suppressed S-phase entry, reduced colony formation, induced apoptosis, and increased sensitivity to cisplatin. Conversely, overexpression of CCND1 rescued these inhibitory effects, confirming target dependence [17]. This work positioned miR-1296 as a cell cycle checkpoint regulator in TNBC and suggested its value as both a prognostic biomarker and a potential chemosensitizer.

Parallel evidence in HER2-positive breast cancer indicated that miR-1296 directly regulates ERBB2 (HER2) expression. Tumor tissue analyses revealed significantly reduced miR-1296 levels in BC compared with adjacent non-tumor tissue, with the most pronounced decrease in HER2-positive tumors. Functionally, enforced miR-1296 expression decreased ERBB2 protein, inhibited proliferation, enhanced apoptosis, and sensitized HER2-positive cell lines to cisplatin and 5-fluorouracil treatment. Mechanistically, this was linked to suppression of the ERBB2/mTORC1/S6 signaling axis [16]. Together, the TNBC and HER2-positive studies converge to define miR-1296 as a tumor suppressor that operates through distinct but subtype-specific oncogenic pathways.

Therapeutic feasibility of miR-1296 replacement was further tested using cationic nanoliposomes for targeted delivery in TNBC models. This approach achieved efficient cytoplasmic uptake, high encapsulation, and robust restoration of miR-1296 activity. Treated MDA-MB-231 cells exhibited markedly reduced viability, induction of apoptosis, and suppression of CCND1 and PARP-1 expression. Importantly, miR-1296-loaded nanoliposomes were more effective than cisplatin in reducing cell viability, underscoring the translational potential of miRNA replacement therapy [49].

Beyond direct protein-coding targets, several studies have highlighted the central role of circular RNAs (circRNAs) that act as competing endogenous RNAs (ceRNAs) by sponging miR-1296 and thereby releasing oncogenic effectors (Figure 4).

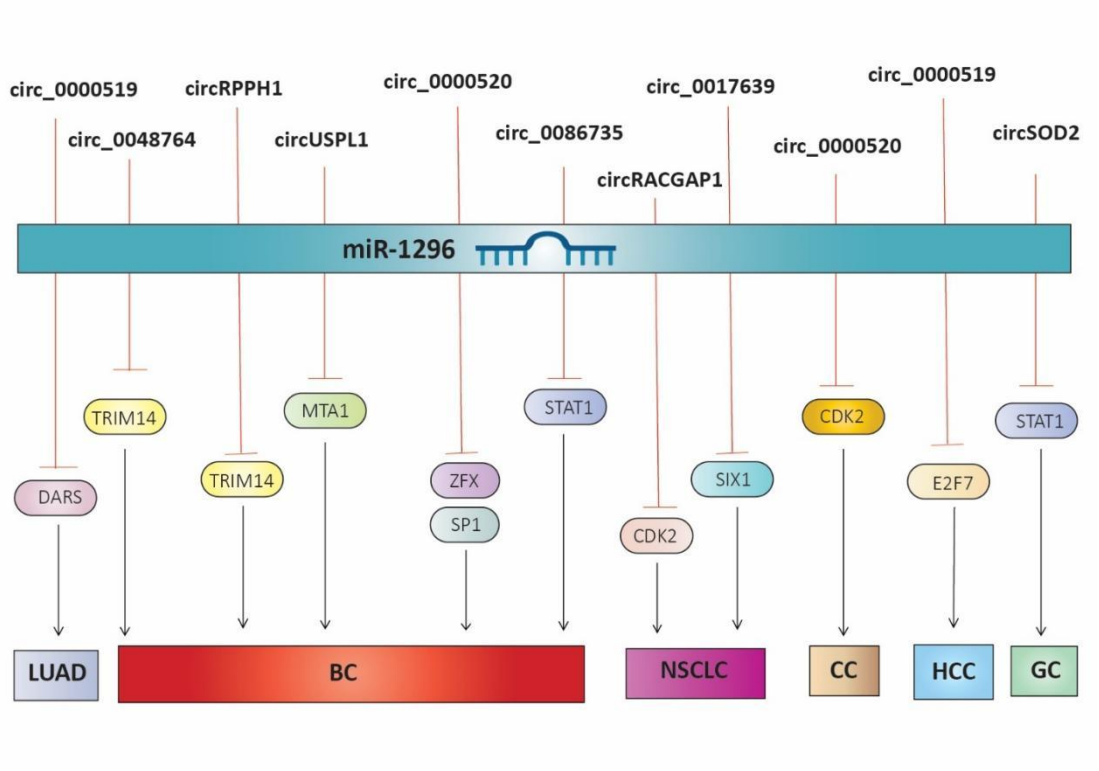

Figure 4. CircRNA-miR-1296-mRNA regulatory networks across human cancers, summarized based on experimentally validated data from published studies. Each axis illustrates a ceRNA interaction in which circRNAs act as molecular sponges for miR-1296, thereby regulating downstream target genes involved in different tumor types.

