

# Overview of microRNA-199a Regulation in Cancer

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**Abstract:** microRNAs (miRNAs) are a class of endogenous short, non-coding RNAs that regulate a multitude of genes at the post-transcriptional level. miR-199, which is a highly conserved miRNA family, consists of miR-199a and miR-199b. Researchers mainly focused on miR-199a over the past few years. Functional studies have demonstrated that mature miR-199a is a key player in the maintenance of normal homeostasis and in the regulation of disease pathogenesis. Here, we summarize the biological functions of miR-199a and review recent research on its roles in the physiological processes of cancer cells, such as proliferation, migration, invasion, apoptosis, autophagy and glycometabolism.

**Keywords:** microRNA-199a, target genes, carcinoma, biomarker, regulatory mechanisms

## Introduction

miRNAs are conserved evolutionary single long non-coding small RNAs about 22 nt long, which regulate the expression of target genes by binding to the mRNA untranslated region (UTR) sequence in complete or incomplete complementary base pairing mode, resulting in restraint of translation or mRNA degradation.<sup>1-4</sup> MicroRNAs are involved in multiple cellular pathways, notably in fundamental processes, such as development, differentiation, proliferation, survival, and death. Combined with some classical markers, miRNAs are important indicators in evaluating the function of tissues and organs as well as the progression and prognosis of various cancers, such as hepatocellular carcinoma (HCC).<sup>5</sup> Furthermore, recent studies have established that circulating miRNAs represent novel, predictable, and non-invasive biomarkers.<sup>6,7</sup> As a member of the most important miRNA families, miR-199 has been reported to be implicated in a variety of carcinomas as either repressors or promoters. Recent evidence showed that miR-199 could even be used as biomarkers for the diagnosis and prognosis of cancer patients.<sup>8,9</sup> This review focuses on biological functions of miR-199 and the mechanisms of miR-199 in cancer, such as the relationship with proliferation, apoptosis, autophagy and glucose metabolism. It also discusses challenges of miR-199 as biomarkers for diagnosis and prognosis or as therapeutic targets.

## Overview of miR-199

Current studies have found two members of the miR-199 family: miR-199a and miR-199b.<sup>10</sup> In 2003, Lagos-Quintana et al<sup>11</sup> cloned miR-199-s (from half of 5') and miR-199-as (from half of 3') from human osteoblast sarcoma cells and mouse skin tissues. Pre-miRNAs have two types in hsa-miR-199a: pre-miR-199a-1 (MI000242) and pre-miR-199a-2 (MI0000281), which are derived from chromosome 19 and chromosome 1, respectively, and are later renamed as miR-199a-5p

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(MIMAT0000231) and miR-199a-3p (MIMAT0000232).<sup>12</sup> There are also two mature forms of hsa-miR-199b (derived from chromosome 9): miR-199b-5p (MIMAT0000263) and miR-199b-3p (MIMAT0004563) (miRBase, <http://www.miRbase.org>). At present, researchers mainly focus on the biological function of miR-199a. A large number of studies have indicated that the two mature types of miR-199a regulate the activities of normal cells to participate in corresponding physiological or pathological processes [Table 1](#). For example, miR-199a-5p is highly expressed in the breast, colon, and testis; relatively low in the thymus, liver, and kidney; and extremely low in the brain.<sup>13</sup> miR-199a-5p is a negative regulator of proliferation of endometrial mesenchymal stem cells.<sup>14</sup> In the striated muscle, overexpression of miR-199a-5p promotes myoblasts but not myotube proliferation, blunted the abnormal muscle fiber myogenic differentiation.<sup>15</sup> However, in the lung, the high expression of miR-199a-5p promotes the formation of pulmonary fibrosis through the activation of the TGF- $\beta$  signaling pathway by Caveolin-1.<sup>16</sup> In cardiomyocytes, the functions of miR-199a mainly include: regulating cell size and proliferation. In regulating cell size, miR-199a-5p causes pathological hypertrophy of rat cardiomyocytes by down-regulating hypoxia-inducible factor 1 (HIF-1 $\alpha$ ) and sirtuin1.<sup>17</sup> However, endogenous silencing of miR-199a-5p causes hypertrophy through peroxisome proliferator-activated receptor  $\gamma$  co-activator 1  $\alpha$  (PGC1 $\alpha$ ), but cardiac morphology and function are not affected.<sup>18</sup> In terms of affecting cell proliferation, An et al found that after decellularization of the right atrium of mice, miR-199a-3p promotes the proliferation of neonatal cardiomyocytes and sinus nodal cells by inhibiting homeodomain-only protein (HOPX) and increasing GATA-binding

