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Review

miR-149 in Human Cancer: A Systemic Review

Yunjie He[1*], Dandan Yu[2*], Lingping Zhu[1*], Shanliang Zhong[2], Jianhua Zhao[2], Jinhai Tang[1, 3]✉

1. The First Clinical School of Nanjing Medical University, Nanjing 210029, P.R. China;
2. Center of Clinical Laboratory, Nanjing Medical University Affiliated Cancer Hospital Cancer Institute of Jiangsu Province, Baiziting 42, Nanjing 210009, P.R. China;
3. Department of General Surgery, the First Affiliated Hospital with Nanjing Medical University, Nanjing 210029, P.R. China.

* Equal contributors

✉ Corresponding author: Jinhai Tang, MD, PHD. Department of General Surgery, the First Affiliated Hospital with Nanjing Medical University, Nanjing 210029, P.R. China. E-mail address: tangjh@njmu.edu.cn

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Abstract

MicroRNAs (miRNAs) are small noncoding RNAs that regulate post-transcriptional gene expression via binding to the 3'-untranslated region (3'-UTR) of targeted mRNAs. They are reported to play important roles in tumorigenesis and progression of various cancers. Among them, miR-149 was confirmed to be aberrantly regulated in various tumors. In this review, we provide a complex overview of miR-149, particularly summarize the critical roles of it in cancers and expect to lay the foundation for future works on this important microRNA.

Key words: miRNA, miR-149, cancer.

Introduction

MicroRNAs (miRNAs), a class of highly conserved noncoding RNA (ncRNA) molecules of approximately 22-nucleotide long, are post-transcriptional regulators that bind specifically to the 3′-untranslated region (3′-UTR) of targeted mRNAs, resulting in translational inhibition.[1] In the last decade, miRNAs have emerged in many aspects of tumorigenesis, tumor development, metastasis, and drug resistance.[2] Among them, miR-149, which can serve as an oncogene (oncomiR) and tumor suppressor, was found to be significantly dysregulated in various cancers, such as head and neck, lung, gastric, breast, prostate cancers and renal cell carcinoma (RCC) (Table 1, 2). In this review, to understand the overview of miR-149 better, we focused on enumerating and summarizing the specific functions and mechanisms of miR-149 in a wide range of cancers.

Structure and chromosomal localization of miR-149

Human miR-149 (hsa-mir-149; MIR149) is located at 2q37.3, encoded by only 1 exon and found to have polymorphisms. The predicted stem-loop structure of miR-149 determined using the RNA structure software is shown in (Figure 1A). The miR-149 hairpin gives rise to the "guide strand" miR-149-5p and the sister "passenger" strand miR-149-3p as shown in (Figure 1B). miR-149-5p is far more prevalent than miR-149-3p according to reads of deep sequencing. And the sequences of miR-149-5p and miR-149-3p are totally dissimilar, indicating inconsistent roles of them involved in human biological behavior.

Technical aspect of miR-149 extraction, detection and confirmation

The researchers initially examined 9 different mouse tissues using tissue-specific cloning and identified 34 novel miRNAs including miR-149, which found expressed higher in mouse heart by northern-blot.[3] Then human miR-149 were identified through combined bioinformatics and sequence-directed cloning methods.[4] Over 250 small RNA libraries were sequenced from 26 different organ systems and cell types of human and rodents.

Detailed and accurate information about mature sequences, precursors, genome location and conservation patterns of miR-149 were provided by this broad research. Moreover, Stephen S.C Chim *et al.* first detected miR-149 in human blood and confirmed that miR-149 was abundant in maternal plasma during pregnancy.[5]

Table 1. Targeted genes and dysregulation of miR-149-5p in various cancers.

Hsa-miR-149-5p	Cancers	Targeted gene
Upregulated		
	Acute myeloid leukemia	FASLG
	Prostate cancer	SOX2, NANOG, Oct4
	Glioblastoma multiforme	Caspase-2
	Metastatic sporadic melanoma	
Downregulated		
	Gastric cancer	ZETB2
	Hepatocellular carcinoma	AKT1, PARP-2
	Glioblastoma multiforme	AKT1, Rap1b
	Renal cell carcinoma	PPM1F
	Lung cancer	FOXM1
	Colorectal cancer	FOXM1, SP1, SRPX2, GPC1, EphB3
	Breast cancer	Rap1a, Rap1b, GIT1, NDST1, ErbB3
	Gastric cancer	IL-6
	Thyroid carcinoma	FOSL1
	Neuroblastoma	Rap1
	Endometrial cancer	
	Laryngeal squamous cell carcinoma	
	Cervical carcinogenesis	
	Astrocytomas	

Table 2. Targeted genes and dysregulation of miR-149-5p in various cancers.

Hsa-miR-149-3p	Cancers	Targeted gene
Upregulated		
	Melanoma	GSK3α
	T-cell acute lymphoblastic leukemia	JunB
	Glioma	
	Liver cancer	
Downregulated		
	Neuroblastoma	AKT1, E2F1
	Gastric cancer	Wnt-1
	Pancreatic cancer	AKT1

The potential interactions of miR-149 with other molecules

The targeted genes and pathways potentially affected by miR-149-5p and miR-149-3p identified using the Diana-MicroT and TagetScan tools are shown in (Figure 1C, D). Undoubtedly, the gene and pathway signatures of miR-149-5p and miR-149-3p are totally different. B4GAL T1, ST3GAL2, B3GNT7, CHST2, B4GAL T2, SLC18A1, MAG, SYK, VEGFA, PIK3R6, AKT1, RHOC, TNS1 and so on were found as the targeted genes of miR-149-5p. AP1B1, GNPTAB, MFSD8, CTNS, CLN5, TPP1, CD68, IL-6, CCR9, CCR4, PDGFC, NCKAP1L and so forth were predicted as the targeted genes of miR-149-3p.

