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Dual role of microRNA-1297 in the suppression and progression of human malignancies

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ABSTRACT

MicroRNAs (miRNAs) are endogenous, non-coding, single-stranded and tiny RNAs that modulate several biological functions, more importantly, the pathophysiology of numerous human cancers. They are bound with target mRNAs and thereby regulate gene expression at post-transcriptional levels. MiRNAs can either trigger cancer progression as an oncogene or alleviate it as a tumor suppressor. Abnormal expression of microRNA-1297 (miR-1297) has been noticed in several human cancers suggesting a distinct role for the miRNA in tumorigenesis. More specifically, it is both up-regulated and down-regulated in various cancers suggesting that it can act as both tumor suppressor and oncogene. This review systematically highlights the different roles of miR-1297 in the pathophysiology of human cancers, explains the mechanisms underlying miR-1297-mediated tumorigenesis, and discusses its potential prognostic, diagnostic, and therapeutic importance.

1. Introduction

Cancer is one of the major public health concerns worldwide and is considered to be the 2nd leading cause of death in the United States. The statistics on 2019 indicate that 1762,450 new cancer cases and 606,880 cancer deaths were recorded in the United States [1], and the corresponding economic losses were estimated to be $94.4 billion in 2015 [2]. These data highlight the importance of seeking novel and efficient prognostic, diagnostic, and therapeutic strategies.

Despite the massive efforts, timely diagnosis and treatment of cancer still continue to be a serious challenge [1]. In a massive effort to explore the mechanisms of carcinogenesis, researchers have recently discovered that numerous genes are dysregulated at the beginning and progression of tumors, including tumor suppressors' shutdown as well as uncontrolled activation of oncogenes and proliferation-related signaling pathways [3]. The recently published papers confirm implication of miRNAs in regulation of functional genes associated with oncogenesis through activation or inactivation of oncogenes and targeting cell signaling pathways [4–6]. Considering their crucial roles in the pathophysiology of various cancers, the involvement of miRNAs in human malignancies should be fully elucidated, to have broad insight into the oncogenesis and enhance therapeutic strategies.

MiRNAs, a group of highly conserved, single-stranded, endogenous, non-coding, small RNAs consisting of 21–23 nucleotides, are post-transcriptional regulators of gene expression by base-pairing with mRNA molecules in the 3′ untranslated region (3′-UTR), controlling the translation process of the target mRNA. The level of complementarity between miRNAs and the target mRNAs determines whether the translation process is blocked or less frequently the target gene may be degraded [7–9]. MiRNAs make up 1–5% of the human genome, acting as a regulator of at least 30% of protein-coding genes [10]. Firm evidence indicates that miRNAs are potentially involved in the pathophysiology of several diseases, including cancer [11–14], atherosclerosis [15–18], varicose disease [19], obesity [20], and neonatal sepsis [21]. Also, they play a crucial role in numerous biological functions including, (but not limited to) cell growth [22], apoptosis [23–25,132], lipid and

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lipoprotein metabolism [26,27], hemostasis [28], and immune responses [9,29]. MiRNAs can be detected in different tissues (e.g., tumor tissues), the circulation, and serum, which enables them to be employed as an excellent tool for non-invasive and quick diagnoses of many diseases, more importantly, cancer [30]. For instance, except for leukemia which is approachable and easily sampled, other types of tumors particularly solid ones require biopsy and surgery for a definite diagnosis. Unfortunately, these invasive techniques are usually used when the disease is at the end-stage. Therefore, miRNAs may be of grave importance for timely and non-invasive diagnosis of malignancies [31, 32]. MiRNAs also contain potential therapeutic capacity; as evidence, miR-208/499 and miR-195 have been introduced as a preclinical therapy for cardiovascular disease, while miR-34 and let-7 for cancer. Miravirsen (codenamed SPC3649), antisense to miR-122 has been entered the phase II clinical trials to treat hepatitis C virus infection [33–35].

2. MiR-1297

MiR-1297 is a small RNA particle comprised of 17 nucleotides, and the following sequence 5′UUCAAGUAAUUCAGGUG3′ located on the 13q14.3 chromosome (Fig. 1). Consistent with the canonical miRNA biogenesis pathway, miR-1297 is biosynthesized in the nucleus and cytoplasm through different steps. Initially, miR-1297 is transcribed in a large double-strand RNA by the RNA polymerase II which is called Pri-mir-1297. Then, an enzyme called Drosha and its related protein, DiGeorge Syndrome Critical Region 8 (DGCR8) turn Pri-mir-1297 into Pre-mir-1297 and then it is transferred to the cytoplasm. In the cytoplasm, Pre-mir-1297 is affected by DICER enzyme and the proteins AGO2 (Argonaute family protein) and TRBP [*trans*-activation response (TAR) RNA binding protein] which lead to formation of mature mir-1297. Now, single-stranded mir-1297 can be guided to the target where it can activate or inactivate one or more functional genes [10].

Within the past decade, the role of miRNAs in cancer has been well-reviewed [31,36–40]. However, papers dealing with a specific miRNA are relatively rare. A glance at major scientific databases clearly shows that miR-1297 has aroused tremendous research interest, and its roles in the pathophysiology of different diseases are currently being investigated (Table 1). As evidence, there were only two papers in 2012 in PubMed, and this was elevated to 15 in 2020. Considering the exponential growth of published papers about miR-1297, it is necessary to summarize the most recent advances. Therefore the current study was conducted to give a comprehensive insight into the potential roles of miR-1297 in the prognosis, diagnosis, and therapy of various cancers. Furthermore, the paper briefly discusses the genes targeted by miR-1297 and summarizes molecular studies conducted on the effect of miR-1297 on different molecular pathways offering the opportunity to identify novel biomarkers and molecular mechanisms.

3. MiR-1297 in cancerous diseases

MiR-1297 as a newly-discovered miRNA has been proved to play a crucial role in tumorigenesis of numerous human malignancies including, colorectal cancer (CRC), hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), esophagus squamous cell carcinoma (ESCC), oral squamous cell carcinoma (OSCC), cervical cancer (CC), testicular germ cell tumor (TGCT), laryngeal squamous cell carcinoma (LSCC), lung adenocarcinoma (LA), pancreatic adenocarcinoma (PA), gastric cancer (GC), non-small cell lung cancer (NSCLC), breast cancer (BC), prostate cancer (PC), melanoma (MM), osteosarcoma (OS), bladder cancer (BlC), glioblastoma (GBM) and glioma (GM). Either induction or suppression of proliferation, migration, invasion, apoptosis, and cell-cycle arrest are distinct roles of miR-1297 in various cancers. Moreover, its expression level is frequently measured to be lower in cancerous tissues than the normal adjacent tissues, suggesting that miR-1297 is a tumor suppressor. On the contrary, in some cancers miR-1297 acts as an oncogene, meaning that the function of miR-1297 in human neoplasms is cancer-type specific. MiR-1297 plays a dual role by targeting different genes, as summarized in Table 2. In several cancers, tumorigenesis occurs following the action of Long non-coding RNAs (lncRNAs) or Circular RNAs (CircRNAs), which targets miR-1297 and acts as a competitive endogenous RNA (ceRNA), the so-called sponge effect (Table 3). Moreover, Fig. 2 summarizes the interaction of miR-1297 with its target genes, lncRNAs, and CircRNAs as well as downstream signalling pathway.

4. MiR-1297 and nervous system cancers

Primary brain and central nervous system (CNS) cancers occur in both children and adults which are diagnosed in all anatomical regions of the CNS. These malignancies mainly affect the brain (>90%), and the

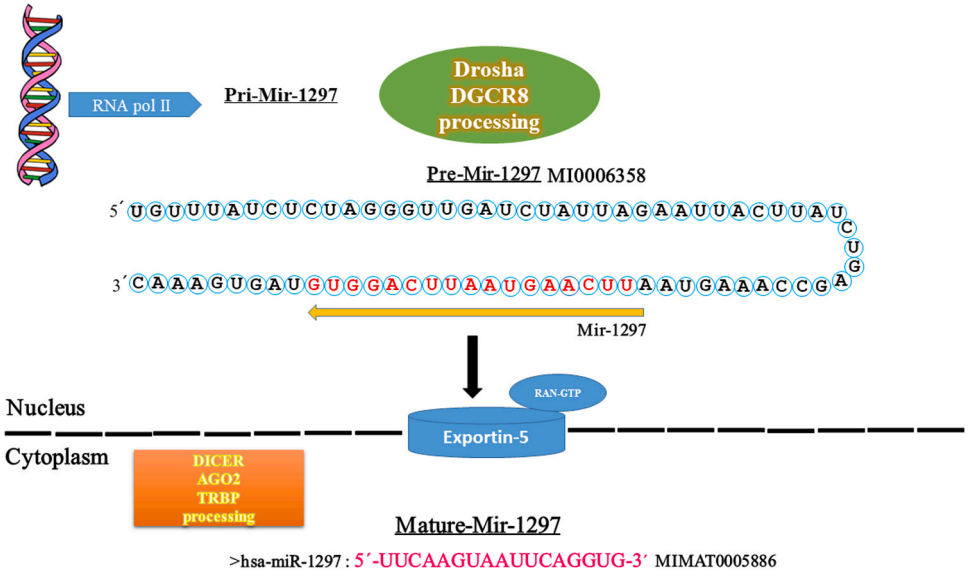

Fig. 1. The hairpin structure of pre-miR-1297 and the sequence of mature miR-1297. The miR-1297 gene is transcribed into a precursor (pre-miR-1297) with 77 nucleotides in the nucleus, and then transferred to the cytoplasm by Exportin-5 for further processing to develop into mature miR-1297 with 17 nucleotides. The sequence of mature miR-1297 is colored in red. The arrow indicates the orientations from 5′ to 3′. The codes of miR-1297 were extracted from miRBase.