4 (Gata4) acetylation. After recellularization, miR-199a-3p mediates the enrichment of cardiomyocytes and sinus nodal cell population, restores the electrical activity as shown by normalization of electrocardiograph (ECG), and significantly improves myocardial function.<sup>19</sup>

## Mechanism of miR-199a in Cancer miR-199a and Cell Proliferation, Migration and Invasion

Growing evidence shows that the aberrant expression of miR-199a is tightly related to tumorigenesis and progression [Table 2](#). miR-199a serves different functions in different cancer cells. For example, samples were obtained from 52 patients with gastric cancer tissue; results showed that miR-199a-3p expression is upregulated in 36 (69.2%) patients. miR-199a-3p is also highly expressed in human gastric cancer cell lines AGS, MKN-45, MKN-28, SGC-7901, NCI-N87, and BGC-823. Further study showed that miR-199a-3p inhibits the expression of zinc fingers and homeoboxes 1 (ZHX1) by binding its 3'UTR, and promotes the growth and proliferation of cancer cells.<sup>20</sup> Recent studies have proved that klotho is a tumor suppressor which is negatively associated with lymph node metastasis and epithelial-mesenchymal transition.<sup>21,22</sup> He et al<sup>23</sup> found that miR-199a-5p, another form of miR-199a, is highly expressed in gastric cancer tissues, and promotes their migration and invasion by targeting klotho, indicating that klotho may be involved in tumorigenesis as an anti-tumor molecule. In situ hybridization further confirmed that high expression of miR-199a-5p may be closely associated with the lymph node metastasis of gastric cancer. Zhang et al identified 39 miRNAs that can target Smad4 from 388 miRNAs and found that miR-199a-5p is

**Table 1** miR-199a Biological Function

Normal Tissues	miRNA	Expression	Targets	Effect of miRNA	Ref.
Uterus	miR-199a-5p	Downregulated	VEGFA	Inhibits the proliferation, movement, and angiogenesis of ectopic endometrial mesenchymal stem cells and alleviates the endometriosis	14
Striated muscle	miR-199a-5p	Downregulated	–	Promotes myoblasts proliferation and inhibit myogenic differentiation	15
Lung	miR-199a-5p	Upregulated	Caveolin-1	Promotes lung fibroblast proliferation, and differentiation	16
Cardiomyocytes	miR-199a-5p	Upregulated	HIF-1 $\alpha$ , Sirtuin1, PGC1 $\alpha$ /HOPX, Gata4	Regulates cell size/proliferation	17–19