The potential mechanisms of miR-149's functions

The two isoforms of miR-149 are both predicted to target oncogene and tumor suppressor, leading to dual impacts among cancers. miR-149-5p participates mostly in ERBB-pathway, insulin signaling pathway, MAPK signaling pathway and chemokine signaling pathway, which are necessary for tumor growth, while miR-149-3p plays roles in toll-like receptor signaling pathway, T and B cell receptor signaling pathway, focal adhesion-pathway, vascular smooth muscle contraction-pathway and lysosome-pathway which also related closely to tumorigenesis and tumor progression. In the following sections, we will focus on discussing central roles of miR-149 related to biological functions of tumor, which were confirmed in various experiments and clinical samples.

miR-149 in cancer proliferation and apoptosis

Accelerated proliferation and decreased apoptosis of cancer cells contribute to the progress of tumor development. Tian P et al. described that miR-149-5p suppressed the apoptosis of the acute myeloid leukemia cell line THP-1 by targeting Fas ligand (FASLG), which in turn negatively affected the phosphorylated form of Fas-associated via death domain (p-FADD) and activation of caspases-2, 3, and 8.[6] Tomomi Fujii et al demonstrated that decreased miR-149-5p expression level was related to syndecan-1 (CD138, SDC-1), one of the four mammalian heparin sulfate proteoglycans silenced in prostate cancer.[7] The increased expression of syndecan-1 contributes to cell survival via regulating NOX-mediated reactive oxygen species (ROS) generation in androgen-independent prostate cancer cells.[8] The mRNA levels of the stem cell-related factors, SOX2, NANOG, and Oct4, increased significantly with decrease in miR-149-5p expression. Cell proliferation assay also showed that miR-149-5p promoted cell proliferation by suppressing these factors via p21 reduction. However, in human gastric cancer (GC), miR-149-5p inhibits proliferation and cell cycle progression via targeting ZBTB2, a repressor of the ARF-MDM2-p53-p21 pathway.[9, 10] ZBTB2 has been identified to either repress the transcription of tumor suppressors ARF, p53, and p21, or induce the expression of MDM2 proto-oncogene. Yanqiong Zhang et al investigated the tumor suppressive role of miR-149-5p via targeting AKT1 in human hepatocellular carcinoma (HCC).[11] In addition, they

identified AKT1 as an unfavorable factor in patients with HCC. miR-149-5p was found to regulate AKT1 expression by integrating bioinformatics and network analysis. The increased expression of miR-149-5p significantly inhibited HCC cell proliferation by regulating AKT1/mTOR pathway. And miR-149-5p inhibited human thyroid carcinoma WRO cells proliferation by targeting FOSL1 according to the study of Hiroki Takeshita et al.[12] In human glioblastoma multiforme (GBM), miR-149-5p was also proved to act as a suppressor of AKT1 expression and inhibit the proliferative activities of U251 cell line, which has a mutation in codon 273 of the p53 gene.[13] Interestingly, Xiaokun Shen et al showed that the stable overexpression of miR-149-5p leads to the promotion of cell viability of U87MG, a wild-type p53 cell line, inhibition of apoptosis, and induction of tumor xenograft growth *in vivo*.[14] miR-149-5p targets caspase-2 via inactivation of the p53 and p21 pathways. In addition, miR-149-5p may exert opposite biological effects in p53 wild-type and p53 mutants; however, the specific underlying mechanisms remain to be investigated. Furthermore, on the basis of the study of Xu Y et al, miR-149-5p was markedly deregulated in neuroblastoma cell lines and primary tumor tissues associated with poor clinical outcome. *In vitro*, it was found that miR-149-5p downregulation promoted proliferation of neuroblastoma cells via targeting the small GTPases: Rap1.[15]

Similar to miR-149-5p, miR-149-3p plays dual roles in cancer. Unlike other cancers, in human melanoma, wild-type p53 is often expressed at high levels.[16] Lei Jin et al detected upregulated miR-149-3p expression in melanoma cell lines in response to endoplasmic reticulum (ER) stress.[17] Next, they demonstrated that under ER stress, p53 binding to the p53-binding region at the GPC1 gene transcriptionally upregulates miR-149-3p expression. Furthermore, miR-149-3p targets the 3′UTR of GSK3α, which is known to target Mcl-1, consequently leading to apoptosis resistance in melanoma cells.[18] miR-149-3p overexpression was observed in fresh human metastatic melanoma isolates. miR-149-3p-mediated pathway provided a reasonable explanation for the ineffectiveness of wild-type p53 in suppressing melanoma. miR-149-3p was also shown to serve as an oncogenic regulator by promoting proliferation and reducing apoptosis in T-cell acute lymphoblastic leukemia (T-ALL) cells via targeting JunB, and subsequently downregulating p21 as well as upregulating cyclin D1, 4EBP1, and p70s6k.[19] However, miR-149-3p was found to suppress the expression of polo-like kinase 1 (PLK1), a critical regulator of cell cycle progression and apoptosis, by targeting the 3′UTR of its mRNA, leading to tumor cell clonogenicity decrease and apoptosis induction.[20] In addition, in human miR-149-3p-transfected neuroblastoma and HeLa cell lines, caspase3,7 activity was induced and cell growth was inhibited significantly.[21] AKT1 and E2F1 were proven to be the direct targets of miR-149-3p. Importantly, an inverse correlation of miR-149-3p with E2F1 expression (P=0.026) was revealed in primary neuroblastoma samples. Furthermore, miR-149-3p was found upregulated in U87-MG cells following treatment of quinidine, a voltage-gated K^+ channel blocker, leading to proliferation inhibition and apoptosis induction of glioma cells.[22]