Two independent studies identified TRIM14 as a recurrent downstream target regulated via distinct circRNAs. The first demonstrated that circ_0048764 was upregulated in BC tissues and cell lines, where it promoted proliferation, invasion, and resistance to apoptosis by sequestering miR-1296-5p and derepressing TRIM14. Restoration of miR-1296 reversed these effects, confirming the ceRNA relationship [50]. Similarly, circRPPH1 was shown to be elevated in tumors and to facilitate proliferation, invasion, migration, and reduced apoptosis. In both in vitro assays and xenograft models, knockdown of circRPPH1 or overexpression of miR-1296-5p suppressed tumor growth, while TRIM14 overexpression abrogated this suppression, firmly establishing the circRPPH1/miR-1296/TRIM14 axis [51]. Overall, the evidence positions TRIM14 as a key oncogenic mediator that becomes derepressed when miR-1296 is sequestered by circRNA networks.

A second group of circRNA studies implicated additional transcriptional and chromatin regulators. circUSPL1 was upregulated in BC tissues and promoted proliferation, migration, invasion, and glycolysis while reducing apoptosis. Functional analyses revealed that circUSPL1 sponged miR-1296-5p to derepress MTA1 (Metastasis-Associated 1), with xenograft validation confirming that silencing circUSPL1 suppressed tumor growth through a circUSPL1/miR-1296/MTA1 pathway [52]. Another circRNA, circ_0000520, displayed context-dependent effects. In TNBC, circ_0000520 was shown to sequester miR-1296, thereby upregulating ZFX (Zinc Finger X-linked) and promoting growth, migration, and invasion; its knockdown inhibited xenograft growth [53]. A complementary study across broader BC cell models identified SP1 as an alternative effector released by circ_0000520 sponging, with miR-1296 loss or SP1 overexpression reversing the anti-tumor effects of circ_0000520 silencing [54]. Together, these results indicate that circ_0000520 may activate different oncogenic pathways depending on cellular context, but in each case it does so by neutralizing miR-1296.

In luminal (ER-positive) breast cancer, an integrated circRNA-miRNA-mRNA network analysis highlighted hsa_circ_0086735 as an upstream regulator that sponges miR-1296-5p, resulting in derepression of STAT1. Experimental validation confirmed these interactions and demonstrated that the hsa_circ_0086735/miR-1296/STAT1 axis promoted proliferation, reduced apoptosis, and conferred resistance to tamoxifen. Clinically, high hsa_circ_0086735 expression correlated with poor overall and distant metastasis-free survival, implicating miR-1296 downregulation in endocrine therapy resistance [55].

Taken together, the body of evidence demonstrates a consistent tumor-suppressive role for miR-1296 in breast cancer across TNBC, HER2-positive, and luminal subtypes. Its restoration suppresses proliferation, invasion, glycolytic reprogramming, and metastasis, while sensitizing tumors to chemotherapy and endocrine therapy. Conversely, its loss - frequently mediated by circRNA sponging - derepresses oncogenic targets including CCND1, ERBB2, TRIM14, MTA1, ZFX, SP1, and STAT1. This recurring pattern underscores the biological importance of miR-1296 as a central regulator of tumor progression. From a translational perspective, these studies point to two promising strategies: direct

miR-1296 replacement therapy using nanocarriers and targeting upstream ceRNA networks that neutralize its tumor-suppressive function.

3.2 Lung Cancer

Lung cancer (LC) is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for nearly 85% of cases [56]. Despite advances in surgery, chemotherapy, targeted therapy, and immunotherapy, long-term survival remains poor due to recurrence, metastasis, and drug resistance [57]. Recent studies have increasingly implicated dysregulation of non-coding RNAs, particularly microRNAs, in LC progression. Among them, miR-1296 has emerged as a recurrently studied tumor-suppressive microRNA whose downregulation fosters proliferation, invasion, metastasis, and chemoresistance across multiple LC subtypes. An early mechanistic study demonstrated that miR-1296 is significantly reduced in NSCLC tissues compared to adjacent normal controls, and low levels correlated with advanced TNM stage and lymph node metastasis. Functionally, miR-1296 restoration suppressed proliferation and invasion by inhibiting Wnt signaling activity, while knockdown enhanced tumorigenic behavior. Importantly, reduced miR-1296 predicted poorer prognosis and was identified as an independent risk factor for survival [19].

Subsequent studies uncovered the role of circRNAs in modulating miR-1296 activity through competitive endogenous RNA (ceRNA) networks. For example, circ_0017639 was found to be upregulated in cisplatin-resistant NSCLC tissues and cell lines. Silencing circ_0017639 reduced proliferation, migration, invasion, and promoted apoptosis in resistant cells. Mechanistically, circ_0017639 acted as a sponge for miR-1296-5p, thereby derepressing SIX1, a transcription factor that drives chemoresistance. Restoring miR-1296 expression re-sensitized resistant NSCLC cells to cisplatin, and in vivo, circ_0017639 knockdown suppressed tumor growth and increased drug response [58].

Another ceRNA axis was identified involving circ_0000519, which is markedly overexpressed in lung adenocarcinoma (LUAD). Elevated circ_0000519 promoted proliferation, migration, invasion, and xenograft tumor growth. Mechanistically, it sponged miR-1296-5p, releasing suppression of DARS (aspartyl-tRNA synthetase). This activation, in turn, triggered the PI3K/AKT/mTOR signaling cascade. Restoration of miR-1296-5p expression or silencing of its downstream effector DARS effectively counteracted the oncogenic activity driven by circ_0000519, delineating a circ_0000519/miR-1296-5p/DARS regulatory axis that promotes LUAD progression [59].