**Table 2** miR-199a and Proliferation, Migration and Invasion of Cancer Cell

Cancer Types	miRNA	Expression	Targets	Effect of miRNA	Ref.
Colorectal cancer	miR-199a-5p	Downregulated	HIF-1 $\alpha$ /VEGF/DDR1	Inhibits the cell proliferation, migration and invasion	31,32
Lung cancer	miR-199a-5p	Downregulated	HIF1 $\alpha$	Inhibits the cell proliferation	33
Gastric cancer	miR-199a-3p	Upregulated	ZHX1	Promotes the cell proliferation	20
	miR-199a-5p	Upregulated	Klotho/Smad4	Promotes migration and invasion/Inhibits cell growth	23,24
ADPKD	miR-199a-5p	Upregulated	CDKN1C/p57	Promotes the proliferation of cyst cells	25
Early/Advanced cervical cancer	miR-199a-5p	Upregulated/ Downregulated	–	Promotes malignant transformation and lymph node metastasis	27,28
Melanoma	miR-199a-5p/3p	Upregulated	ApoE/DNAJA4	Promotes melanoma metastasis and angiogenesis	30
Esophageal cancer	miR-199a-5p	Downregulated	MAP3K11	Inhibits the proliferation	34
Breast cancer	miR-199a-3p/5p	Downregulated	Ets-1	Inhibits cell proliferation and cycle progression/ Reduces the risk of breast cancer	35–37
Cutaneous squamous cell carcinoma	miR-199a-5p	Downregulated	BCAM/FZD6/DDR1	Inhibits the migration of keratinocytes	40
Bladder cancer	miR-199a-5p/3p	Downregulated	Integrin 3	Inhibits cell migration and invasion, and is a potential prognostic marker in bladder cancer	38
HCC	miR-199a-5p	Downregulated	RGS17/FZD7	Inhibits the cell proliferation	43,44
	miR-199a-3p	Downregulated	mTOR, c-Met/PAK4	Reduces invasive capability, enhanced susceptibility to hypoxia or doxorubicin/inhibit the cell growth	41,42

upregulated in 67% of gastric cancer tissues (10/15), negatively regulates SMAD family member 4 (Smad4), and inhibits transforming growth factor beta (TGF- $\beta$ ) induced gastric cancer cell growth arrest in vitro; thus, miR-199a-5p plays a carcinogenic role in human gastric tumorigenesis and predicts potential therapeutic targets for future gastric cancer patients.<sup>24</sup> In autosomal dominant polycystic kidney disease (ADPKD), miR-199a-5p is upregulated, which promotes the proliferation of cyst cells by inhibiting the expression of cyclin-dependent kinase inhibitor 1C (CDKN1C)/p57 gene and plays a key role in the proliferation of cyst epithelial cells.<sup>25</sup> Moreover, high expression levels of miR-199a-3p and miR-199a-5p in esophageal adenocarcinoma are associated with poor prognosis in patients.<sup>26</sup> In cervical cancer, Lee et al<sup>27</sup> found that miR-199a-5p is significantly overexpressed in early squamous cell carcinomas of the cervix (SCCC), and then transfection of anti-miR-199a-5p oligonucleotides into cervical cancer cell lines in vitro (Siha and ME180) inhibits cell growth. Thus, miR-199a-5p is presumed to promote the

growth of cervical cancer cell lines. For advanced SCCC, however, Huang et al<sup>28</sup> found that the significant downregulation of miR-199a-5p is significantly associated with lymph node metastasis and decreases prognosis survival in patients with SCCC. It is suggested that miR-199a-5p may be an important indicator for the prognosis and diagnosis of patients with SCCC. Interestingly, both miR-199a-3p and miR-199a-5p significantly differentiate between high metastatic and low metastatic groups of patients with uveal melanoma, with the former having higher expression.<sup>29</sup> Pencheva et al further observed that miR-1908 and miR-199a-3/5p cannot promote tumor cell proliferation but can regulate melanoma metastatic invasion, angiogenesis, and endothelial cell recruitment by targeting Apolipoprotein E (ApoE) and the heat-shock factor DnaJ heat shock protein family (Hsp40) member A4 (DNAJA4).<sup>30</sup>

miR-199a also plays a negative regulatory role in the proliferation, migration and invasion of cancer cells Table 2. HIF-1 $\alpha$  is regulated by phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) pathways. Ye et al<sup>31</sup> found that miR-