miR-149 in cancer migration and invasion

Cancer metastasis accounts for almost all cancer-related deaths. Metastasis is a multistep process, involving tumor cell dissemination from the primary tumor and colonizing distant organs.[23] The improved ability of tumor cells to undergo migration and invasion contributes to the first step of this process. miR-149-5p was significantly downregulated in RCC tissues. The overexpression of miR-149-5p contributed to the suppression of cancer cell proliferation and migration.[24] Forkhead box transcription factor (FOXM1) is a typical transcription factor and defined as having a common DNA-binding domain called Forkhead or winged-helix domain.[25] FOXM1 regulates both G1-S and G2-M phases of cell cycle and mitotic spindle integrity, and its overexpression leads to tumor angiogenesis and metastasis.[26] And in colorectal cancer, miR-149-5p suppresses cell migration and invasion by targeting FOXM1,[27] in non-small cell lung cancer, epithelial-to-mesenchymal (EMT) of cancer cells are inhibited by miR-149-5p via targeting FOXM1.[28] Luo G et al demonstrated that miR-149-5p repressed the metastasis of hepatocellular cells *in vitro* and *in vivo* by targeting the actin-regulatory proteins PPM1F.[29] PPM1F can promote the formation of stress fibers, which play an important role in metastasis.[30] Moreover, miR-149-5p was found able to suppress migration and invasion of human colonic carcinoma HCT116 and SW620 cell lines by targeting an oncogene: EphB3.[31] The study by Bischoff A et al showed that miR-149-5p functioned as a tumor suppressor via impairing cell spreading, migration, and invasion of basal-like breast cancer cells via targeting the small GTPases :Rap1a, Rap1b and downstream of integrin receptors. Cell metastasis depends on the activation of Rac, which is known to drive mesenchymal type of cancer cell motility.[32] miR-149-5p has been proven to reduce Rac activation indirectly by Rap1a/b co-depletion. They also verified

miR-149-5p was able to block the growth factor heregulin (HRG) and PI3K-Akt passway via targeting ErbB3, whose deregulated expression contributes to the transformed phenotype of breast cancer cells.[33] Moreover, cancer cells transfected with miR-149-5p blocked lung colonization *in vivo*. miR-149-5p targets G-protein-coupled receptor kinase-interacting protein (GIT1), another member of integrin signaling.[34] It has been known that GIT1 plays a central role in regulating fibronectin-induced focal adhesion formation and cell migration.[35, 36] Overexpression of miR-149-5p reduced the phosphorylation of focal adhesion kinase and paxillin, but enhanced the degradation of paxillin and α5β1 integrin. GIT1 depletion reduced α5β1-integrin-mediated cell adhesion to fibronectin. High GIT1 level and low miR-149-5p level were significantly associated with the advanced stages of breast cancer, especially lymph node metastasis.