In a complementary study, circRACGAP1 was shown to enhance NSCLC proliferation and suppress apoptosis. Clinical samples revealed circRACGAP1 and CDK2 upregulation alongside miR-1296 downregulation. Functional assays confirmed that circRACGAP1 promoted cell cycle progression, increased BCL2, and decreased BAX expression. Restoration of miR-1296 expression neutralized the proliferative and invasive effects induced by circRACGAP1 through direct repression of CDK2, thereby defining a circRACGAP1/miR-1296/CDK2 regulatory circuit that sustains tumor growth in NSCLC [60]. Together, these ceRNA studies converge on the view that oncogenic circRNAs neutralize the tumor-suppressive activity of miR-1296, thereby releasing diverse downstream effectors (SIX1, DARS, CDK2) and enabling malignant progression.

Beyond circRNA-mediated regulation, therapeutic restoration of miR-1296 offers translational promise. Several experimental systems have shown that increasing miR-1296 expression sensitizes NSCLC cells to chemotherapy and reduces invasive phenotypes. Furthermore, bioinformatic analyses suggest miR-1296 controls broad signaling programs including Wnt and PI3K/AKT/mTOR, reinforcing its role as a master regulator of tumor growth and drug resistance [19,59]. In summary, the available evidence converges on a model in which miR-1296 functions primarily as a tumor suppressor in lung cancer. Its downregulation enables activation of multiple oncogenic programs, including cell-cycle acceleration, metabolic reprogramming, epithelial-mesenchymal transition, and chemoresistance. A recurring mechanism underlying this loss of function is the upregulation of circular RNAs that sequester miR-1296, thereby freeing their downstream oncogenic targets. Conversely, restoring miR-1296 expression - either directly or through disruption of these competing ceRNA networks - suppresses proliferation, invasion, and metastasis, while also enhancing sensitivity to chemotherapy. This integrated view highlights miR-1296 not only as a prognostic biomarker but also as a promising therapeutic target in both NSCLC and LUAD.

3.3 Colorectal Cancer

Colorectal cancer (CRC) ranks among the leading causes of cancer morbidity and mortality worldwide. Despite improvements in screening, surgery, chemotherapy, and targeted therapy, the prognosis for advanced or metastatic CRC remains unsatisfactory [61]. Molecular insights into non-coding RNAs have revealed that dysregulated miRNAs contribute significantly to CRC pathogenesis by altering proliferation, invasion, and metastatic potential. Among them, miR-1296 has been increasingly recognized as a context-dependent regulator with oncogenic potential in CRC.

One of the earliest studies to define the role of miR-1296 in CRC was conducted by Tao et al. (2018), who demonstrated that miR-1296 is significantly upregulated in CRC tissues and cell lines compared with adjacent normal mucosa [30]. High expression correlated with advanced tumor size, lymph node metastasis, and TNM stage III/IV. Survival analysis revealed that patients with elevated miR-1296 had poorer outcomes. Functionally, silencing miR-1296 suppressed proliferation, migration, and invasion both in vitro and in xenografts, confirming its oncogenic role. Mechanistically, SFPQ, an RNA-binding protein implicated in RNA splicing and transcriptional regulation, was validated as a direct target

of miR-1296. Loss of SFPQ paralleled high miR-1296 levels in CRC tissues, suggesting that miR-1296 promotes tumor progression at least partly via SFPQ downregulation.

Expanding on this oncogenic profile, Chen et al. uncovered a ceRNA network involving lncRNA GAS6-AS1 and miR-1296-5p [62]. GAS6-AS1 was markedly elevated in CRC tissues and associated with poor prognosis. Functional assays demonstrated that GAS6-AS1 enhanced proliferation, invasion, and EMT, while its silencing suppressed tumorigenic behavior. Mechanistically, GAS6-AS1 sponged miR-1296-5p, relieving repression on TRIM14, a pro-tumorigenic E3 ubiquitin ligase. This GAS6-AS1/miR-1296-5p/TRIM14 axis promoted CRC progression in vitro and in xenografts, underscoring how non-coding RNA interactions disable miR-1296's tumor-suppressive function and redirect it into oncogenic circuitry.

Complementary evidence comes from studies of circulating miRNAs. Nagy et al. (2019) examined matched tissue and plasma samples across normal, adenoma, and carcinoma stages and found significant overexpression of miR-1296 in CRC plasma compared with healthy controls [63]. This mirrored tissue findings and indicated that miR-1296 alterations are detectable in circulation, making it a promising non-invasive biomarker for CRC detection. Importantly, elevated plasma miR-1296 was not limited to tumor tissue origin but could also reflect systemic responses, highlighting its diagnostic value in liquid biopsy approaches.

Finally, Bobowicz et al. (2016) identified miR-1296 as part of a five-miRNA prognostic signature predictive of distant metastasis-free survival in stage II-III colon cancer patients treated with surgery alone [64]. The miRNA panel, which included miR-1296 alongside miR-135b, miR-539, miR-572, and miR-185, achieved strong sensitivity and specificity in stratifying patients by recurrence risk. This finding emphasizes miR-1296's translational relevance not only as a mechanistic driver but also as a potential clinical biomarker guiding postoperative management.