Table 1
The roles of miR-1297 in health (physiology) and diseases (excluding cancer).

Types of disease and health conditions	Aim of study	Role of miR-1297	References
Myocardial fibrosis	Investigation of the role and underlying mechanisms of miR-1297 in myocardial fibrosis (MF) in mice model.	MiR-1297 was downregulated while ULK1, as the target gene was up-regulated in the MF model. The protein levels of Col1a1 and α-SMA in primary myocardial fibroblasts were downregulated through the overexpression of miR-1297 or the knockdown of ULK1. More importantly, the regulatory effect of miR-1297 on MF was reversed by ULK1 overexpression. However, miR-1297 via down-regulating ULK1 overcame MF.	[41]
Osteoporosis	Investigation of the regulatory effect of mir-1297 on osteogenesis and osteoporosis in hBMSCs (human bone marrow mesenchymal stem cells)	Downregulation of MiR-1297 enhanced the osteogenesis of hBMSCs by overexpression of WNT5A, as the target gene and overexpression of osteogenesis-related markers (RUNX2, OSX, ALP, OCN, OPN, and COL1A1)	[42]
Panic disorder	Investigation of the altered expression of miR-1297 in the serum of panic disorder patient	MiR-1297 expression was up-regulated in the patients, suggesting that it can potentially be employed as a diagnostic biomarker.	[43]
Non-Ischemic Heart Failure (HF)	Investigation of potential biomarkers in the serum of HF patients using mining strategy	COX-2 and miR-4649–3p were significantly upregulated, and miR-1297 was remarkably downregulated, suggesting that both miRNAs could be utilized as novel biomarkers for non-ischemic HF patients.	[44]
Glaucoma	Investigation of a precise function of the lncRNA-associated ceRNA network using downloaded data from the Gene Expression Omnibus database (GSe126170) containing human trabecular meshwork cell (HTMC) samples under oxidative stress	Demonstration of differential expression profiles of 24 lncRNAs confirmed the upregulation of 19 lncRNAs and downregulation of 5 lncRNAs. Also, 24 miRNAs (including miR-1297) and 40 mRNAs were constructed as a lncRNA-associated ceRNA network in HTMCs under oxidative stress. Finally, an innovative pathological mechanism or a possible therapeutic purpose for glaucoma was identified.	[45]
Bone formation	Investigation of the relation between miRNAs and mRNA expression in tension force-induced bone formation in periodontal ligament cells	Downregulation of target genes and proteins such as WDR33, HSPH1, ERBB3, RIF1, IKBKB, CREB1, FGF2, and PAG1 through hub miRNAs including miR-1297, 195–5p, 424–5p, 3607–5p,145–5p, 4328, 224–5p related to tension force-induced bone formation in PDLC confirmed valuable evidence to advance investigation of the regulatory network in this complex process	[46]
Neural stem cell (NSCs) differentiation and viability	Investigation of the role of miR-1297 in the evolution of NSCs	Upregulation of miR-1297 improved NSCs proliferation and differentiation by directly targeting Hes1. Also, downregulation of mir-1297 leaded to decreased and increased expression of GFAP and β-tubulin III, respectively. Therefore, mir-1297 can be considered as a novel therapeutic approach for neurological disorders.	[47]
Unstable angina (UA)	Investigation of miRNA expression profile alterations in UA patients utilizing gene-chip analysis	MiR-1297 was up-regulated, suggesting a possible role as a biomarker for the diagnosis and treatment of UA.	[48]
Subarachnoid hemorrhage (SAH)	Investigation of the expression levels of miRNAs in the serum of SAH patients and their relationships with the severity and clinical outcome of SAH	miRNAs 1297, 502–5p, 4320 were remarkably upregulated, and miR-4320 was noticed to be a potential diagnostic biomarker of SAH. However, miR-502–5p and miR-1297 were identified to be biomarkers of the diagnosis, severity, and prognosis of SAH	[49]
Diabetic nephropathy (DN)	Investigation of the role of mir-1297 in D-Glucose-treated HK-2 cell lines (used to mimic DN status)	MiR-1297 enhanced cell proliferation and suppressed inflammation by targeting the COL1A2 gene. Furthermore, knockdown of COL1A2 improved the protecting effects of miR-1297 on high glucose-stimulated HK-2 cells. Therefore, mir-1297 can be considered as a novel therapeutic approach for DN development.	[50]
Aneurysmal subarachnoid	Investigation of serum expression of miR-	Different levels of mir-1297 expression of at	[5]

(continued on next page)

Table 1 (*continued*)

	hemorrhage (aSAH)	1297 over multiple periods in aSAH patients	various time points were noticed. Additionally, a meaningful correlation of miR-1297 concentrations in serum with severity in aSAH was confirmed. Therefore, serum levels of miR-1297 can be considered as a prognosis biomarker for aSAH patients.
Neurotoxicity	Investigation of the role of miR-1297 in sevoflurane-induced neurotoxicity	Up-regulation of miR-1297 was confirmed in sevoflurane-exposed mice. Overexpression of miR-1297 in the in vitro model reduced cell proliferation, but increased apoptosis, and LDH activity. Further experiments revealed that miR-1297 intensifies sevoflurane-induced neurotoxicity via suppressing Akt/GSK3b signaling pathway and induction of PTEN proteins expression.	[51]
Metabolic-associated fatty liver disease (MAFLD)	Investigation of the role of lipotoxic exosomal miR-1297 in MAFLD	Up-regulation of miR-1297 was confirmed in palmitic acid-treated primary hepatocytes. Moreover, overexpression of miR-1297 in exosomes derived from lipotoxic hepatocytes stimulated the progression of liver fibrosis by activation and proliferation of hepatic stellate cells through the modulating of PTEN/PI3K/AKT signaling pathway.	[52]
Human retinal tissues	Investigation of the lncRNA-miRNA-mRNA (ceRNA) network in human retinal tissues following detachment with proliferative vitreoretinopathy (PVR)	Differential lncRNA expression profiles that influenced the mentioned network, such as HCP5–1297-ADM in detached human retinas consisting of 9 PVR-specific lncRNAs, as well as 27 miRNAs and 73 mRNAs were demonstrated. These results could enhance understanding of the pathogenesis of human retinal detachment with PVR and provide new lncRNAs as possible therapeutic objectives.	[53]

rest affect the meninges, spinal cord, and cranial nerves [54]. The incident cases of CNS tumors were reported to be 330,000 in 2016, and 227,000 deaths were recorded, worldwide. Between 1990 and 2016, the age-standardized incidence rates of CNS malignancy expanded globally by 17.3% [54]. Therefore, the molecular basis of GM should urgently be elucidated which pave the way for investigation of innovative targets to generate novel therapeutic and diagnostic approaches for this life-threatening illness. Dysregulation of many miRNAs have been reported in GM. Accordingly, Wang et al. in 2016 for the first time reported that miR-1297 takes part in gliomagenesis by directly targeting and downregulating the expression of the high mobility group protein A1 (HMGA1) in GM cells. HMGA1 is usually intensely expressed during development and plays key roles in organizing normal cell proliferation, embryonic cell growth, and cell differentiation. Although the expression of HMGA family proteins in adult tissues is scarcely detectable, HMGA1 expression is stimulated in various types of human tumors. Moreover, it has been proven that HMGA1 is involved in cancer progression and can be considered as a biomarker for tumor diagnosis and remedy. The studies conducted by Wang et al. confirmed that miR-1297 expression levels in tissue specimens and cell lines were remarkably down-regulated, and HMGA1 gene expression was elevated. Furthermore, they showed that ectopic overexpression of miR-1297 in vitro reduces cell viability and proliferation as well as inhibits the growth of xenograft tumor in vivo through downregulation of HMGA1 [55]. One of the hallmarks of cancer cells is reprogramming glucose metabolism and the consequent high glycolysis rate, also known as the Warburg effect. As a member of the karyopherin family, karyopherin subunit alpha 2 (KPNA2) is involved in the transportation of macromolecules such as transcription factors into the nucleus and correlated with metabolism reprogramming. KPNA2 can be considered a fundamental regulator of glycolysis in many cancers, including GBM. In this regard, Wang et al. in 2020 exhibited that KPNA2 is notably up-regulated both in tissue samples of GBM patients and cell lines, resulting in improved glycolytic metabolism. As evidenced, lactate levels, glucose uptake, and extracellular acidification rate (ECAR) as an indicator of the Warburg effect and oxygen consumption rate (OCR) as a reflector of mitochondrial respiration dramatically were promoted. Also, it was reported that KPNA2 enhanced glycolytic metabolism via activation of c-Myc signaling. Their study revealed that the expression level of miR-1297 both in tissue specimens and cell lines was considerably downregulated and correlated with the poor prognosis of the patients. However, forced overexpression of miR-1297 in cell lines downregulated KPNA2 to control expression of crucial genes involved in glycolysis and subsequently inhibited cell proliferation and glucose metabolism in GBM. As evidenced, ectopic overexpression of miR-1297 decreased enzymatic activities of critical enzymes, including PFK, PKM, and HK2 in the glycolytic pathway [56,57]. Recently, the critical roles of CircRNAs in tumorigenesis, metastasis, invasion, malignant transformation, signal transduction, and angiogenesis were explained. Oncogenic functions of hsa_circ_0030018 in promotion of tumorigenesis and invasiveness in numerous human tumors have already been confirmed [58,59]. With this aspect, Song et al. in 2021 revealed high expression of hsa_circ_0030018 and low expression of miR-1297 in GM tissue and cell lines. They found that miR-1297 is a direct target of hsa_circ_0030018. Their results also demonstrated that hsa_circ_0030018 silencing or forced overexpression of miR-1297 might decrease cell proliferation, metastasis as well as promote apoptosis, and cycle arrest in GM cell lines via targeting Ras-Related Protein Rab-21 (RAB21). Besides, knockdown of hsa_circ_0030018 repressed tumor progression in vivo. Therefore, hsa_circ_0030018 silencing might undermine its anti-tumor functions by mediating the miR-1297/RAB21 signaling pathways via upregulation of miR-1297 [58]. LncRNAs are considered to be important molecules to manage CNS tumors, especially GM [60]. LncRNAs with longer than 200nt in length consist of the principal part of human RNA and exert functions via regulation of gene expression at both transcriptional and post-transcriptional levels through interactions between DNA, RNA, and proteins. Recently, dysregulated expression of lncRNAs in multiple human neoplasms and their regulatory roles in cellular and biological function were proved [61–63]. In this regard, Liu et al. in 2021 established the oncogenic capacities of lncRNA DLGAP1 antisense RNA 1