miR-149 in drug sensitivity and resistance

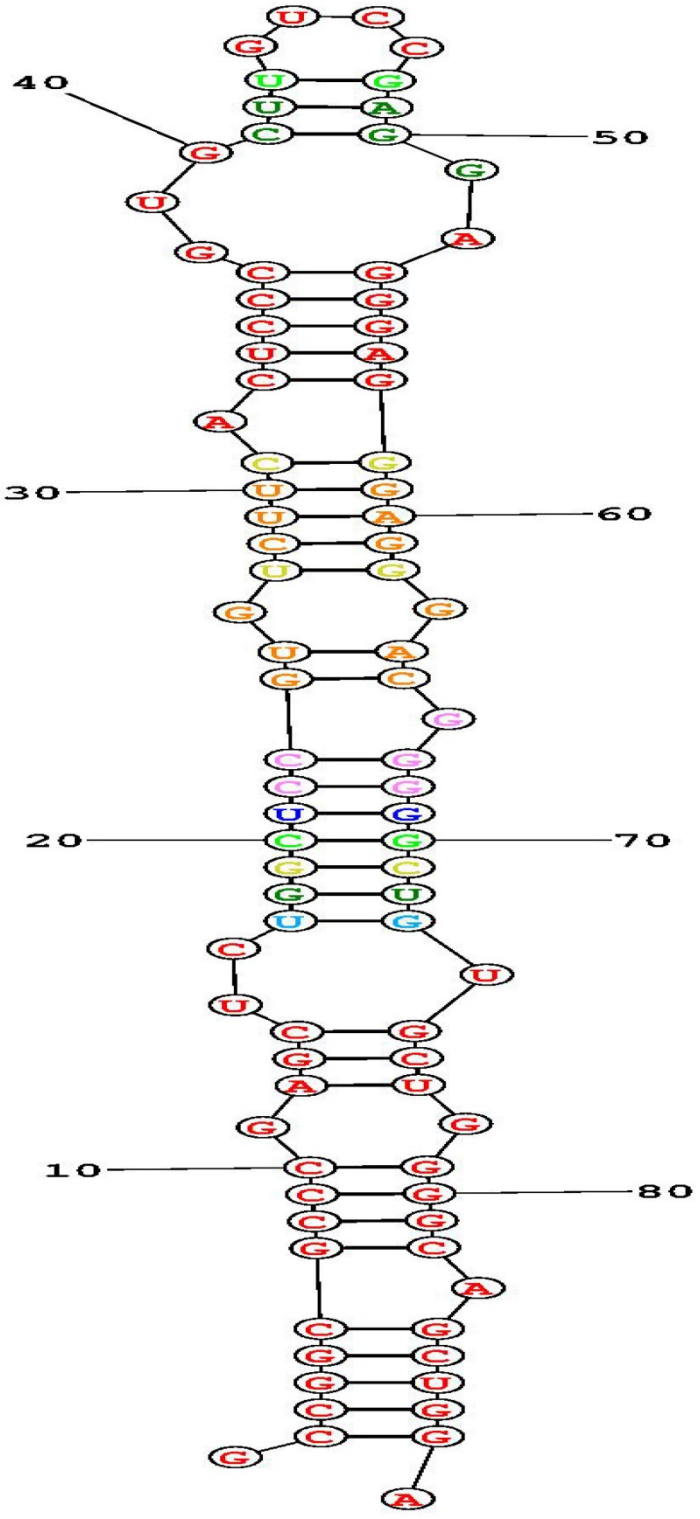
Cancer resistance to chemotherapy, molecularly targeted therapies, and other anti-cancer drugs limits treatment effectiveness.[37] Studies have shown that miR-149 participates in regulating drug sensitivity and cancer resistance. In GBM, miR-149-5p was downregulated, while the chemosensitivity of glioblastoma cells to temozolomide (TMZ) was enhanced via targeting Rap1b.[38] Recent years, studies have shown that one type of dietary restrictions (DR): short time starvation (STS) is able to make chemotherapy more suitable.[39] Higher expression level of miR-149-5p in breast cancer cells: MDA-MB-231 and normal mammary epithelial cells: MCF10A treated with doxorubicin under STS for 48h could explain that miR-149-5p was involved in pathways related to increase drug sensitivity.[40] In adriamycin (ADM)-resistant human breast cancer cells, He DX et al demonstrated that the downregulation of miR-149-5p was attributed to hypermethylation of its 5′-UTR.[41] Chemoresistance was suppressed by miR-149-5p through targeting GlcNAc N-deacetylase/N-sulfotransferase-1(NDST1). NDST1 has the ability to activate a heparin sulfate-related pathway involving heparanase, which contributes to chemoresistance. miR-149-5p not only decreases cell migration and invasion, but also increases the sensitivity of colorectal cancer cells to 5-Fluorouracil (5-FU) via targeting FOXM1.[42] In 5-FU-responding colorectal cancer tissues, the expression of miR-149-5p was significantly higher than that in non-responding tissues and inversely correlated with the mRNA level of FOXM1. It has been found that high level of bisphenol A (BPA) is one of risk factors to induce endometrial cancer (EC). The expression of miR-149-5p was reduced after BPA exposure, then leads to down-regulate DNA repair gene ADP-ribosylation factor 6 (ARF6) and tumor protein p53 (TP53).[43] These finding revealed a potential epigenetic mechanism among the risk of endometrial carcinogenesis. However, miR-149-5p was found upregulated in gefitibib-resistant human lung adenocarcinoma cell line and involved in the acquired gefitinib resistance.[44]

The study by Donghui Cao *et al*. revealed that 18β-glycyrrhetinic acid (GRA) could attenuate the severity of gastritis, suppress gastric tumorigenesis in transgenic mice, ameliorate the inflammatory microenvironment through the inhibition of COX-2 expression, and upregulate the expression of miR-149-3p which targeted Wnt-1.[45] In addition, dioscin, a natural product, is an active ingredient in some medicinal plants and has shown anti-tumor effects against many cancers.[46] In pancreatic cancer, dioscin was found to induce apoptosis and suppress the tumor growth of ASPC-1 and PANC-1 cell xenografts by upregulating miR-149-3p expression which targeted AKT1, increasing the expression levels of Bax, Apaf-1, cleaved caspase-3/9, and cleaved PARP, and suppressing Bcl-2 levels, which results in cytochrome c release.[47] Bafilomycin A1 is an inhibitor of the c subunit of the V-ATPase and has been investigated able to inhibit the proliferation and metastasis of cancer cells.[48] miR-149-3p was also found upregulated in BEL-7402 liver cancer and HO-8910 ovarian cancer cell lines following bafilomycin A1 treatment.[49] However, on the basis of the study of Ma J et al, microcystin-LR (MC-LR) has been identified as one of risk factors for human primary hepatocellular cancer.[50, 51] Exposure of MC-LR was found promoted the expression of miR-149-3p, promoting miR-149-3p may be involved in MC-LR-hepatotoxicity, hepatitis and liver carcinoma.[52]

miR-149 in tumor microenvironment

Tumor microenvironment is now recognized as an important participant in metastatic progression and therapeutic responses.[53] Extracellular matrix (ECM) and numerous stromal cells, including blood endothelial cells, lymphatic endothelial cells, cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), mesenchymal stem cells (MSCs), immune cells, leukocytes, and adipocytes, constitute the tumor microenvironment.[54, 55]