199a-5p can inhibit the proliferation, migration and invasion of colorectal cancer cells via the HIF-1 $\alpha$ /vascular endothelial growth factor (VEGF) pathway. Another study identified that overexpression of miR-199a-5p results in the downregulation of discoidin domain receptor family, member 1 (DDR1), matrix metalloproteinase-2 (MMP2), N-cadherin and vimentin and up-regulation of E-cadherin, thereby reducing the colony formation, invasive and migratory capabilities of colorectal cancer cell lines LOVE1 and LOVO cells.<sup>32</sup> miR-199a-5p also suppresses angiogenesis in hypoxic-treated non-small cell lung cancer cells by HIF1 $\alpha$  approach.<sup>33</sup> When overexpressed, miR-199a-5p can bind to mitogen-activated protein kinase kinase kinase 11 (MAP3K11), which results in the downregulation of MAP3K11, blunted G2/M arrest, and proliferation of esophageal cancer cells.<sup>34</sup> In breast cancer cells, miR-199a/b-3p is significantly decreased in highly metastatic breast cancer cells such as MDA-MB-231, CAL120, and HCC1395 compared with MCF-7, a weak metastatic breast cancer cell line. Further experiments confirmed that miR-199a/b-3p inhibits MDA-MB-231 cell proliferation and cell cycle progression by regulating the PAK4/MEK/ERK pathway.<sup>35</sup> Studies have shown that miR-199a-5p can downregulate the level of  $\beta$ -integrin by targeting the 3'-UTR of Ets-1 through the FAK/Src/Akt/mTOR signaling to alleviate breast cancer invasion.<sup>36</sup> Li et al also confirmed that miR-199a-5p inhibits the migration and invasion of MCF-7 and MDA-MB-231 by binding to Ets-1 in vitro.<sup>37</sup> Sakaguchi et al found that the expression levels of miR-199 family members (miR-199a-3p/-5p and miR-199b-3p/-5p) are downregulated in bladder cancer by targeting Integrin 3, and the survival rate of patients is significantly improved after the restoration of miR-199 expression.<sup>38</sup> Ecker et al further proposed that miR-199a-3p is an important indicator in evaluating the prognosis of patients with muscle-invasive bladder cancer after radical cystectomy.<sup>39</sup> The latest research shown that endogenous

miR-199a-5p targeted basal cell adhesion molecule (BCAM), frizzled class receptor 6 (FZD6) and DDR1, significantly inhibited the migration of skin keratinocyte instead of proliferation, indicating that miR-199a-5p also plays an important role in cutaneous squamous cell carcinoma.<sup>40</sup> It is basically a consensus that miR-199a presents downregulated tendency, and elevating levels of miR-199a may have therapeutic benefits and increase sensitivity to chemotherapy drugs in HCC.<sup>41</sup> For example, miR-199a-3p can suppress HCC growth by targeting tumor-promoting the mammalian target of rapamycin (mTOR), tyrosine-protein kinase Met (c-met)<sup>42</sup> and p21 (RAC1) activated kinase 4 (PAK4);<sup>41</sup> Zhang<sup>43</sup> and Song<sup>44</sup> team also found that the overexpression of miR-199a-5p significantly suppresses the proliferation and survival of HCC cell by binding to the 3'-UTR of Regulators of G-protein signaling (RGS17) and frizzled type 7 receptor (FZD7), respectively. These studies suggest that two mature forms of miR-199a have different target genes in various tumors and exert different regulatory functions. miR-199 expression is an important cause of the proliferation, migration, or invasion of various tumor cells, but the regulatory effects of miR-199a are diverse and cannot be generalized. In addition, the role of SCCC is still controversial and needs further exploration. A variety of indicators, such as tolerance, different forms of miR-199a, duration of action, tissue cell specificity, drug resistance, and experimental standardization, must be considered before reaching a conclusion.