Table 2
Target genes of miRNA-1297 responsible for its tumor suppressive or oncogenic properties in different cancers.

Malignancy	Gene	Location	Cell lines Normal	Cancerous	No. of tissue samples	Expression of miRNA tissue	Expression of miRNA Cell lines	Outcomes[b]	references
GM	HMGA1	6p21.31	NHA	U251, U87, A172, LN 340, TJ905, U373	10p	↑	↑	Induced apoptosis and inhibited cell proliferation	[55]
	RAB21	12q21.17	c	c	c	↑	↑	Induced apoptosis and cycle arrest; inhibited cell proliferation and metastasis	[58]
	EZH2	7q36.1	NHA	U251, T98G, U87 and LN229	24[a]	↑	↑	Inhibited cell proliferation, migration, and invasion	[60]
GBM	KPNA2	17q24.2	N/A	U87MG, U138MG	49[a]	↑	↑	Inhibited cell proliferation and glucose metabolism	[56]
LSCC	PTEN	10q23.31	N/A	Hep-2	10p	↓	↓	Inhibited cell viability, migration, and tumorigenesis	[65]
NSCLC	Skp2 PTEN AKT	5p13.2 10q23.31 14q32.33	N/A	A549, NCI-H460	16p	↓	↓	Inhibited cell proliferation	[66]
LA	TRIB2	2p24.3	N/A	A549, LTEP-a-2	Not-mentioned	↑	↑	Inhibited cell viability and induced apoptosis	[67]
PA	MTDH	8q22.1	N/A	PANC-1, BxPC-3	22p	↑	↑	Inhibited cell proliferation, migration, and induced apoptosis	[124]
OS	PFKFB2	1q32.1	hFOB1.19	MNNG-HOS, U-2OS Saos-2 and MG63	40[a]	↑	↑	Inhibited cell proliferation, metastasis, and aerobic glycolysis; Induced apoptosis	[125]
MM	PTEN	10q23.31	HaCaT	WM-115, Malme-3 M, MSK-MEL-1 and A375	63p	↓	↓	Inhibited cell proliferation, migration, and EMT	[126]
TGCT	PTEN	10q23.31	N/A	NCCIT	33p	↓	↓	Inhibited cell growth	[102]
TGCT	PTEN	10q23.31	N/A	NCCIT	Not-mentioned	↓	↓	Inhibited cell proliferation	[101]
	TET3	2p13.1	MCF-10A	MCF-7, SW626, HCC1937	20p	↓	↓	Inhibited cell proliferation, migration, invasion, and EMT	[73]
BC	PTEN	10q23.31	MCF-10A	T47-D, MCF-7, MDA-MD-231, MDA-MB-453, BT-549	116p	↓	↓	Inhibited cell cycle and induced apoptosis	[77]
	TAZ	3q25.1	MCF-10 A	MDA-MB-231, MCF-7, and MDA-MB-468	Not-mentioned	↑	↑	Inhibited cell proliferation, cell cycle, and migration	[74]
	FA2H	16q23.1	N/A	MDA-MB-231	Not-mentioned	↓	↓	Inhibited EMT	[81]
PC	AEG-1	8q22.1	RWPE-1	PC-3, LNCaP, DU-145 and 22RV-1	20p	↑	↑	Inhibited cell proliferation and invasion	[130]
	PTEN	10q23.31	RWPE-2 (CRL-11610)	DU145 (HTB-81), VCaP (CRL-2876), PC-3 (CRL-1435) and LNCaP (CRL-1740)	90p	↓	↓	Inhibited cell migration and invasion	[128]
CC	AEG-1	8q22.1	H8	C33A, HeLa, CaSki and SiHa	117p	↑	↑	Inhibited cell migration, invasion and EMT	[98]
	PTEN[d]	10q23.31	N/A	HeLa	Not-mentioned	↑	↑	Inhibited cell proliferation and induced apoptosis	[100]
	PTEN[d]	10q23.31	N/A	SSC-4	16p	↑	↑	Inhibited cell proliferation	[121]
OSCC	GSK3β	3q13.33	SCC-090	UM-SCC6	Not-mentioned	↓	↓	Inhibited apoptosis and induced cell proliferation	[122]
BlC	EphA2	1p36.13	N/A	T24	Not-mentioned	↑	↑	Inhibited cell proliferation and induced apoptosis	[103]
	HMGA2	12q14.3	N/A	HepG2 and SMMC7721	Not-mentioned	↑	↑	Inhibited cell proliferation and migration; Induced apoptosis	[87]
	ROCK1	18q11.1	LO2 and HEK293	MHCC97H, HCCLM3, SK-HEP-1, Hep3B, and Huh7	60p	↑	↑	Inhibited cell proliferation, migration, and invasion	[91]
HCC	EZH2	7q36.1	N/A	Hep3B and HepG2	35p	↑	↑	Inhibited cell proliferation and induced apoptosis	[90]
	RB1	13q14.2	N/A	HepG2	496p	↓	↓	Inhibited cell proliferation	[92]
	MAT2A	2p11.2	N/A	Huh7, HCC-LM3, SK-Hep-1, and Hep3B	50p	↑	↑	DNA Hypomethylation	[93]
	CCND2	12p13.32	293 T	SW480	32p	↑	↑	Inhibited cell proliferation and metastasis	[108]
CRC	COX2	1q31.1	N/A	LOVO, HCT116, SW480, SW-620, HT29 and HCT8	20p	↑	↑	Inhibited growth, migration, and invasion of cells; repressed tumorigenesis in vivo	[84]
	xCT	4q28.3			119p			Inhibited cell proliferation	[89]

(*continued on next page*)

Table 2 (*continued*)

			CCD-112Con and CCD 841	LoVo, SW 620, SW 1116, SW 480 and RKO		↑	↑	
	CDC6	17q21.2	GES-1	SGC-7901, MKN-45, and BGC-823	38p, 43[a]	↑	↑	Inhibited cell proliferation and colony formation; Induced apoptosis [114]
	EZH2	7q36.1	N/A	N/A	85p	↑	↑	Inhibited cell proliferation and invasion [113]
GC	HMGB2	4q34.1	GES-1	MKN45, MKN28, BGC-823, and SGC-7901	78p	↑	↑	Inhibited cell proliferation, invasion, and metastasis [115]
	CREB1	2q33.3		MKN-45 and SGC-7901	62p	↑	↑	Inhibited cell growth in vitro and in vivo [85]
	E2F3	6p22.3	GES-1	MKN74 and HGC27)	51p	↑	↑	Inhibited cell proliferation, invasion, migration; Induced apoptosis and cell cycle arrest [131]

Notes:
[a]Tissue specimens are not in pairs. The genes' names were abbreviated according to GenBank.
[b]after treatment with miRNA mimic or inhibitor; knockdown of target gene or lncRNA and circRNA.
[c]Lack of access to the full-text article to complete the required information.
[d]PTEN is recognized as a tumor suppressor gene, evidenced by down-regulation in various tumors; however, it displays oncogenic roles in CC and OSCC. Therefore, these inconsistencies need further investigation in future studies.

Table 3
Oncogenic circ RNA and lncRNA act as ceRNA for miR-1297 in different cancers.