A



B

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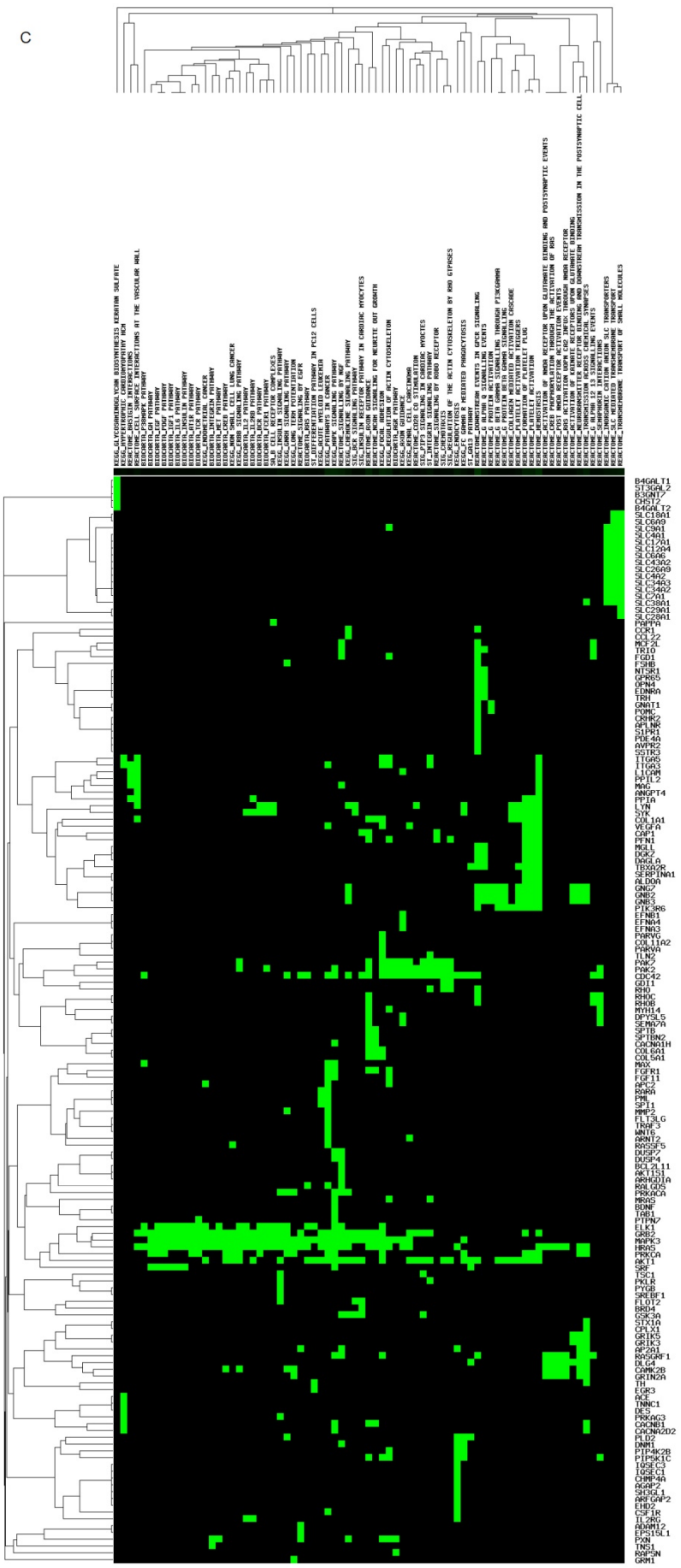
C
KEGG_GLYCOSAMINOGLYCAN BIOSYNTHESIS KERATAN SULFATE
KEGG_PEROXISOME
REACTOME_PEPTIDE LIGAND-BINDING RECEPTORS
REACTOME_G ALPHA (I) SIGNALLING EVENTS
BIOCARTA_P38MAPK PATHWAY
BIOCARTA_EGF PATHWAY
BIOCARTA_IGF1 PATHWAY
BIOCARTA_TCRA PATHWAY
BIOCARTA_AT1R PATHWAY
BIOCARTA_PTEN PATHWAY
KEGG_ENDOMETRIAL CANCER
BIOCARTA_MET PATHWAY
KEGG_SMALL CELL LUNG CANCER
KEGG_ERBB SIGNALING PATHWAY
BIOCARTA_PDGF PATHWAY
BIOCARTA_IL2RB PATHWAY
BIOCARTA_PPARA PATHWAY
BIOCARTA_FCER1 PATHWAY
KEGG_NEUROTROPHIN SIGNALING PATHWAY
KEGG_INSULIN SIGNALING PATHWAY
KEGG_ERBB SIGNALING PATHWAY
REACTOME_SIGNALING BY EGFR
BIOCARTA_TCR PATHWAY
ST_DIFFERENTIATION PATHWAY IN PC12 CELLS
KEGG_LEUKOCYTE TRANSENDOTHELIAL MIGRATION
KEGG_PATHWAYS IN CANCER
KEGG_MAPK SIGNALING PATHWAY
KEGG_CHEMOKINE SIGNALING PATHWAY
SIG_INSULIN RECEPTOR PATHWAY IN CARDIAC MYOCYTES
REACTOME_AKAP95 STAGE
REACTOME_SIGNALING FOR NEURITE OUT GROWTH
KEGG_FOCAL ADHESION
BIOCARTA_RAS PATHWAY
KEGG_ACUTE MYELOID LEUKEMIA
KEGG_RENAL CELL CARCINOMA
SIG_INSULIN RECEPTOR PATHWAY IN CARDIAC MYOCYTES
ST_PI3 SIGNALING IN CARDIAC MYOCYTES
ST_INTERLEUKIN SIGNALING PATHWAY
BIOCARTA_IL1R PATHWAY
SIG_CHEMOTAXIS
REACTOME_REGULATION OF THE ACTIN CYTOSKELETON BY RHO GTPASES
KEGG_ENDOCYTOSIS
ST_GA13 PATHWAY
REACTOME_FCERI MEDIATED PHAGOCYTOSIS
REACTOME_G ALPHA (I) SIGNALLING EVENTS
REACTOME_G ALPHA (Q) SIGNALLING EVENTS
REACTOME_G PROTEIN ACTIVATION
REACTOME_G PROTEIN BETA GAMMA SIGNALLING
REACTOME_PLATELET ACTIVATION TRIGGERS
REACTOME_PLATELET ACTIVATION
REACTOME_HEMOSTASIS
REACTOME_ACTIVATION OF NMDA RECEPTOR UPON GLUTAMATE BINDING AND POSTSYNAPTIC EVENTS
REACTOME_CREB PHOSPHORYLATION THROUGH THE ACTIVATION OF RAS
REACTOME_RAS ACTIVATION UPON CA2 INFLUX THROUGH NMDA RECEPTOR
REACTOME_ACTIVATION OF RAC1 DOWNSTREAM OF NMDAR