Together, these studies reveal a complex picture of miR-1296 biology in CRC. In contrast to breast and liver cancers, where miR-1296 largely behaves as a tumor suppressor, in CRC it is consistently upregulated and exerts oncogenic functions by repressing tumor suppressors such as SFPQ and participating in lncRNA-mediated ceRNA networks. Clinically, high miR-1296 expression associates with advanced disease stage, poor survival, and increased risk of metastasis. Its detection in plasma further positions it as a candidate for non-invasive monitoring.

The apparent shift of miR-1296 from a tumor-suppressive to an oncogenic regulator in colorectal cancer may reflect broader systems-level determinants of microRNA function. Such context-dependency could arise from factors such as the differential abundance of its mRNA targets (such as SFPQ and TRIM14), alterations in ceRNA networks due to mutations or dysregulation of lncRNAs like GAS6-AS1, and the distinct metabolic and inflammatory microenvironment of the colorectal tissue. These interconnected factors can collectively reprogram post-transcriptional gene regulation, and may thereby account for the dual roles observed in miRNAs such as miR-1296. This concept aligns with recent frameworks emphasizing the context-dependent functional plasticity of miRNAs in cancer, particularly CRC [65]. Integrating these multi-layered regulatory influences will be crucial for fully understanding the functional role of miR-1296 across diverse tumor settings. Future studies should address whether therapeutic inhibition of miR-1296 can improve outcomes in aggressive CRC, and whether combining miR-1296 profiling with other biomarkers can enhance risk stratification and treatment personalization.

3.4 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and a major cause of cancer-related deaths worldwide. Despite progress in surgical resection, locoregional interventions, and systemic therapies, prognosis remains poor due to high recurrence, metastasis, and therapeutic resistance. MiRNAs have emerged as critical regulators of HCC biology, acting as either oncogenes or tumor suppressors. Among these, miR-1296 has consistently been reported as a tumor-suppressive miRNA whose loss is associated with more aggressive disease features.

The first mechanistic evidence was presented by Xu et al. (2017), who demonstrated that miR-1296 expression is significantly downregulated in HCC tissues and cell lines compared with adjacent non-tumor liver [66]. Functional assays showed that overexpression of miR-1296 inhibited migration, invasion, and epithelial-mesenchymal transition (EMT), while knockdown enhanced these malignant phenotypes. Mechanistically, miR-1296 directly targeted SRPK1, leading to reduced PI3K/AKT signaling and suppression of pro-metastatic pathways. Clinically, low miR-1296 expression correlated with recurrence and poor patient survival. Importantly, hypoxia reduced miR-1296 levels, linking the tumor microenvironment to EMT and metastasis.

A more recent study by Liu et al. (2023) identified a novel circRNA-miRNA-mRNA regulatory axis involving miR-1296 in HCC [67]. They reported that circ_0000519 is upregulated in HCC and functions as a sponge for miR-1296, thereby derepressing E2F7, a transcription factor involved in proliferation and angiogenesis. Silencing circ_0000519 or restoring miR-1296 suppressed proliferation, induced G0/G1 arrest, reduced invasion, and impaired angiogenic capacity in vitro and in xenograft models. Conversely, E2F7 reintroduction rescued these phenotypes. This circ_0000519/miR-1296/E2F7 pathway links loss of miR-1296 to enhanced vascularization and tumor growth.

Complementary evidence comes from a bioinformatic and clinical analysis by Mei et al. (2018), who examined differentially expressed miRNAs between cirrhotic and non-cirrhotic HCC using TCGA data [68]. miR-1296 was identified as one of four miRNAs significantly altered in non-cirrhotic HCC, with associations to tumor

stage and patient outcomes. Although not as mechanistically detailed as experimental work, this study situates miR-1296 in broader subtype-specific regulation of HCC biology.

Evidence across studies converges on a consistent tumor-suppressive function of miR-1296 in hepatocellular carcinoma. Its downregulation promotes invasion and EMT through SRPK1/PI3K/AKT, facilitates angiogenesis via circ_0000519/E2F7, and correlates with advanced pathological stages in clinical cohorts. Although current evidence is limited, the convergence of findings strongly suggests that restoring miR-1296 or targeting its negative regulators (such as circRNAs) could provide therapeutic benefit.

Notably, the PI3K/AKT pathway also emerges as a recurrent downstream axis of miR-1296 in other epithelial malignancies, particularly gastric cancer (GC). In both hepatocellular carcinoma (HCC) and GC, miR-1296 acts as a key regulator of cell proliferation and invasion through modulation of PI3K/AKT signaling - either by repressing upstream activators such as SRPK1 in HCC [69] or by targeting receptor tyrosine kinases such as ERBB2 in GC [18]. This cross-cancer convergence highlights the pathway-level role of miR-1296 as a context-dependent modulator of PI3K/AKT signaling, suggesting that shared molecular circuitry may underlie its tumor-suppressive effects across gastrointestinal cancers. Future work should focus on validating its prognostic potential and testing miR-1296 mimics in preclinical HCC models.

3.5 Gastric Cancer

Gastric cancer remains among the leading causes of cancer mortality worldwide, with poor survival largely attributable to late diagnosis, recurrence, and resistance to systemic therapies [70]. Molecular studies have increasingly highlighted the dysregulation of microRNAs in gastric tumorigenesis, progression, and therapy response. Within this context, miR-1296-5p has emerged as a recurrently studied miRNA with tumor-suppressive properties in GC, acting across multiple oncogenic pathways and ceRNA networks.