RNA	Malignancy	Cell lines		No. of tissue samples	Outcomes	References
		Normal	Cancerous			
LncRNA-SNHG6	HCC	N/A	Huh7, HCC-LM3, SK-Hep-1, and Hep3B	50p	Induced cell proliferation and invasion;Inhibited apoptosis	[93]
Hsa_circ_101141		LO2 and HEK293	MHCC97H, HCCLM3, SK-HEP-1, Hep3B, and Huh7	60p	Induced cell proliferation, migration, and invasion	[91]
LncRNA-GAS5	OSCC	SCC-090	UM-SCC6	Not-mentioned	Induced apoptosis and inhibited cell proliferation	[122]
	CCA	HIBEC	RBE, CCLP1, HuCCT1 and HCCC-9810	59[a]	Induced cell proliferation and invasion	[63]
Hsa_circ_001418	BlC	N/A	T24	Not-mentioned	Induced cell proliferation and inhibited apoptosis	[103]
Hsa_circ_PGPEP1		GES-1	MKN74 and HGC27)	51p	Induced cell proliferation, invasiveness and migration; Inhibited apoptosis	[131]
LncRNA-MALAT1	GC	GES-1	MKN45, MKN28, BGC-823, and SGC-7901	78p	Induced cell proliferation, invasiveness, and metastasis	[115]
LncRNA-HOXA11-AS		N/A	N/A	85p	Induced cell proliferation and invasiveness	[113]
Hsa_circ_0091074	BC	MCF-10 A	MDA-MB-231, MCF-7, and MDA-MB-468	Not-mentioned	Induced cell proliferation and invasiveness	[74]
Hsa_circ_0030018	GM	b	b	b	Inhibited apoptosis and cell cycle arrest; Induced cell proliferation and metastasis	[58]
LncRNA- DLGAP1-AS1		NHA	U251, T98G, U87 and LN229	24[a]	Induced cell proliferation, migration and invasion	[60]
LncRNA-Meg3	TGCT	N/A	NCCIT	33p	Inhibited cell growth	[102]

Notes: [a] Tissue specimens are not in pairs
[b] Lack of access to the full-text article to complete the required information

(DLGAP1-AS1) and enhancer of zeste homolog 2 (EZH2) in GM progression as well as the tumor-suppressive function of miR-1297 in repressing GM. According to their results, lncRNA- DLGAP1-AS1 and EZH2 were up-regulated in GM tissue and cell lines; however, the expression of miR-1297 was down-regulated. EZH2 as a direct target gene of miR-1297 caused histone methylation and gene silencing via post-translational histone alterations, but DLGAP1-AS1 by sponging miR-1297 accelerated the expression of EZH2 and promoted invasion, migration, and proliferation in GM cell lines. Furthermore, they noticed that silencing DLGAP1-AS1 not only suppressed GM progression but also restrained tumorigenicity in vivo [60]. Taking together, the above-mentioned studies demonstrate that miR-1297 acts as a tumor suppressor in CNS malignancies and can be considered as a novel diagnostic and therapeutic target.

5. MiR-1297 and respiratory system cancers

Respiratory diseases are consistently considered to be the main threat to public health and are listed among the fatal diseases in developed countries [64]. Of significant importance, lung cancer with the highest morbidity and mortality worldwide is the most frequent malignant neoplasm. Small cell lung cancer (SCLC) and NSCLC are two main types of lung cancer. It has been claimed that respiratory malignancies in the United States were responsible for 147,510 deaths in 2019 [1]. With this aspect, rapid diagnosis and timely treatment of the patients are essential for improving life and survival rate.

According to available evidence, miR-1297 is implicated in both upper and lower respiratory tract neoplasms. In this regard, Li et al. in 2019 noticed that the expression of mir-1297 was high in LSCC in cancerous cell lines and clinical tissue samples compared to the adjacent non-neoplastic tissues, suggesting that it might act as an oncogene by regulating phosphatase and tensin homolog deleted on chromosome ten (PTEN) related signaling pathway. Additional experiments validated that high expression levels of miR-1297 through downregulation of PTEN can promote cancer cell proliferation, migration, and tumorigenesis. Numerous studies have proved that PTEN as a tumor suppressor gene is downregulated in various primary human cancers, and its activity notably declines via mutations or promoter methylation. Therefore, the lack of PTEN function results in the accumulation of PIP3, stimulating the activation of its downstream effectors, particularly

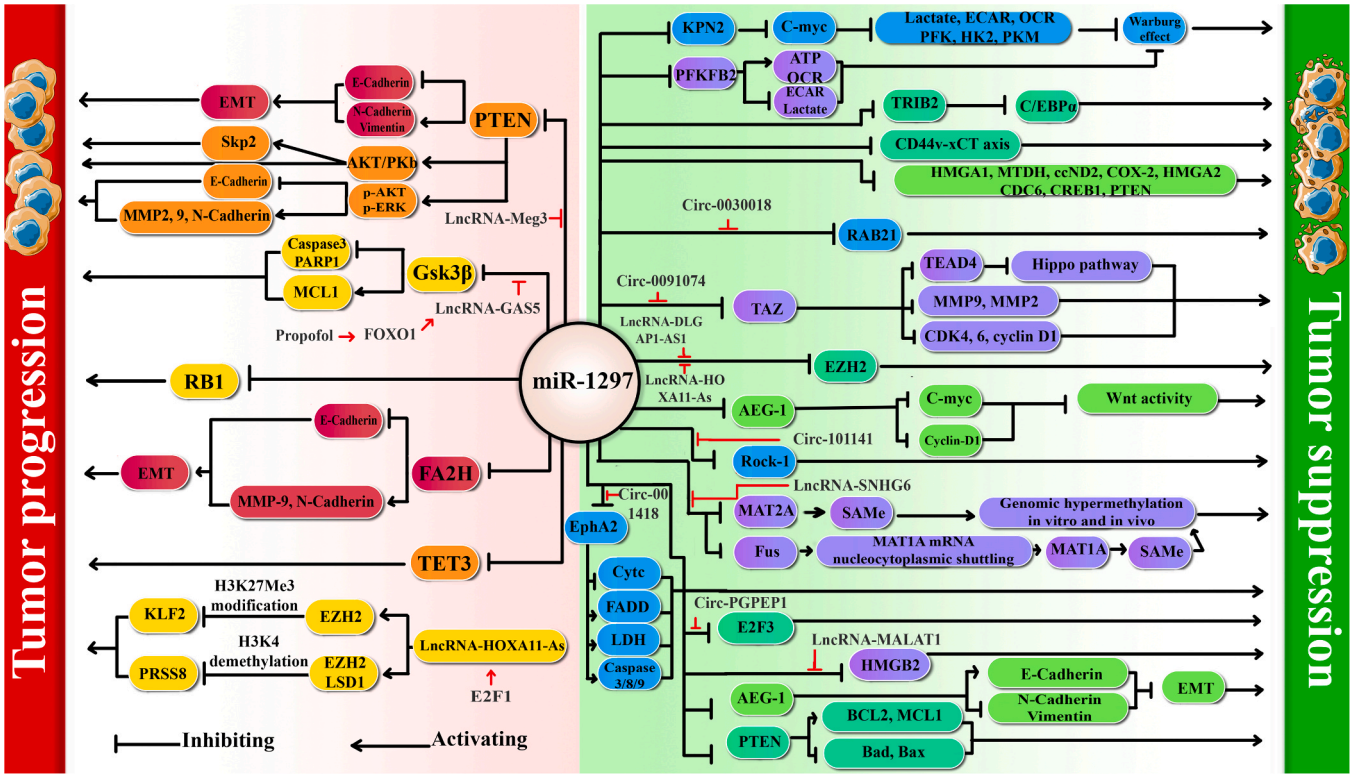

Fig. 2. MiR-1297 regulates tumorigenesis by targeting different genes and downstream signaling pathways, as illustrated [55,56,58,60,63,65–67,73,74,77,81,84,85,87–93,98,100–103,108,113–115,121,122,124–126,128,130,131]. For example, miR-1297 represses tumorigenesis by suppressing the expression of the HMGB2 gene, but lncRNA-MALAT1 reverses the anti-tumor effect of miR-1297. On the other hand, miR-1297 promotes tumorigenesis by suppressing the expression of the GSK3β gene. Propofol stimulates expression of the FoxO1 transcription factor, then FoxO1 attaches to the promoter of GAS5, promoting its transcription; subsequently, GAS5 sponged the miR-1297 and caused cancer progression. miR-1297 directly inhibits the expression of the AEG-1 gene then indirectly suppresses C-Myc and Cyclin D1 as components of the Wnt signaling pathway, causing tumor suppression. miR-1297 could directly bind to the FUS 3′-UTR mRNA as an RNA binding protein (RBP) and inhibits its expression. Therefore, MAT1A mRNA nucleocytoplasmic shuttling was activated, causing promoted MAT1A mRNA and protein in the cytoplasm, subsequently significantly increases SAMe. Also, miR-1297 suppresses MAT2A expression and increases SAMe concentration. Thus, overall, cancer suppresses via instability genome. However, SNHG6 reverses the anti-tumor effect of miR-1297. HOXA11-AS may function as a scaffold and directly bind with EZH2 and LSD1 at their 5′ and 3′ regions, respectively. EZH2 and LSD1 inhibit PRSS8 and KLF2 as a novel tumor suppressor gene through methylation modification, causing tumor progression. In this process, E2F1 stimulated HOXA11-AS transcription.