REACTOME_ANTIGEN ACTIVATES B CELL RECEPTOR (BCR) LEADING TO GENERATION OF SECOND MESSENGERS
REACTOME_NEUROTRANSMITTER RECEPTOR BINDING AND DOWNSTREAM TRANSMISSION IN THE POSTSYNAPTIC CELL
REACTOME_TRANSMISSION ACROSS CHEMICAL SYNAPSES
REACTOME_NEURONAL SYSTEM
REACTOME_GENPEPTIDER INTERACTIONS
REACTOME_ION CHANNEL TRANSPORT
REACTOME_SLC MEDIATED TRANSMEMBRANE TRANSPORT
REACTOME_TRANSMEMBRANE TRANSPORT OF SMALL MOLECULES
B4GALT1
SI3GAL2
B3GNT7
CHST2
B4GALT2
SLC18A1
SLC6A9
SLC9A1
SLC4A1
SLC17A1
SLC12A4
SLC6A6
SLC43A2
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SLC34A3
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MGF2L
TR10
FGD1
F5HB
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GPR65
GPN4
EDNRA
TRH
GNAT1
POMC
CRHR2
APLNR
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AVPR2
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MA6
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LYN
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VEGFA
CAP1
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DGK2
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ALDOA
GNG7
GNB2
GNB3
PIK3R6
EFNB1
EFNA4
EFNA3
PARVG
COL11A2
PARVA
TLN2
PAK2
PAK2
CDC42
GDI1
RHO
RHOC
RHOB
MYH14
DFY3L5
SEMA7A
SPTB
SPTBN2
CACNA1H
COL6A1
COL5A1
MAX
FGFR1
FGF11
APC2
RARA
PML
SPI1
MMP2
FLT3LG
TRAF3
WNT6
ARNT2
RASSF5
DUSP7
DUSP4
BCL2L11
AKT1S1
ARHGDIA
RALGDS
PRKACA
MRAS
BDNF
TAB1
PTPN7
ELK1
GRB2
MAPK3
HRAS
PRKCA
AKT1
SRF
TSC1
PKLR
PYGB
SREBF1
FLOT2
BRD4
GSK3A
STX1A
CLY1
GRIK5
GRIK3
AP2B1
RASGRF1
DLG4
CAMK2B
GRIN2A
TH
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ACE
TNNC1
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PRKAG3
CACNB1
CACNA2D2
PLD2
DNM1
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IQSEC3
IQSEC1
CHMP4A
AGAP2
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EHD2
CSF1R
TLR6
ADAM12
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PXN
TNS1
RAPGN
GRM1