## miR-199a and Apoptosis

The relationship between miR-199a and apoptosis is well documented; past studies showed that miR-199a can induce apoptosis either by up-regulating the level of pro-apoptotic protein or decreasing the expression of anti-apoptotic protein in most situations Table 3. Kim et al found that miR-199a-3p causes more pronounced apoptosis than miR-199a-5p in

**Table 3** miR-199a and Apoptosis

Varieties	miRNA	Expression	Targets	Effect of miRNA	Ref.
DLBCL	miR-199a	Upregulated	–	No significant	45
A549	miR-199a-5p/3p	-	MET	Promote apoptosis	13
Bladder cancer	miR-199a-5p	Downregulated	MLK3	Promote apoptosis	46
Ovarian cancer	miR-199a-5p	-	mTOR	Promote apoptosis	47
HCC	miR-199a-5p	Downregulated	FZD7	Promote apoptosis	48
Cardiomyocyte	miR-199a-5p	Upregulated	HIF-1 $\alpha$	Inhibit apoptosis	49
Colorectal cancer	miR-199a-3p	Upregulated	–	Inhibit apoptosis	50
SzS	miR-199a-3p	Upregulated	EVL	Inhibit apoptosis	51
UUO	miR-199a-3p	Upregulated	SOCS7	Inhibit apoptosis	52

cancer cells, such as A549, PC3, KB, and MCF7. In A549 cells, the apoptosis pathway induced by miR-199a-5p is caspase-dependent, whereas that induced by miR-199a-3p is caspase-independent. After transfection with miR-199a-5p/3p mimetics, MET proto-oncogene and its downstream effector mitogen-activated protein kinase 1 (ERK2) are downregulated.<sup>13</sup> Another study identified that the expression of seven miRNAs, including miR-199a, is upregulated in Diffuse Large B-cell Lymphoma (DLBCL). However, high expression of miR-199a is associated with higher overall survival ( $p = 0.007$ ); moreover, miR-199a significantly enhances the killing effect of rituximab, vincristine, and doxorubicin chemotherapy on cancer cells in a dose-dependent manner. Interestingly, overexpression of the miR-199a does not result in any difference of cell growth or apoptosis in four lymphoma cell lines.<sup>45</sup> Song et al,<sup>46</sup> reported that miR-199a-5p induces apoptosis by inhibiting the Mixed Lineage Kinase 3 (MLK3)/NF- $\kappa$ B pathway in bladder urothelial carcinoma. Similarly, miR-199a-5p increases the sensitivity of ovarian cancer OV2008 cells to cisplatin and promotes apoptosis by inhibiting the expression of mTOR.<sup>47</sup> In addition, Shi et al<sup>48</sup> demonstrated that a long non-coding RNA, microvascular invasion in hepatocellular carcinoma (MVIH), is generally overexpressed in HCC, si-MVIH treatment inhibited cell viability and promoted apoptosis of HCC, but this effect was reversed by miR-199a inhibitor. This indicates that miR-199a promotes tumor cell apoptosis.

However, in some cases, miR-199a involves in the anti-apoptosis effect. Research has also shown that miR-199a-5p is down-regulated and apoptosis is increased on a decline in oxygen tension of cardiac myocytes. Dual-luciferase reporting system assay revealed that HIF-1 $\alpha$  is a targeted gene of miR-199a-5p. The results also showed that silent information regulator1 (Sirt1) is a direct target of miR-199a-5p and is responsible for downregulating prolyl hydroxylase 2, which is required for the stabilization of HIF-1 $\alpha$ . This result indicates that miR-199a can inhibit cardiac myocytes apoptosis under hypoxic conditions.<sup>49</sup> Wan et al<sup>50</sup> found that the transfection of SW480 cells with miR-199a-3p inhibitor causes