PDK1, Akt/PKB, and Rac1/cdc42 leading to cancer progression. Additionally, they showed that downregulation of miR-1297 inhibits cancer progression in vitro and attenuates tumorigenesis in vivo [65]. Consistent with the previous study, Bu and Lou also in 2017 determined that miR-1297 might be oncogene by regulating the PTEN/Akt/Skp2 signaling pathway in NSCLC. Their study confirmed the downregulation of PTEN in NSCLC samples compared to the paired normal tissues. They also observed that S-phase kinase-associated protein 2 (Skp2) in NSCLC tissues and cell lines were conversely correlated with the expression levels of PTEN. As an essential enzyme, Skp2 plays a central role in the process of cell cycle development, signal transduction, and transcription through the ubiquitination and consequent proteasomal degradation of target proteins. Overexpression of Skp2 in multiple human malignancies was described, and it has been demonstrated that Spk2 induces cancer cell expansion and progression. Also, Spk2 in PC cells is correlated with chemotherapeutic drug resistance. Furthermore, they showed that transfection of miR-1297 mimic in NSCLC cell lines via downregulation of PTEN and upregulation of Skp2 increases cell proliferation. On the other side, the miR-1297 inhibitor could repress cancer progression through reversing the expressions of PTEN and Skp2 via enhancing levels of phosphorylation of Akt. Therefore, in NSCLC patients, PTEN and Spk2 can be considered as potential targets for gene therapy [66]. Contrary to the above-discussed studies, another research disclosed that miR-1297 and miR-511 might be a tumor suppressor gene via regulating the tribbles pseudokinase 2/ CCAAT/ enhancer-binding protein alpha (TRIB2-C/EBPα) signaling pathway. As an inhibitor of mitosis, Tribbles participate in the regulation of cell proliferation, migration, and morphogenesis during the development. It has been reported trib1, trib2, and trib3 genes are responsible for encoding tribbles homologs in mammals. Substantial evidence also illustrated that TRIB2 has an oncogenic role in various human neoplasms, for instance, acute myeloid leukemia (AML) via inhibiting the downstream factor of TRIB2 (C/EBPα). Tribbles proteins enhance the degradation of C/EBPα and C/EBPβ transcription factors via promotion of ubiquitin-dependent degradation pathway. TRIB2 requires an intact C-terminal constitutive photomorphogenesis 1(COP1)-binding site to deteriorate C/EBPα. TRIB2 via binding to the C/EBPα blocks its binding to DNA; thus, the transcriptional activity of C/EBPα is lost. Zhang et al. in 2017 recorded TRIB2 upregulation and downregulations of miR-1297 and miR-511 in human LA compared to the control tissue samples. These results may support a potential oncogenic function for TRIB2 and suppressor role for miR-1297 and miR-511 in the pathological alterations of LA. They also demonstrated that transfection with miR-1297 and miR-511 mimics could inhibit cell proliferation in vitro and in vivo by suppressing TRIB2 and further enhancing C/EBPα expression. Also, the findings confirmed that high levels of miR-1297 and miR-511 expression could remarkably enhance the apoptotic rate [67]. In summary, although these findings are remarkable and exciting, further studies should be conducted to clarify the specific roles of miR-1297 as a tumor suppressor gene or oncogene in respiratory system cancers. Furthermore, its association with ceRNA and lncRNA in progression or suppression of related tumors should be further investigated.

6. MiR-1297 and breast cancer

BC is one of the most common malignancies in women worldwide and the leading cause of 15% of cancer deaths in women [68]. According to GLOBOCAN 2020 estimates, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases [69]. In the recent decades, the mortality rate because of BC has decreased dramatically due to effective advances in treatment and diagnosis. However, the prognostic predictors and precise mechanisms involved in BC progression have not yet been well understood [70]. Therefore, an accurate understanding of BC's molecular mechanisms is essential to identify more ideal biomarkers and new therapies. MiRNAs are one of the molecular factors involved in the development of BC. More specifically, miRNAs have been shown to act as a regulatory factor in BC's molecular mechanisms [71,72]. To date, several articles have been published on the role of miR-1297 in the pathogenesis of BC [11,73–77]. These studies indicate that miR-1297 takes part in the pathogenesis of BC, through regulation of proliferation, migration, invasion, and apoptosis in BC cells. Nevertheless, contradictory results have been reported regarding whether miR-1297 is a tumor suppressor or an oncogene in BC.

The first study by Liu et al. in 2017 investigated the effect of miR-1297 on BC cell growth to identify related signaling pathways [77]. In BC clinical tissue specimens and cell lines, it was proved that miR-1297 expression was elevated. Overexpression of miR-1297 was also found to induce cell proliferation and inhibit apoptosis. This study stated that PTEN is a direct target of miR-1297 and its expression level is reduced in BC cell line and tissue samples. Thus, miR-1297 by suppressing PTEN increases cell proliferation and cell cycle as well as inhibits apoptosis via activation of PI3K/AKT signaling. This study also revealed that miR-1297 induces cyclin D1 and inhibits p27 via the PTEN/PI3K/AKT pathway [77]. According to previous studies, activation of the PI3K/AKT pathway leads to development and progression of BC through induction of cell proliferation and migration and inhibition of apoptosis [78,79]. The authors concluded that miR-1297 is an oncogene in BC, and PTEN has a tumor-suppressing effect by inhibiting the PI3K/AKT pathway [77]. Another study was conducted in 2019 by Xueyun et al. to evaluate the effect of miR-1297 on BC cells and elucidate its molecular mechanism [73]. The results showed that miR-1297 expression levels in BC tissues and MCF-7 cells increased significantly which were associated with the activation of malignant biological behaviors, including promoted proliferation, invasion, migration, and epithelial-mesenchymal transition (EMT) of cells, through down-regulation of TET3, as a direct target. The decrease in miR-1297 also reversed cellular behaviors [73]. The family of ten-eleven translocation (TET), as DNA demethylases, are tumor suppressors required to maintain genomic instability. According to the available evidence, TET3 acts as an oncogene or tumor inhibitor in ovarian cancer [80]. TET affects tumorigenesis through increasing chemotherapy sensitivity. Therefore, Xueyun and colleagues concluded that miR-1297, as an oncogene, by inhibiting the expression of TET3, leads to the activation of malignant behaviors in BC tissues and MCF-7 cells [73]. To have a better insight into the molecular mechanisms of BC tumorigenesis, Li et al. (2020) investigated the role of miR-1297 in BC cell lines and tissues samples [81]. The results showed that miR-1297 inhibitor significantly reduced cell proliferation, suppressed EMT, and increased apoptosis in-vitro. Moreover, the elevation of FA2H (fatty acid 2-hydroxylase) expression also inhibits cell proliferation and induces apoptosis. The bioinformatics analysis and different experiments showed that miR-1297 targets FA2H directly [81]. Several studies have examined the effect of FA2H on tumorigenesis [82,83]. It was reported that FA2H is involved in several cellular signaling pathways, such as the mTOR and AMPK [82]. The expression level of FA2H decreases in BC and GC tissues [82,83]. Additionally, FA2H can reduce drug resistance in tumor cells. Therefore, it was suggested that FA2H could play a role in inducing the drug's sensitivity by modulating endocytosis and excretion of drugs through cell membranes. Based on Li et al. investigation, it can be concluded that miR-1297, as an oncogene, increases cell proliferation by inhibiting the expression of FA2H (as a tumor suppressor) in BC [81]. On the other hand, some studies have reported that miR-1297 is a tumor suppressor because of its reduced expression in BC cells [74,75]. For example, Hu et al. in 2020 found that hsa_circ_0091074 expression levels increase in BC cells which acts as an endogenous sponge for miR-1297 leading to reduction of miR-1297 expression. It was also found that the TAZ as a direct target of miR-1297, is overexpressed in BC following action of hsa_circ_0091074. TAZ is a critical downstream factor in the Hippo signaling pathway, which plays an essential function in modulating cell proliferation, tissue growth, and regeneration. It was shown that an increase in the TAZ is directly related to the invasive type of BC and the induction of EMT cells [74]. In 2019, Mosapour et al. reported that miR-1297 could be a tumor suppressor in BC cells [75]. It was shown that the expression level of miR-1297 in malignant breast tumors is significantly lower than in benign breast tumor samples [75]. The results are consistent with several other studies in which miR-1297 expression was downregulated in malignant tumors such as pancreas, lung, gastric, and colon cancers [84,85]. Next, they examined the relationship between miR-1297 and very-low-density lipoprotein (VLDL) receptor in benign and malignant breast tumors because it was predicted that VLDL receptor is a direct target for miR-1297. However, the experiments showed that expression of VLDL receptor and miR-1297 in malignant tumors are declined. The VLDL receptor is a multifunctional receptor and can be involved in developing tumors by regulating the proliferation and apoptosis of BC cells [76]. In brief, the above-mentioned studies illustrate that miR-1297 plays a crucial role in tumor-suppressing or progressing of BC, suggesting that miR-1297 might be an important target for both prognosis and treatment of BC. However, the specific role of miR-1297 in BC should be illuminated with the investigation of massive genes and signaling pathways which can be affected by miR-1297 or investigation of lncRNAs and circRNAs which can modify miR-1297 expression level.

7. MiR-1297 and hepatocellular carcinoma

Today, HCC is recognized as the most common type of liver cancer and the fifth most frequently diagnosed cancer, globally [86,87]. Also, it is the third leading cause of cancer death [86]. According to the literature, the incidence of HCC is gradually increasing in developed and developing countries [87]. Despite significant advances in conventional therapies, the average survival for HCC patients is about nine months, excluding liver transplantation [87]. Liver transplantation is the gold standard treatment for liver cancer, but it cannot always be conducted everywhere [86].