The earliest mechanistic evidence came from work by Shan et al., who focused on HER2-positive gastric cancer [18]. They reported that miR-1296-5p was significantly downregulated in GC tissues compared to normal counterparts, and further reduced in lymph-node metastatic lesions. Functional assays in SNU-216 and NUGC-4 cells demonstrated that miR-1296-5p directly targets the 3′UTR of ERBB2 (HER2), leading to decreased ERBB2 expression, reduced Rac1 activation, and suppression of migration and invasion. Importantly, restoration of miR-1296-5p phenocopied the effects of trastuzumab, and its anti-invasive effect could be rescued by overexpression of ERBB2 or constitutively active Rac1, positioning miR-1296-5p as a tumor suppressor within the ERBB2/Rac1 signaling axis.

Subsequent work expanded this paradigm beyond HER2-positive disease. Jia et al. reported that miR-1296-5p was consistently downregulated in gastric cancer tissues and cell lines, with lower expression correlating with advanced stage [33]. Using SGC-7901 and MGC-803 cells, they showed that overexpression of miR-1296-5p inhibited proliferation, migration, and invasion, while inhibition promoted malignant traits. Mechanistically, two novel targets were validated: CDK6, a core regulator of the G1-S cell cycle transition, and EGFR, another key oncogenic receptor tyrosine kinase. By repressing both CDK6 and EGFR, miR-1296-5p exerted broad tumor-suppressive activity that curtailed proliferative and invasive signaling. This dual targeting underscores the centrality of miR-1296-5p loss in enabling hyperactive cell cycle progression and growth factor signaling in GC.

More recently, attention has turned to the role of miR-1296 within the tumor immune microenvironment and chemotherapy resistance. Qu et al. described a novel axis involving the circular RNA circSOD2, which is highly expressed in M1 macrophages [71]. circSOD2 functions as a sponge for miR-1296, thereby relieving repression of STAT1. In co-culture and xenograft models, circSOD2 overexpression promoted M1 polarization, enhanced cisplatin sensitivity, and increased apoptosis of GC cells, effects mediated through the circSOD2/miR-1296/STAT1 pathway. This study highlights a context-dependent role of miR-1296, where its suppression by circSOD2 indirectly contributes to therapy sensitization through immune modulation, contrasting with the direct tumor-suppressive actions observed in epithelial GC cells.

Together, these studies present miR-1296-5p as a multifunctional tumor suppressor in gastric cancer, primarily by targeting oncogenes such as ERBB2, EGFR, and CDK6. Its loss fosters proliferation, invasion, and metastasis, whereas its modulation through circRNAs can also shape chemotherapy response and immune cell behavior. Although the number of available reports remains limited, the convergence of data strongly supports further evaluation of miR-1296 as both a prognostic biomarker and a therapeutic candidate in GC.

3.6 Prostate Cancer

Prostate cancer (PCa) remains one of the most prevalent malignancies among men, with disease progression often linked to dysregulation of DNA replication machinery and cell cycle control [72]. A seminal study by Majid et al. identified miR-1296 as a critical regulator of the minichromosome maintenance (MCM) gene family, which is essential for DNA replication licensing. Expression profiling showed that MCM genes were significantly upregulated in prostate tumor samples compared to adjacent normal tissue, correlating with enhanced proliferation. Importantly, miR-1296 expression itself was downregulated in PCa tissues, suggesting a tumor-suppressive role [73]. Functional assays in PC3 prostate cancer cells demonstrated that enforced overexpression of miR-1296 markedly reduced MCM2 mRNA and protein levels, leading to decreased S-phase entry and proliferation arrest. Conversely, inhibition of miR-1296 upregulated MCM2, reinforcing the direct regulatory link. The effects of miR-1296 resembled those induced by *genistein*, a dietary

isoflavone, and trichostatin A (TSA), both of which downregulated MCM expression and suppressed cell cycle progression. These results indicate that miR-1296 acts as a molecular brake on DNA replication by targeting MCM2 and related regulatory factors such as CDT1, CDC7, and CDK2 [73].

Clinically, the loss of miR-1296 in prostate cancer may contribute to unchecked replication and tumor aggressiveness, whereas therapeutic restoration could sensitize tumors to anti-proliferative agents. This study provided the first mechanistic evidence of miR-1296 functioning as a tumor suppressor in prostate cancer, highlighting its potential as a therapeutic target alongside natural compounds like genistein.

3.7 Cervical Cancer

Cervical cancer (CC) ranks among the most common gynecological malignancies [74], and recent studies have uncovered a role for miR-1296 in regulating proliferation and apoptosis through ceRNA (competing endogenous RNA) networks.

A study by Zheng et al. demonstrated that hsa_circ_0000520 was significantly upregulated in cervical cancer tissues and cell lines, correlating with increased CDK2 expression. Mechanistic experiments confirmed that circ_0000520 acts as a sponge for miR-1296, sequestering it and thereby derepressing CDK2. Silencing circ_0000520 inhibited proliferation, blocked cell cycle progression, and enhanced apoptosis, effects that were potentiated by miR-1296 overexpression. These findings define a circ_0000520/miR-1296/CDK2 axis, in which suppression of miR-1296 contributes to uncontrolled cell cycle progression and tumor growth [75].