G0/G1 arrest, decreases the percentage of cells in the S and G2/M phases, and induces cell apoptosis. In patients with Sezary Syndrome (SzS, T-cell lymphoma), upregulation of miR-199a-3p inhibits the expression of Enah/VASP-like (EVL), which in turn mediates its anti-apoptotic effect by up-regulating TNF superfamily member 11(TNFSF11).<sup>51</sup> A recent study has also indirectly illustrated the inhibitory effect of miR-199a-3p on apoptosis. Yang et al demonstrated that kidney biopsies with IgA nephropathy and diabetic nephropathy exhibit substantial activation of p53 and increase in miR-199a-3p. Interestingly, p53 knockout attenuates renal fibrosis, apoptosis, and inflammation, accompanied by the suppression of miR-215-5p, miR-199a-5p/3p, and signal transducer and activator of transcription 3 (STAT3) in unilateral urethral obstruction (UOU) mice model. Furthermore, overexpression of miR-199a-3p suppresses suppressor of cytokine signaling 7 (SOCS7) for STAT3 activation and renal fibrosis. These results demonstrate the novel p53/miR-199a-3p/SOCS7/STAT3 pathway is involved in renal interstitial fibrosis.<sup>52</sup>

## miR-199a and Autophagy

Autophagy is a catabolic process initiated by the accumulation of damaged organelles or protein aggregates under cellular stress conditions.<sup>53</sup> Since the first report revealing the link between miR-30a and autophagy in 2009,<sup>54</sup> more and more miRNAs have been found to play an important role in autophagy. For example, miR-26a/b can regulate the formation of Atg1/unc-51 like autophagy activating kinase (ULK1) complex to inhibit autophagy and promote the apoptosis of HCC cells.<sup>55</sup> miR-155 and miR-7 negatively regulate PI3K/AKT signaling pathway to induce autophagy.<sup>56</sup> At present, some literatures have reported about the relationship between miR-199a and autophagy [Table 4](#). Overexpression of miR-199a-5p can impair autophagy and activate the mTOR/GSK3 $\beta$  signaling pathway; inhibit the activity of proteins, such as Atg5, Atg12, BECN1, and LC3B; and induce cardiac hypertrophy in mice.<sup>57</sup> Yi et al<sup>58</sup> also observed that miR-199a-5p exerts bidirectional regulation in breast cancer MCF7 and MDA-MB-231 cells. In specific, miR-199a-5p

**Table 4** miR-199a and Autophagy

Varieties	miRNA	Expression	Targets	Effect of miRNA	Ref.
Cardiomyocyte	miR-199a-5p	Upregulated	mTOR	Inhibit autophagy	57
Breast cancer (MCF7/MDA-MB-231)	miR-199a-5p	-	DRAM1/BECN1	Inhibit/Activate autophagy	58
Ovarian cancer	miR-199a-5p	-	mTOR	Inhibit autophagy	62
HCC	miR-199a-5p	Downregulated	Atg7	Activate autophagy	65

mimic treatment significantly suppresses radiation-induced autophagy in MCF7 cells, and enhances radiation-induced autophagy in MDA-MB-231 cells. However, the target genes are the same in both cells: DNA damage regulated autophagy modulator 1 (DRAM1) and BECN1. BECN1 can bind to cofactors, such as Atg14L, UVRAG, Bif-1, Rubicon, Ambra1, HMGB1, nPIST, VMP1, SLAM, IP3R, PINK, and survivin, to regulate lipid kinase Vps-34 activity and promote the formation of the Beclin 1-Vps34-Vps15 complex; BECN1 can also form a complex with Bcl-2 through the BH3 domain to participate in the regulation of autophagy.<sup>59</sup> The differences in the regulation of autophagy by miR-199a-5p between the two types of breast cancer cells may be due to the different regulation effects of miR-199a-5p on the cell cycle. Treatment of MDA-MB-231 cells with miR-199a-5p mimic increases the ratio of G2/M phase cells, but does not significantly affect the cell cycle of MCF7. This result may be due to the different cytogenetic background because MDA-MB-231 is a highly aggressive and estrogen receptor-negative breast cancer cell line, whereas MCF7 is a non-invasive and estrogen receptor-positive breast cancer cell line. These studies suggest that miR-199a-5p exerts cell-specific effects on DRAM1 and Beclin1.