Therefore, understanding the molecular mechanisms in the process of tumorigeneses, such as proliferation, migration, and cellular apoptosis, is essential for the development of new treatments for HCC [87]. MiRNAs are one of the influential factors in signaling pathways and miR-1297 plays vital roles in various human cancer pathogenesis [88,89]. Recently, the role of miR-1297 in the pathogenesis of HCC was deeply investigated [86,87,90–93]. However, conflicting results have been reported regarding the oncogene or tumor suppressor role of miR-1297. Although, each of these articles has reported the effect of miR-1297 on separate signaling pathways, the common point is that all of these signaling pathways are involved in tumorigenesis, including proliferation, migration, and apoptosis of cells. Therefore, it can be said that miR-1297 is a molecular regulator in the signaling pathways of HCC, but the signaling pathways and the obtained results are slightly controversial. In this regard, Liu et al. in 2015 investigated the role of miR-1297 in regulating the proliferation and apoptosis of HCC cell lines by targeting the HMGA2 [87]. The results showed that the HMGA2 is a direct target of miR-1297. The overexpression of miR-1297 by suppressing HMGA2 led to significant inhibition of cell proliferation and migration, as well as induction of apoptosis in-vitro. Therefore, miR-1297 was introduced as a tumor suppressor and the HMGA2 as an

oncogene. In general, HMGA2 is active in several malignancies (such as cancers of lung, breast, and pancreas), and its inhibition by miR-1297 can contribute to inhibition of tumor growth and metastasis and induction of apoptosis [87,94]. Another study conducted by Liu et al. in 2015 on HCC examined the effect of miR-1297 on proliferation and apoptosis of cells by directly targeting the EZH2 (histone-lysine N-methyltransferase) [90]. The results showed that the miR-1297 expression was significantly lower in HCC cells, and inversely, the EZH2 expression was elevated. The overexpression of miR-1297 led to a significant reduction in cell proliferation and induction of apoptosis in HCC cells. The knockdown of the EZH2 also led to the recording of the same results [90]. Enzyme EZH2 is involved in maintaining the transcriptional suppression of many genes by DNA methylation. Abnormal expression of EZH2 has been reported in lymphoma, PC, and HCC, indicating that it plays an important role in tumorigenesis. Therefore, miR-1297, by inhibiting the EZH2, could be an ideal treatment for HCC [90,95]. A study conducted by Liu et al. in 2016 investigated the role of miR-1297 in the proliferation of liver cancer cells by targeting the RB1 (retinoblastoma protein1) [92]. The results showed that overexpression of miR-1297, as an oncogene, leads to an increase in cell proliferation, and miR-1297 inhibitor leads to inhibition of cell proliferation. Also, miR-1297 increased cell proliferation by suppressing the RB1 expression. It has been proven that RB1 is a tumor suppressor and through negative regulation of the cell cycle, inhibits cell proliferation in several cancers, such as liver cancer [92,96]. In 2018, Guo et al. studied the effect of miR-1297 and lncRNA SNHG6 on HCC cells [93,129]. Preliminary results showed high levels of lncRNA SNHG6 in HCC cells and decreased expression levels of miR-1297. Also, the MAT2A (methionine adenosyltransferase-A2) was identified as a direct target for miR-1297. MATs are essential enzymes for the mediate formation of SAMe (S-adenosylmethionine) in mammalian cells. MATA1 has a high concentration in quiescent liver cells and leads to an increase in the SAMe. Conversely, MATA1 in cancer cells is decreased, and the level of MAT2A enzyme is increased. In HCC cells, the lncRNA SNHG6 increases the level of the MAT2A by sponging miR-1297. As a result, the lncRNA SNHG6, with an increase in MAT2A, leads to a decrease in the SAMe, resulting in hypomethylation of HCC cells [93]. In 2020, Zhang et al. examined the effect of circRNA human_circ_101141 on HCC cell's tumorigenesis by regulating the miR-1297/ROCK1 pathway [91]. Recently, it has been reported that circRNAs, as a new class of non-coding RNAs, are involved in cell development and function by regulating gene expression during transcriptional and post-transcriptional phases. However, their role in the pathogenesis of HCC is still unclear. The results of this study showed that the ROCK1 and circ_101141 expressions are up-regulated in HCC cells. The downregulation of the circ_101141 was accompanied by inhibition of growth, migration, and invasion of cells. miR-1297 inhibits growth, migration, and invasion of cells by directly targeting ROCK1 in normal cells. However, circ_101141 increases ROCK1 in HCC cells through sponging miR-1297. Thus, circ_101141 increases the growth, proliferation, and invasion of cancer cells by increasing the ROCK1. ROCK family members, such as ROCK1, can regulate cell actin skeleton organization and cell motility by phosphorylation. Thus, ROCK1 is involved in tumor invasion [91,97]. In 2019, a high throughput study was conducted by Felgendreff et al. to detect expression profiles of miRNAs in HCC [86]. The study aimed to introduce miRNAs involved in HCC pathogenesis to be used as a promising biomarker. The results showed that the expression level of miR-1297 in tumor-associated cirrhosis was lower than cirrhosis without HCC. Therefore, no significant relationship was observed between miR-1297 and HCC tumor [86]. Overall, the majority of the conducted studies suggest that miR-1297 acts as a tumor suppressor in HCC; however, there are still some disagreements. Therefore, the precise function of miR-1297 in HCC, particularly lncRNAs or circRNAs-miR-1297-related genes and signaling pathways, should be elucidated in future investigations.

8. MiR-1297 and genitourinary cancers

Genitourinary cancers are a general classification of those cancers arising from the urinary and reproductive systems in men and women. The most important ones include bladder, kidney, prostate, cervical, testicular, and ovarian cancers. CC was recently estimated to be one of the most common cancers in women and the third or fourth leading cause of cancer death worldwide. Despite significant advances in the diagnosis and treatment of CC, full recovery and long-term prognosis still remain poor. Also, the precise molecular mechanisms involved in CC's initiation and progression still need to be elucidated [98]. In 2017, Wang et al. studied the role of miR-1297 in the tissues and cell lines of CC. The results showed that the expression of miR-1297 in the cell lines were decreased. In this regard, overexpression of miR-1297 inhibited migration, invasion, and EMT of cells, and downregulation of miR-1297 reversed the tumorigenic behaviors in vitro. Bioinformatics and experimental methods proved that the AEG-1 (astrocyte elevated gene-1) is a direct target for miR-1297. It has been reported that AEG-1 increases in the variety of cancers. It induces proliferation of CC cell via the signaling pathway of FOXO1/PI3K/AKT. Also, AEG-1 may increase EMT of CC cell via the signaling pathway of Wnt/β-catenin. Finally, the study concluded that miR-1297 acts as a tumor suppressor by inhibiting the AEG-1. It has previously been shown that miR-1297 inhibits prostate cancer progression via suppression of the AEG-1/Wnt signaling pathway [98,99,130]. Also, in 2018, Chen et al. investigated the biological role of miR-1297 in CC. Like many other studies, they found that miR-1297 targets PTEN. MiR-1297 expression in CC tissues was lower than normal tissue, and PTEN expression was negatively correlated with miR-129. Furthermore, overexpression of miR-1297 was shown to inhibit proliferation and induce apoptosis in vitro. The PTEN silencing also had the same effects. It was concluded that miR-1297 could reduce cell proliferation by suppressing the PTEN expression[100]. However, many studies have reported controversial results regarding PTEN function [77,101,102].

TGCT is another cancer that is classified as genitourinary cancer. TGCT is the most common cancer among young men aged 25–34 in the United States. The majority of TGCT patients are currently being treated well. However, the treatment outcome depends on early diagnosis before metastasis [101]. Therefore, further research into the identification of molecular mechanisms could introduce efficient biomarkers. In 2014, Yang et al. studied the roles of miR-1297 and PTEN on cell proliferation in TGCT. Initially, it was determined that PTEN is a direct target for miR-1297. The results also showed that the increase in miR-1297 was associated with suppressing PTEN and promoting cell proliferation. The authors, like many others, concluded that miR-1297 acts as an oncogene and PTEN plays a tumor suppressor role in TGCT [101]. In another study, Yang et al. in 2016 investigated the role of Meg3 (maternally expressed gene 3) and miR-1297 in regulating cell growth in TGCT. The study showed that miR-1297 directly targets PTEN. Thus, miR-1297 suppresses PTEN which leads to activation of PI3K/AKT pathway, resulting in increased cell proliferation. It was found that the lncRNA-Meg3 acts as a sponge of miR-1297 and prevents the suppression of PTEN, but its expression in TGCT is significantly reduced. Overexpression of lncRNA-Meg3 was shown to increase PTEN and thus inhibit cell proliferation in TGCT [102].

Bladder carcinoma is another cancer that is classified as genitourinary cancer. It is the most common tumor of human urinary system and is one of the leading causes of cancer death, worldwide. This cancer is more common in men and occurs in middle age or above. Histological types of BlC are transitional cell carcinoma or squamous cell carcinoma [103].