In parallel, Liu et al. explored the impact of a synthetic pan-PIM kinase inhibitor (PI003) in cervical cancer. MicroRNA profiling revealed that PI003 altered the expression of multiple miRNAs, including miR-1296, which was implicated in modulation of the PIM1-STAT3 oncogenic pathway. Functional assays demonstrated that PI003 induced apoptosis via both mitochondrial and death-receptor pathways, with miR-1296 among the miRNAs contributing to these effects. Although this study did not focus exclusively on miR-1296, it highlighted its potential role as a mediator of therapeutic response in cervical cancer [76].

Together, these studies suggest that miR-1296 acts predominantly as a tumor suppressor in cervical cancer. Its inhibition - via circRNA sponging or oncogenic signaling pathways - fosters proliferation and resistance to apoptosis, while restoring its expression or indirectly enhancing its activity may improve therapeutic outcomes.

3.8 Osteosarcoma

Osteosarcoma (OS) remains the most common primary malignant bone tumor in adolescents and young adults, with metastasis and chemoresistance driving poor outcomes [77]. Within this context, miR-1296-5p emerges as a tumor-suppressive microRNA that constrains proliferative and invasive phenotypes by targeting key cell-cycle and survival circuits. In human OS models, enforced expression of miR-1296-5p suppresses proliferation, migration, and invasion, whereas miR-1296-5p depletion has the opposite effect - promoting growth and motility. Mechanistically, NOTCH2 was validated as a direct target of miR-1296-5p through 3′-UTR binding; restoration of NOTCH2 rescues the anti-tumor effects of miR-1296-5p, placing NOTCH2 downstream in this axis [78]. Clinically oriented studies should verify whether low tumor miR-1296-5p (or high NOTCH2) correlates with metastasis, poor response to chemotherapy, and inferior survival, and whether a miR-1296-5p/NOTCH2 signature improves risk stratification beyond current clinicopathologic models.

In summary, available evidence suggests that miR-1296-5p functions as a tumor suppressor in osteosarcoma primarily through direct targeting of NOTCH2. Its downregulation facilitates tumor cell proliferation, invasion, and migration, while restoration of its expression can reverse these malignant traits. Thus, miR-1296-5p/NOTCH2 may represent a promising prognostic marker and therapeutic axis in OS.

3.9 Papillary Thyroid Carcinoma

Papillary thyroid carcinoma (PTC) generally carries a favorable prognosis, yet aggressive variants recur and metastasize [79]. A case-control profiling study identified aberrant expression of five miRNAs in papillary tumors, including a downregulation of miR-1296-5p in a subset classified as “A-PTC” relative to benign nodules (A-benign) [80]. Although this study was not designed for mechanistic dissection, two clinically relevant inferences follow. First, diminished miR-1296-5p is consistent with a tumor-suppressive role, mirroring its behavior in other epithelial cancers in which it restrains ERBB family signaling, cell-cycle drivers, and invasive programs. Second, the diagnostic performance of the reported miRNA panel (that includes miR-1296-5p) suggests potential to complement cytology in indeterminate nodules, pending external validation.

Overall, current data indicate that miR-1296-5p is downregulated in aggressive forms of PTC, aligning with its tumor-suppressive role reported in other cancers. While mechanistic pathways remain to be elucidated in thyroid tissue, its expression pattern suggests utility as part of a diagnostic or prognostic biomarker panel, with potential clinical relevance in risk stratification.

3.10 Glioma

Diffuse gliomas exhibit relentless infiltration and therapeutic resistance [81]. In this setting, miR-1296 has been reported to inhibit glioma cell growth by directly targeting ABL2, a non-receptor tyrosine kinase implicated in cytoskeletal dynamics, migration, and proliferation [32]. Experimentally, miR-1296 overexpression reduces viability and colony formation, suppresses migration and invasion, and promotes apoptosis in glioma lines; luciferase and mutational assays confirm ABL2 as a direct target, and ABL2 re-expression attenuates the anti-tumor phenotype,

establishing pathway dependence [32]. Findings consistently show that miR-1296 suppresses glioma progression via ABL2 inhibition. By suppressing proliferation, migration, and invasion while promoting apoptosis, miR-1296 represents a candidate therapeutic target whose restoration could counteract glioma aggressiveness and improve patient outcomes (Table 1).

Table 1. miR-1296 roles across different cancers.