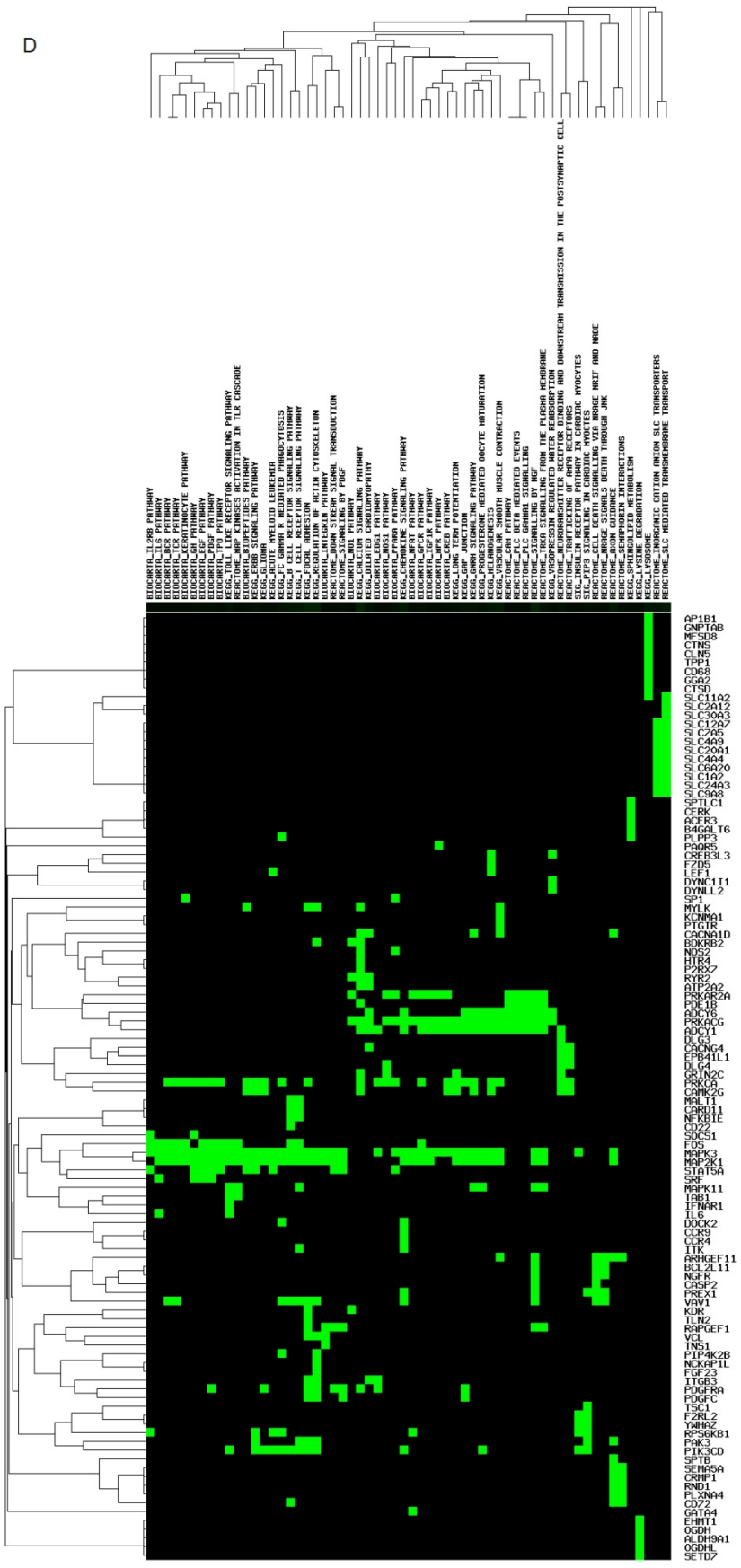

Figure 1. Structure, targeted genes and pathways of miR-149. (A): The predicted stem-loop structure of miR-149 determined using the RNA structure software. (B): The sequence of miR-149. (C, D): The targeted genes and pathways potentially affected by miR-149-5p and miR-149-3p identified using the Diana-MicroT and TagetScan tools.

Among the stromal cells, heterogeneous populations of CAFs are key players in multicellular stromal-dependent alterations that contribute to malignant initiation and progression.[56] In addition, crosstalk between CAFs and tumor cells lead to tumor progression. CAFs are usually considered to be derived from normal fibroblasts (NFs), and they communicate with tumor cells via growth and inflammation factors.[57, 58] Inflammatory signaling pathways are considered highly promising targets to block the crosstalk between tumor cells and CAFs.[59] Pu Li et al demonstrated that miR-149-5p links PGE2 and IL-6 signaling in mediating the communication between tumor cells and CAFs in GC.[60] They showed that miR-149-5p regulated fibroblast activation protein (FAP) expression via targeting IL-6, and its expression was downregulated in GC CAFs. miR-149-5p was found to inhibit fibroblast activation by reducing IL-6 expression. In addition, CAFs enhanced epithelial-to-mesenchymal transition and the stem-like properties of GC cells in a miR-149-IL-6-dependent manner. Besides IL-6, PGE2 receptor 2 (PTGER2/EP2) was revealed as another target of miR-149-5p. *H.pylori* infection, a leading cause of human GC, caused the hypermethylation of miR-149-5p and induced COX-2/PGE2 as well as IL-6 signaling pathways.

Fibroblast growth factors (FGFs) and their receptors (FGFRs) regulate numerous cellular processes, especially in the endothelial cells.[61] Glypicans (GPCs) are frequently overexpressed in many cancers and recognized to play a role in tumorigenesis and angiogenesis.[62] GPC1 promoted FGF2 binding to its receptor (FGFR1), subsequently enhancing FGF2-FGFR1 activation and signaling. miR-149, including miR-149-5p and miR-149-3p, was found to be located within the first intron of GPC1 gene and showed targeting activity towards both GPC1 and FGFR1 in endothelial cells.[63] Decreased FGF2 signaling in endothelial cells and reduced neovascularization were observed *in vivo* following miR-149 overexpression. Notably, FGF2 was found to stimulate the expression of miR-149, thereby assuring the steady state of FGF2-induced responses in endothelial cells.

miR-149 as potential therapeutic targets

As we discussed above, miR-149 plays important roles in tumorigenesis and tumor progression of various cancers. There also have been a large number of studies about exploring the effect using miR-149 as therapeutic targets. Chen Y et al observed a reduction in proliferation and increase in the apoptosis of prostate cancer stem cells from TSU cell line via the downregulated expression of miR-149-5p.[64] Proliferation inhibition and apoptosis induction were observed using expression enhancement of miR-149-3p in glioma cells.[22] Moreover, among various cancers, metastasis was repressed using transfecting miR-149-5p mimics *in vitro* and *in vivo*.[29, 35, 36] And chemoresistance to 5-Fluorouracil was suppressed by introducing miR-149-5p mimics in colorectal cancer cells.[42] Furthermore, fibroblast activation inhibition and neovascularization reduction were achieved by increasing expression of miR-149-5p in CAFs and endothelial cells.[60, 63]