Activation of autophagy may be a necessary homeostasis process to remove damaged organelles and recover macromolecules to prevent cancer.<sup>60,61</sup> Interestingly, it was observed that the expression levels of miR-199a-5p are higher in OV2008 cells (cisplatin-sensitive) compared with C13\* cell (cisplatin-resistant), the reason was that miR-199a-5p increases the sensitivity of OV2008 cells to cisplatin by inhibiting mTOR, which is a negative regulator of autophagy.<sup>62</sup> Similarly, Fornari et al<sup>42</sup> confirmed that miR-199a-3p reduces invasive capability and enhances sensitivity to doxorubicin-induced apoptosis by targeting mTOR and c-Met in HCC cells. However, some researchers have shown that autophagy is also involved in the regulation of chemoresistance by attenuating the autophagy activity of cancer cells. Yoon et al<sup>63</sup> found that autophagy contributes to the sustained survival of breast cancer cells through DNA repair by the ATM-mediated activation of DNA-PKcs and PARP-1. In leukemia cells, endogenous high mobility group box-1 (HMGB1) activates autophagy and enhances the chemoresistance of leukemia cells through the PI3K/Akt/mTORC1/autophagy pathway.<sup>64</sup> The study found that miR-199a-5p expression is down-regulated in cisplatin-treated HCC patients. The possible reason is the reduction of miR-199a-5p enhances cell autophagy and promotes cell proliferation

by targeting Atg7/p62, thus increasing the development of drug resistance.<sup>65</sup> Overall, these findings provide evidence for the new role of miR-199a-5p in autophagy. Thus, this study may be used as a basis in understanding the autophagy networks regulated by miRNA and improving the strategies of cancer treatment.