Cancer Type	Expression Pattern	Main Targets / Pathways	Functional Role	Clinical/Translational Implication	References
Breast cancer (TNBC, HER2+, Luminal)	↓ (downregulated)	CCND1, ERBB2, TRIM14, MTA1, ZFX, SP1, STAT1	Tumor suppressor (cell cycle arrest, apoptosis, ↓ invasion, ↑ chemosensitivity)	Prognostic biomarker; miRNA replacement; targeting ceRNA networks (circRNAs)	[17,16-55]
Lung cancer (NSCLC, LUAD)	↓	Wnt signaling, SIX1, DARS, CDK2	Tumor suppressor (↓ proliferation, ↓ invasion, ↑ chemosensitivity)	Prognostic marker; therapeutic sensitizer; circRNA sponging critical (circ_0017639, circ_0000519, circRACGAP1)	[19,58-60]
Hepatocellular carcinoma (HCC)	↓	SRPK1/PI3K/AKT, E2F7 (via circ_0000519)	Tumor suppressor (↓ EMT, ↓ angiogenesis)	Predicts poor survival; therapeutic mimic candidate; circRNA-based regulation important	[66-69]
Colorectal cancer (CRC)	↑ (upregulated)	SFPQ, TRIM14 (via GAS6-AS1)	Oncogene (↑ proliferation, ↑ invasion, EMT)	Diagnostic/prognostic marker; circulating biomarker; possible target for inhibition	[30,62-65]
Gastric cancer (GC)	↓	ERBB2, EGFR, CDK6, STAT1 (via circSOD2)	Tumor suppressor (↓ proliferation, ↓ invasion, ↑ chemosensitivity)	Potential prognostic biomarker; mimics may complement trastuzumab/EGFR inhibitors	[18,33,71]
Prostate cancer (PCa)	↓	MCM2, CDT1, CDC7, CDK2	Tumor suppressor (blocks DNA replication licensing)	Therapeutic target; natural compounds (genistein) mimic effects	[72,73]
Cervical cancer (CC)	↓	CDK2 (via circ_0000520), PIM1–STAT3 axis	Tumor suppressor (↓ proliferation, ↑ apoptosis)	Biomarker; therapeutic target; potential mediator of drug response	[75,76]
Osteosarcoma (OS)	↓	NOTCH2	Tumor suppressor (↓ proliferation, ↓ invasion, ↓ migration)	Prognostic marker; possible therapeutic axis (miR-1296/NOTCH2)	[77,78]
Papillary thyroid carcinoma (PTC)	↓	Not defined (panel study)	Likely tumor suppressor	Component of diagnostic/prognostic miRNA panels	[79,80]
Glioma	↓	ABL2	Tumor suppressor (↓ proliferation, ↓ invasion, ↑ apoptosis)	Candidate therapeutic target to counteract aggressiveness	[32]

4. Clinical and Translational Relevance of miR-1296

miR-1296, encoded on chromosome 10, exhibits context-dependent activity - acting as a tumor suppressor in some malignancies and oncogenic in others [32,80]. Mechanistic studies have defined direct regulatory links between miR-1296-5p and oncogenic effectors, including repression of EGFR and CDK6 in gastric cancer [31], antagonism of ABL2 in glioma [32], targeting of NOTCH2 in osteosarcoma [78], modulation of CDK2 in cervical and lung cancer [32], and regulation of SFPQ in colorectal carcinoma [30]. These interactions form the biological foundation for translational applications based on control of proliferation, apoptosis, migration, and invasion [31,32,78].

Clinical and cohort studies show that altered miR-1296 expression correlates with tumor aggressiveness and patient outcomes. Reduced miR-1296 predicts adverse prognosis in non-small cell lung cancer and hepatocellular carcinoma [19,82]. Cross-tumor analyses further identify miR-1296 as a component of diagnostic and prognostic panels, particularly in tissue-specific or female-specific carcinoma signatures [83,84].

The tumor-suppressive mechanisms of miR-1296 provide a rationale for therapeutic modulation. Replacement strategies using miRNA mimics, including nanoliposome delivery systems, have shown anti-invasive effects in triple-negative breast cancer [49]. Likewise, interventions that release miR-1296 from sponging circular RNAs restore its function in hepatocellular, cervical, and lung cancers [82]. Conversely, its oncogenic role in colorectal carcinoma underscores the need for tumor-type-specific therapeutic design and biomarker-guided patient selection [30,80].

Multiple studies report the presence of miR-1296-5p in extracellular vesicle (exosomal) fractions of patient plasma, confirming its release into circulation and supporting its value as a non-invasive biomarker. Exosome-derived miRNAs often show superior diagnostic accuracy compared with unfractionated plasma miRNAs, indicating that exosome-based detection of miR-1296 may be preferable [85,86]. In the broader literature, circulating miRNAs are stabilized by encapsulation within extracellular vesicles or binding to AGO2 or HDL complexes, enabling cfRNA-based detection [87,88].

Most reports focus on the mature strand miR-1296-5p, which shows tissue-restricted expression, though high-resolution analyses of its isomiRs remain limited [82,85]. Drawing on evidence from other miRNA biomarkers, incorporating strand-specific or isomiR-resolved assays

could improve diagnostic precision and minimize confounding from non-tumor sources [87,89,90].

Translation of miR-1296 from tumor expression to a plasma-based signature entails demonstration of its tumor origin, recovery from exosomal fractions, and validation in independent cohorts. Pilot exosome analyses indicate that miR-1296 meets key translational criteria and can be integrated into multiplex liquid biopsy panels, provided that tumor-type-specific validation is performed [33,83,85-87].

miR-1296 displays mechanistic links to major oncogenic pathways, detectable circulation in exosomal fractions, and emerging diagnostic and therapeutic relevance. Its dualistic biology highlights the need for mechanistic anchoring and tumor-context validation. Taken together, available data support miR-1296 as a strong candidate for liquid biopsy–based applications and, in suitable contexts, as a therapeutic target requiring further validation and technical harmonization.