Peng et al. in 2021 studied the effects of miR-1297 and circ-001418 in bladder carcinoma. The results showed that overexpression circ-001418 is associated with increased cell proliferation and decreased apoptosis. Declined expression of circ-001418 was also associated with inhibition of cell proliferation and promotion of apoptosis. Moreover,

EPH receptor A2 (EphA2) was identified as the direct target for miR-1297, which increases in the cancer cells. Additionally, circ-001418 increased EphA2 expression by the suppression of miR-1297, in bladder carcinoma cells. EphA2 is expressed in many human cell lines and is considered as a regulator of cell proliferation. Therefore, it is involved in developing the nervous system, angiogenesis, growth, migration, and differentiation of cells [103,104].

Epithelial ovarian cancer (EOC) is another malignancy that is classified as genitourinary cancer. EOC is the most common tumor in women, accounting for approximately 90% of malignant ovarian tumors. About 70% of the patients are diagnosed within the advanced stages of the disease, when the prognosis is poor [105]. Therefore, further studies are needed to identify biomarkers and more ideal prognosticators. In this regard, Dou et al. in 2017 studied the expression of integrated mRNA and miRNA signatures in lymphocytes of EOC patients. The results showed that the expression of miR-1297 was decreased in the patients. Based on bioinformatics studies, MGEA5 and TAOK1 were introduced as direct targets of miR-1297. Therefore, miR-1297 can be employed as novel biomarkers of EOC; however, more studies are needed in this field [105]. According to the available studies, it can be concluded that the potentially tumor-suppressive or oncogenic role of miR-1297 in genitourinary system cancers depends on the types of organs. For example, miR-1297 represents a tumor-suppressive role in CC, but it acts as an oncogene in TGCT. Therefore, additional investigations of multiple signaling pathways that influence miR-1297 expression levels or are affected by miR-1297 utilizing larger tissue specimens and various cell lines in all organs should be conducted to illuminate the exact function of miR-1297 in genitourinary system neoplasms.

9. MiR-1297 and gastrointestinal cancer

Gastrointestinal (GI) cancers are one of the most common cancers, worldwide. Common GI cancers include oral, gastric, esophageal, pancreatic, and colon cancers. They are often diagnosed by endoscopy, followed by biopsy of the target tissue. However, researchers have investigated some novel and non-invasive epigenetic biomarkers for GC within the past decade [106,107].

This section first looks at colon cancer, the most common malignant tumor of the GI tract. According to previous reports, more than one million new cases of CRC are diagnosed worldwide each year, and its mortality rate in developed countries is around 33% [108]. Its average annual incidence has increased by more than 5% in China from 1992 to 2005 [84]. With more understanding of its molecular mechanisms in recent years, patient's overall survival rate has improved. In 2012, Hamfjord et al. analyzed miRNA's differential expression profile in CRC tissues and reported that miR-1297 expression was significantly reduced in CRC tissues [109]. In 2014, Chen et al. studied the role of miR-1297 and cyclo-oxygenase-2 (Cox2) in the growth, migration, and invasion of CRC cells and noticed that miR-1297 expression was reduced, and conversely, Cox2 expression was elevated. MiR-1297 directly targeted Cox2 and leaded to suppression of Cox2 in the normal cells. Therefore, miR-1297, by suppressing Cox2, inhibits the growth, migration, and invasion of CRC cells [84]. Several articles have reported that Cox2 promotes CRC by producing prostaglandins (PGs) and chronic inflammation in cells. In 85% of CRC tissues, the Cox2 gene was up-regulated, and levels of PGs were increased, accordingly. PGs, especially PGE2, have been reported to induce proliferation, invasion, and CRC cell migration. It has also been shown to inhibit apoptosis and induce angiogenesis [84,110]. The role of redox status and miR-1297 in SP (stem-like side-population) cells of CRC was studied by Qiang et al. in 2016 and according to the results, miR-1297 expression was reduced significantly in CRC-SP. The xCT (glutamate-cysteine transporter) within the plasma membrane was identified as a direct target of miR-1297, and its expression levels were inversely related to miR-1297 expression in CRC-SP cells [89]. The xCT expression is increased in CRC and leads to reduction of ROS levels in CRC-SP cells. GSH (reduced glutathione) levels are increased following interaction between the xCT and CD44 variant leading to reduction of ROS levels in cancer cells which is an important modulator of cancer cell proliferation through the CD44v-xCT axis. Therefore, miR-1297 is a tumor suppressor and inhibits CRC-SP cell proliferation by decreasing GSH levels in CRC-SP cells [89,111]. Wang et al. in 2017 identified cyclin D2 (CCND2) as a direct target of miR-1297 in CRC cells. They discovered that miR-1297 expression is reduced in CRC cells, and conversely, CCND2 expression is significantly increased. The CCND2 is involved in progression of various types of cancer through induction of G1 cell cycle. Overexpression of miR-1297 decreases cell proliferation and metastasis potential in SW480 cells by declining CCND2 expression [108]. In 2018 Yan et al. studied miRNA expression profile in SW480 (colon adenocarcinoma cells) and SW620 (cell metastatic) by high-throughput methods [112]. The results showed that miR-1297 expression is reduced in SW620 despite SW480. Also, potential target genes of miR-1297 was shown to be PTEN, COX2, HMGA2, EZH2, TRIB2, and C/EBPalpha. The genes can be involved in the proliferation, invasion, and apoptosis of cells [112].

In this section, it is necessary to review studies on the role of miR-1297 in the pathogenesis of GC, which is one of the leading causes of cancer death, globally [113]. There are many advances in surgical and chemotherapy techniques for the treatment of GC with high recovery rates, as long as it is diagnosed timely. One of the reasons for the late diagnosis of GC is lack of potent prognostics [113]. To recognize more valuable and effective prognostics, a better understanding of the pathogenesis of GC is needed [114]. In this regard, Sun et al. in 2016 studied the effect of the lncRNA- HOXA11-AS and miR-1297 on GC tissues [113]. The results demonstrated that HOXA11-AS expression in GC tissues was increased, and, conversely, the miR-1297 expression was reduced, significantly. Additionally, miR-1297 directly targeted EZH2 and could be sponged by HOXA11-AS, leading to elevation of EZH2 expression and induction of proliferation and invasion of GC cells. Therefore, miR-1297 as a tumor suppressor inhibits proliferation and invasion by suppressing EZH2 expression in non-cancer cells. This study found that the lncRNA-HOXA11-AS expression was significantly increased in GC tissues compared to normal tissues by sequencing and microarray techniques [113]. In 2017 Liu et al. studied the expression of lncRNA-MALAT1 and miR-1297 in GC [115]. The results showed MALAT1 expression was up-regulated in GC tissues, and, conversely, the miR-1297 expression was reduced significantly. Moreover, MiR-1297 directly targets HMGB2 and can be sponged by MALAT1. It has been shown that MALAT1 increases HMGB2 expression and leads to induction of proliferation and invasion in GC. Therefore, MALAT1/miR-1297/HMGB2 axis is an important regulator of proliferation and invasion in GC tumorigenesis [115]. The effect of MALAT1 on various cancers has been studied and available evidence shows that it plays a vital role in carcinogenesis. Accordingly, MALAT1 has been shown to induce growth and metastasis of cancer cells through EMT in oral carcinoma. Also, the effect of HMGB2 on various cancers has been studied and its increased expression has been reported to be associated with the progression of HCC. On the contrary, HMGB2 knockdown reduced the chemo-resistance in GC cells [115,116]. In 2018 Gao et al. studied the role of miR-1297 and CREB1 (cAMP-responsive element-binding protein1) in GC [85]. They reported that miR-1297 expression was significantly reduced in GC tissues. Furthermore, overexpression of miR-1297 suppressed colony-forming abilities and cell proliferation in GC cell lines, significantly. Also, overexpression of miR-1297 suppressed the growth of GC tissues. In this study, CREB1 was identified as the target of miR-1297, and increased expression of CREB1 promoted the growth of GC cells [85]. CREB1 has been reported as an oncogene on various cancers; for example, upregulation of CREB1 in GC was associated with metastasis. However, suppression of CREB1 could inhibit cell growth in human gastric adenocarcinoma [85,117]. In 2019 Zhang et al. studied the effect of miR-1297 on proliferation and apoptosis of GC cells [114]. The results showed that miR-1297

expression was reduced in vitro and in vivo, significantly. Additionally, overexpression of miR-1297 suppressed colony-forming abilities and enhanced apoptosis in vitro. Conversely, inhibition of miR-1297 extended colony-forming abilities and suppresses apoptosis. All of the miR-1297 roles are due to targeting CDC6 (cell division control protein 6) oncogenes in GC cells [114]. CDC6 is a molecular factor which is essential for the initiation of DNA replication. Also, it has an important role in maintaining the mechanisms of the checkpoint in the cell cycle. CDC6 has been reported to be associated with oncogenic activity in human cancers. For instance, the elevation of CDC6 could increase cell proliferation, in ovarian cancer. CDC6 may be an appropriate therapeutic target for reducing chemo-resistance in BC [114,118]. In 2021 Wang et al. studied the roles of miR-1297 and circ_PGPEP1 in GC [131]. They found that knockdown of circ_PGPEP1 increased apoptosis and reduced proliferation, invasion, and migration of GC cells. Additionally, miR-1297 targeted E2F3 (E2F transcription factor 3) and thus suppressed its expression in normal cells. However, circ_PGPEP1 sponged miR-1297 and thereby increased E2F3 expression in GC cells [131]. The transcriptional regulatory family of E2F has an important effect on tumorigenesis biological behaviors, including cell cycle, apoptosis, and proliferation. Some studies have reported that E2F3 is increased in different types of cancer, especially in GC cells; it leads to increased cell proliferation and metastasis [108,119]. In 2020 Wu et al. investigated the mRNA polymorphisms (SNP) in human GC to identify novel biomarkers for the diagnosis and screening [120]. MiR-1297 rs9536676 polymorphism was found to be significantly associated with susceptibility to GC risk. Therefore, miR-1297 rs9536676 polymorphism can be used as a novel biomarker for GC [120].