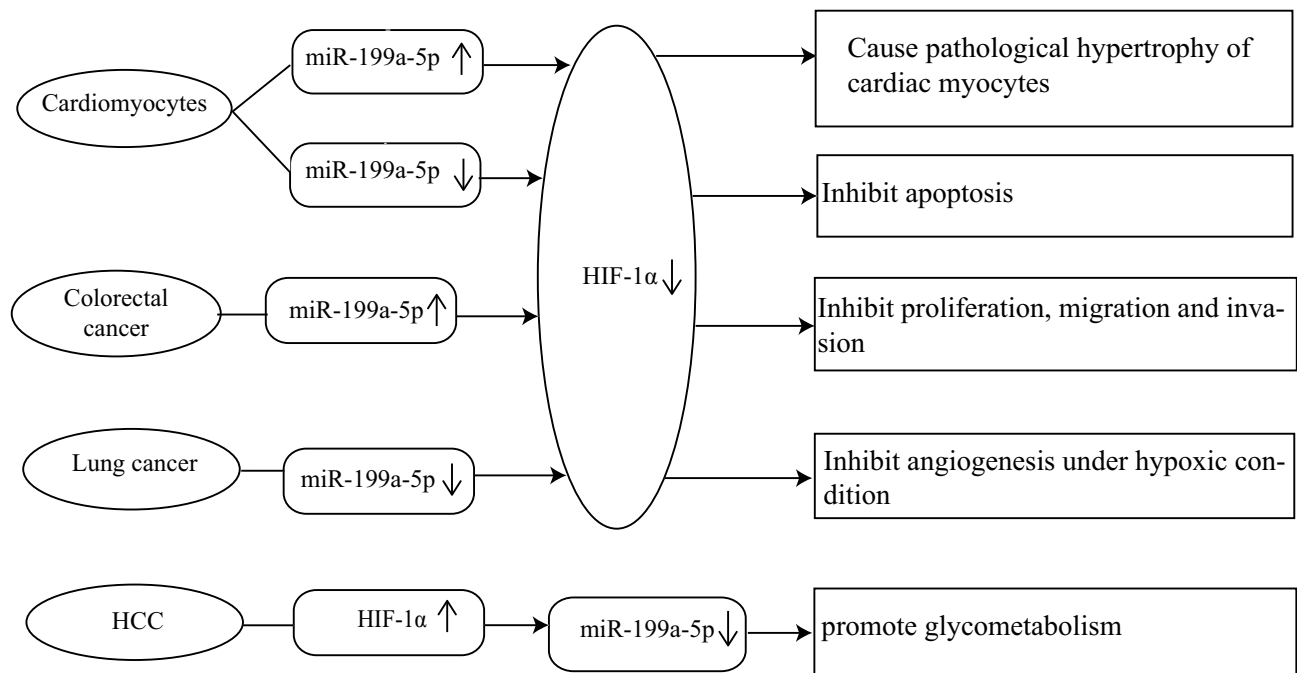
## miR-199a and Glucose Metabolism

Lactate overproduction is usually associated with poor prognosis. With the analysis of Genome Atlas and GSE10694 data, Guo et al<sup>66</sup> found that the expression of six types of glycometabolism-regulating miRNAs (miR-29c-3p, miR-126-3p, miR-148a-3p, miR-188-5p, miR-191-5p, and miR-199a-5p) is dysregulated in HCC. Moreover, only miR-199a-5p significantly inhibits lactate production in Huh-7, HepG2 and Hep3B cells by targeting hexokinase 2 (HK2). However, miR-199a-3p exerts no effect on lactate production in HCC cells. Conversely, up-regulation of HIF-1 $\alpha$  under hypoxia can inhibit the expression of miR-199a-5p and promote the glycolysis of HCC cells.<sup>66</sup> This study largely expanded our knowledge to further understand the role of miR-199a in the pathogenesis of cancer.

## Problems and Prospects

The last ten years have brought a surfeit of new knowledge about how miRNAs are associated with disease states. Thus, we now understand better the links between the miR-199a and cancer. We also found that HIF-1 $\alpha$  is an important factor affecting the regulation of miR-199a-5p in cancer [Figure 1](#). This finding may be a breakthrough that can elucidate the mechanism of miR-199a in cancer, and future work is still needed.

Although considerable studies involving miR-199a have been conducted over the years, much research is still needed for the diagnosis and treatment of cancer and other diseases. One of the challenges is to identify the targets of miR-199a for each cancer type. At present, most studies only focused on the basic stage of miR-199a binding to target genes and their regulation. However, the studies in vivo are deficient, and the related signaling pathways and molecular mechanisms still need to be illustrated. In addition, miRNA has different UTR region binding sites for the target gene mRNA. Although miRNA mainly binds to the 3'-UTR of the target gene to inhibit its transcription level, it can also bind to the 5'-UTR of the target genes. This phenomenon may cause differences in miRNA-regulated target genes and affect their biological functions. With the increasing reports on the 5'-UTR binding of miRNAs target genes, relative bio-predictive tools have been



**Figure 1** The relationship between HIF-1 $\alpha$  and miR-199a-5p.

developed successively.<sup>67,68</sup> These tools are very helpful in exploring the mechanism of miR-199a in different contexts. Recently, great enthusiasm has evolved for extracellular vesicles, which are nanoscale membrane vesicles secreted by almost all cells, and can convey nucleic acids, proteins etc. from one cell/tissue to another.<sup>69,70</sup> It has been demonstrated that differential expression of extracellular vesicles-derived miRNAs made them promising targets for detection and therapeutics to some diseases especially cancers.<sup>71</sup> The latest study reported serum and extracellular vesicles miRNAs as biomarkers for pathology in acute graft-versus-host disease (aGvHD). Results showed that the miR-423, miR-199, and miR-93 levels of serum extracellular vesicles are lower at D14 in post hematopoietic stem cell transplantation patients who later developed aGvHD; conversely, these miRNAs show higher expression in D14 patients remaining aGvHD-free in the extracellular vesicles fraction.<sup>72</sup> This study has largely expanded our horizons to further understand the pathogenesis of diseases and implies that miR-199a derived from extracellular vesicles is an important indicator in cancers. Future works using molecular biology techniques will be helpful to elucidate the mechanism of miR-199a in cancers and explore the potential targets of miR-199a for diagnosing and treating cancers.

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## Disclosure

The authors report no conflicts of interest in this work.

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