5. Future Directions and Conclusions

Although current evidence strongly implicates miR-1296 in diverse aspects of tumor biology, many questions remain unanswered. Future research should aim to clarify the precise contexts in which miR-1296 functions as a tumor suppressor versus an oncogene, since its behavior appears to be highly dependent on cancer type and cellular environment. Large-scale, multicenter studies integrating molecular profiling with clinical outcomes are required to establish its real prognostic and predictive value. Complementary evidence from large-scale pan-cancer databases, including The Cancer Genome Atlas (TCGA) and miRDB, also supports variable expression of miR-1296 across tumor types. These datasets provide a valuable framework for cross-validating experimental findings and refining biomarker hypotheses through integrative bioinformatic analyses [16,91-93]. Nevertheless, large-scale transcriptomic resources such as TCGA inherently carry both technical and biological biases stemming from sample heterogeneity and data-processing variability, as highlighted in recent methodological evaluations [94-96].

In addition, there is a need to develop safe and efficient delivery platforms for miR-1296 mimics or inhibitors that can achieve tumor-specific targeting without off-target toxicity. Nanoparticle-based systems, viral vectors, and lipid formulations hold promise, but further optimization and preclinical validation are essential before moving toward clinical trials.

Several practical challenges hinder the development of tumor-specific delivery systems for miR-1296-based therapeutics. These include poor stability in circulation, rapid renal clearance, low uptake by target cells, and the risk of off-target effects in normal tissues. Emerging strategies to overcome these issues involve the engineering of delivery vehicles such as exosomes decorated with tumor-specific ligands or RNA aptamers [97]. For instance, coating bovine milk-derived exosomes with hyaluronic acid (HA) has enabled targeted delivery of miRNAs to CD44-overexpressing tumor cells with minimal systemic toxicity [98]. Lipid nanoparticles and polymeric carriers have also shown promise when functionalized with peptides or antibodies that guide them to tumor-associated receptors [99]. Continued optimization of these platforms, including surface modification and payload control, will be crucial to translate miR-1296 therapeutics into clinically viable options.

Another priority is to explore how miR-1296 interacts with other components of the non-coding RNA network, such as long non-coding RNAs and circular RNAs, which frequently act as sponges to neutralize its function. Although ceRNA-based studies have provided valuable mechanistic insight into the post-transcriptional regulation of miR-1296, several limitations should be acknowledged. Most available evidence relies mainly on in vitro qRT-PCR and dual-luciferase reporter assays conducted in a limited number of cell lines, which, while informative, do not confirm in vivo physiological relevance. Few studies assess direct RNA-RNA binding stoichiometry, subcellular localization, or employ large patient cohorts for validation. Therefore, future work integrating in vivo functional assays, CLIP-seq or RIP analyses, and multi-omic datasets will be necessary to substantiate ceRNA network models and strengthen their translational interpretation. Moreover, to make multi-omic integration involving miR-1296 more actionable, specific computational approaches can be employed. Machine learning frameworks such as Random Forests, Support Vector Machines (SVM), and autoencoder-based deep learning models have been shown effective in integrating miRNA with transcriptomic and proteomic data to identify cancer-specific signatures [100]. Dimensionality reduction methods like PCA and t-SNE, followed by clustering algorithms (e.g., k-means, hierarchical clustering), can uncover miR-1296-driven molecular subtypes or druggable modules. For example, integrating miR-1296 expression profiles with protein-level data can help identify regulatory axes that converge on critical pathways such as PI3K-Akt or p53. Emerging tools like iOmicsPASS, MOFA (Multi-Omics Factor Analysis), and DeepMOCCA enable the construction of co-expression networks and pathway enrichment maps, facilitating hypothesis generation for therapeutic targeting [101]. Such integration also aids in prioritizing composite biomarker panels for patient stratification in precision oncology trials.

Finally, integrating miR-1296 analysis into multi-omic platforms that combine genomic, transcriptomic, and proteomic data could provide a holistic understanding of its role in tumor evolution and treatment response. Such systems-level approaches may pave the way for its use not only as a standalone biomarker, but also as part of composite panels guiding personalized oncology.

Beyond these general research directions, future studies should also examine how miR-1296 may act as a molecular bridge between metabolic signaling and immune modulation within the tumor microenvironment. Evidence from gastric cancer, where circSOD2 in macrophages regulates cisplatin sensitivity through the miR-1296/STAT1 axis, highlights a unique form of

intercellular communication that links metabolic stress to immune activation [71,102]. Building on this concept, combining miR-1296 modulation with immune checkpoint blockade or metabolic pathway inhibitors could represent an innovative therapeutic approach worth exploring in preclinical models.

miR-1296 has emerged as a critical regulator of cancer biology, displaying dual roles as either a tumor suppressor or oncogene depending on the cellular and molecular context. Across multiple malignancies, its dysregulation has been shown to influence key hallmarks of cancer, including proliferation, migration, invasion, apoptosis, therapy resistance, and metastatic spread. In most tumor types, reduced expression of miR-1296 is associated with aggressive clinical behavior and poor outcomes, underscoring its potential as a prognostic biomarker and therapeutic target. Conversely, in certain cancers such as colorectal carcinoma, its upregulation appears to drive oncogenic processes, highlighting the complexity of its function. Taken together, the available data support the view that miR-1296 is not only a mechanistic player in tumorigenesis but also a promising candidate for translation into clinical applications. Future integration of miR-1296 profiling into diagnostic, prognostic, and therapeutic strategies may contribute to more precise and personalized cancer management.

Conflict of Interest Statement

The author declares that they have no competing interests.

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