Another GI cancer is ESCC which is the eighth most common cancer and the sixth leading cause of cancer death in the world. The incidence of ESCC depends on the age and gender of the individual. In 2016, it was reported that about 90% of its prevalence is in China and other countries in the East Asian region [88]. Despite advances in treatment and diagnosis in recent years, the response to treatment is still unsatisfactory and molecular studies are still needed to identify new biomarkers. In 2016 Wang et al. evaluate the diagnostic potential of serum miR-1297 in patients with ESCC and noticed that miR-1297 level was statistically lower than the normal group [88]. Therefore, serum miR-1297 can be used as an ideal biomarker for the diagnosis of ESCC [88].

Another GI cancer is oral OSCC which is the sixth most common malignancy globally and accounts for 90% of all oral cancers [121]. It is also known as one of the most common head and neck cancers which the incidence is increasing, especially in younger people [122]. Therefore, the diagnostic and therapeutic measures should urgently be adopted. In this regard, Liang et al. in 2018 studied the biological role of miR-1297 and PTEN in OSCC [121]. The results showed that miR-1297 expression was suppressed in OSCC tissues, and conversely, PTEN expression was up-regulated. It was also reported that overexpression of miR-1297 and PTEN knockdown reduces OSCC cell growth rate in vitro. There have been many studies on the effect of PTEN on tumorigenesis, and conflicting results have been reported, but this is the only article that investigates its effect on OSCC [77,100,101,121]. Furthermore, Gao et al. in 2019 studied the role of miR-1297 and lncRNA GAS5 (growth arrest-specific 5) on cell apoptosis in OSCC [122]. The results showed that miR-1297 expression level was elevated in the cancerous cells and following treatment with propofol (anesthetic drug), GAS5 was upregulated and through sponging miR-1297 increased GSK3β expression which identified as a direct target for miR-1297. Moreover, it was discovered that Mcl1, is an anti-apoptosis protein, and GSK3β could decrease Mcl1 protein in the cells. Therefore, propofol through GAS5/GSK3β axis induced anti-tumor effect in OSCC cells. Several studies have reported that GAS5 has tumor suppressor effects in different cancers [122,123]. In another study conducted by Li et al., the oncogenic role of GAS5 in CCA was confirmed. They determined that the expression level of GAS5 was up-regulated in CCA tissue compared to adjacent tissue which was associated with lymph node metastasis. Also, functional analyses revealed that GAS5 promoted invasion and cell proliferation through sponging miR-1297, in vitro [63]. In general, the majority of researches indicate that miR-1297 acts as a tumor suppressor in GI cancers. Accordingly, it might be employed as a potential diagnostic, prognostic and therapeutic tool for GI neoplasms.

10. MiR-1297 and other malignancies

Pancreatic cancer is a malignant, highly invasive, and metastatic tumor which is considered as the seventh leading cause of cancer-related mortality globally, with higher occurrence in developed countries. Lack of proper diagnosis, therapy, and cataloging strategies leads to variable mortality rates in these patients. Considering that the individuals are asymptomatic till the advanced stage of the illness, it remains one of the fatal malignancies that caused 466,003 deaths in 2020 (GLOBOCAN 2020 estimates) [69,124]. Thus, it is required to explore the exact molecular mechanisms of pancreatic cancer to develop novel diagnostic and reliable treatment strategies. In this regard, Chen et al. in 2018 reported downregulation of miR-1297 and upregulation of metadherin (MTDH) as a direct target of miR-1297 in pancreatic adenocarcinoma tissues and cells compared to paired adjacent normal tissues and control cell lines. Additionally, they proved that overexpression of miR-1297 or knockdown of MTDH causes suppression of cell apoptosis and decreases cell proliferation, migration, and metastasis. Therefore, it can be said that the miR-1297/MTDH pathway is an innovative diagnostic tool and possible therapeutic target for patients with pancreatic cancer [124].

Bones and joints tumors are responsible for 1660 deaths in the United States in 2019. OS is the most commonly diagnosed primary bone tumors which is usually reported in adolescents and children, and overall survival in OS patients has remained approximately steady for over two decades. However, remarkable progressions have been made in the diagnosis and therapy of OS [11]; thus, exploring the mechanism underlying OS development and investigating the useful therapeutic targets are of grave importance. Recent researches suggest that miR-1297 represents a tumor-suppressive function in OS. With this aspect, Pan et al. in 2020 assessed the diminished expression of miR-1297 in human OS tissue specimens associated with the advanced pathological staging and cell lines. They showed that lower expression of miR-1297 promotes cell proliferation correlated with Warburg effect. The remarkable increase in glucose uptake and the generation of lactate even in the presence of oxygen and entirely functional mitochondria in tumors or other cells under development is known as the Warburg effect. The process plays a central role in supporting proliferation, aggressiveness, and drug resistance of OS. The enzyme fructose-2, 6-bisphosphatase 2 (PFKFB2), as a bifunctional enzyme, regulates fructose 2, 6-bisphosphate (Fru-2,6-P2) and previous researches have demonstrated significant upregulation of PFKFB2 in numerous tumors that improves glycolysis and proliferation. Notably, they demonstrated that overexpression of miR-1297 suppressed aerobic glycolysis evidenced by reduced ECAR as an index of glycolytic rate and lactate production as well as enhanced mitochondrial respiration (OCR) and ATP production. Moreover, the upregulation of miR-1297 decreased cell proliferation and induced cell apoptosis via inhibiting PFKFB2 as a direct target gene. In contrast, overexpression of PFKFB2 diminished all the above mentioned anti-tumor effect of miR-1297. Collectively their study proposed that miR-1297 could be a possible tool for OS therapy [125].

MM is the most malignant and fatal skin tumor that stems from the unlimited proliferation of melanocytes-pigment-producing cells and is known to distant metastasis. The most frequent MM form is cutaneous; however, it can be found in other parts including mucosal surfaces, the uveal tract, and leptomeninges. Considering that MM's global incidence has increased quickly over the last 50 years, exploring precise mechanisms involved in regulation of gene expression during metastases is essential for improving efficient therapeutic strategies in metastatic MM. Firm evidence revealed that dysregulation of miRNAs executes a crucial function in the expansion and progression of MM. In this regard, Han

et al. in 2019 noticed that miR-1297 is upregulated in MM tissues and cells compared to those of control. They also found that the regulation was associated with the advanced tumor-node-metastasis (TNM) stage in patients with MM suggesting possible oncogenic roles of miR-1297. Moreover, they showed that anit-miR-1297 suppresses cell viability evidenced by the downregulation of Ki67 protein and can inhibit EMT progression in vitro through up-regulating PTEN as a tumor suppressor. EMT plays a vital role in embryonic development, chronic inflammation, tissue remodeling, cancer metastasis, and multiple fibrotic disorders. Reducing the expression of cell adhesion molecules such as E-cadherin, promoting N-cadherin expression, and improving the conversion of cytoskeletal proteins to Vimentin are the principal hallmarks of EMT. Interestingly, Han et al. documented that in MM cell lines treated with anti-miR-1297, E-cadherin's protein level was reduced. However, N-cadherin's protein level and Vimentin were increased by preventing miR-1297 with its target-PTEN. In conclusion, miR-1297 might be a new therapeutic target for MM, and anti-miR-1297 can be considered as a novel gene therapy molecule [11,126,127]. In line with these findings, Wang et al., in 2021, reported that anti-miRNA-1297 restrains cell invasion and migration of PC through upregulating PTEN and repressing the AKT/ERK signaling pathway [128].

11. Conclusions

In summary, the available studies indicate that miR-1297 is both upregulated and downregulated in different cancers. It also plays a dual role in various malignancies, as sometimes it is a tumor suppressor, and on other occasions, it is an oncogene. This huge controversy deserves further investigation in future studies. Particularly the current research is mainly limited to cell culture and clinical tissue samples. However, more clinically oriented studies using animal models are required to elucidate the precise role of miR-1297 in different cancers.

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CRediT authorship contribution statement

Shahin Alizadeh-Fanalou: Conceptualization, Writing - original draft preparation, Software, Validation, Visualization, Supervision, Project administration. **Mohsen Khosravi**: Writing - original draft preparation. **Fatemeh Alian**: Original Search, Find Full Text Articles and sorting. **Shirin Rokhsartalb-Azar**: Effective in article revision (software, new search). **Ali Nazarizadeh**: Edit English and grammar. **Maryam Karimi-Dehkordi:** Visualization, Supervision, Project administration. **Forogh Mohammadi:** Visualization, Supervision, Project administration, Writing - review & editing and revision.

Conflict of interest statement

The authors do declare that they have conflicts of interests.

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