miR-149 as potential biomarkers

Numerous considerable efforts have been devoted to identifying suitable miRNAs as diagnostic, prognostic markers, owing to their remarkably stable forms and abnormal expression in cancer patients compared to that in healthy individuals.[65] Single-nucleotide polymorphisms (SNPs) in microRNA represent another type of genetic variability that can influence the risk and outcome of human disease.[66] In Rong GQ, Dikeakos P and Li L et al's study, miR-149-5p gene polymorphisms was found associated with susceptibility to CRC and GC,[67-69] particularly in males.[70] In Pan XM, Liu XX and Du W et al's study, they also revealed that single nucleotide (SNPs) rs2292832 in miR-149-5p was related to high CRC susceptibility.[71, 72] Jia H , Wang XH and Feng Y et al respectively confirmed that rs2292832 in miR-149-5p contributed to the risk of hepatocellular cancer and breast cancer,[73-75] especially in HBV-infected HCC patients.[76] PS and Wei WJ et al also found miR-149-5p rs2292832 C>T contributed to the development of oral squamous cell carcinoma in South Indian Population and the risk of papillary thyroid cancer in Chinese population.[77, 78] In addition, pre-miR-149-5p rs71428439 polymorphism was investigated associated with increased cancer risk in hepatocellular carcinoma and head and neck squamous cell carcinoma. The mechanism of this SNP possibly involved downregulated miR-149-5p expression and upregulation targeted gene AKT1 expression.[79, 80] The study from Wang Z et al also demonstrated that the GG genotypes of miR-149-5p rs71428439 increased the risk of clear cell renal cell carcinoma.[81] But miR-149-5p rs2292832 T/C polymorphism could decrease digestive cancer susceptibility in Li L et al's meta-analysis study.[82] Wang et al found that pre-mir-149-5p rs2292382 had significantly better survival in laryngeal squamous cell carcinoma.[83] Huang GL et al demonstrated miR-149-5p rs2292832 contributed to the progression rather than the initiation of nasopharyngeal cancer.[84] Furthermore, miR-149-5p C-containing genotypes of miR-149-5p

rs2292832 was verified associated with better over survival (OS), and might function through DNA topoisomerases 1 (TOP1) pathway in non-small cell lung cancer.[85, 86] And in colorectal cancer, miR-149-5p was found to be epigenetically silenced, which was associated with the hypermethylation of the neighboring CpG Island. miR-149-5p acts as a tumor suppressor via targeting a potential oncogenic protein, Specificity Protein 1 (SP1).[87, 88] Wilting SM et al also demonstrated methylation-mediated transcriptional repression of miR-149-5p participated in human papillpmavirus (HPV) induced cervical carcinogenesis.[89] Another study demonstrated that miR-149-5p was downregulated in colorectal cancer, and it regulated the expression of SRPX2.[90] AKT1 was identified as an unfavorable prognostic factor for patients with HCC. Zhang Y et al found that miR-149 functions as a tumor suppressive miRNA via targeting AKT1 in patients with HCC by using five online programs for miRNA target prediction.[11] Lin L et al studied the expression of miR-149-5p and PARP-2 in HCC tumor tissues, and their roles in sensitizing chemo/radiotherapy. The high expression level of PARP-2 and low expression level of miR-149-5p were found to be correlated with larger tumor mass, increased capsular and vascular invasion, and lymph node metastases. High PARP-2 and low miR-149-5p levels were identified as poor prognosis factors, and they reduced sensitivity to chemotherapy and radiotherapy in xenogratft HCC animal models.[91] Xue L et al aimed to investigate the prognostic value of miR-149-5p in glioma.[92] They found that the expression of miR-149-5p was significantly lower in tumor tissues compared to that in normal tissues. Improved survival duration and lower mortality risk were also observed using Kaplan-Meier and multivariate analysis. Furthermore, it was revealed that AKt/mTOR signaling was hyperactive in low miR-149 expressing tissues. miR-149-5p was also proven to play critical roles in astrocytomas and laryngeal squamous cell carcinoma.[93, 94] miR-149-5p expression was significantly lower in tumor tissues than in normal brain and vocal cord polyp tissues. Shorter survival duration was seen in patients with lower miR-149-5p expression. However, in Yang C et al' s study, the expression of miR-149-5p was reported to be increased in NSCLC tissues using either small RNA-sequencing or qRT-PCR validation.[95] miR-149-5p was also found overexpressed in castration-resistant prostate cancer. And in upper tract urothelial carcinoma, miR-149-5p was identified as independently associated with cancer-specific survival.[96] Besides, overexpression of miR-149-3p was found in plasma of melanoma patients compared with healthy controls. miR-149-3p was identified as a biomarker with high diagnostic power in early stage of melanoma.[97] And miR-149-3p overexpression was also investigated strongly correlated in uveal melanoma patients with liver metastasis.[98]

Recently, serum or plasma exosomal miRNAs have emerged as novel markers for diagnosis and prognostic evaluation in patients with various cancers.[99] Extracellular vesicles (EVs) and exosomes are membrane-derived vesicles that are actively secreted by cells. EVs with a diverse range of sizes (100–1,000 nm in diameter) contain microvesicles and ectosomes, which originate by budding from the plasma membrane of cells. Exosomes, typically smaller than 150 nm in diameter, are generated inside multivesicular endosomes or multivesicular bodies (MVBs). When these compartments fuse with the plasma membrane, exosome secretion is activated.[100] A previous study showed that EVs and exosomes contain numerous molecules, such as cell-specific proteins, lipids, mRNAs, and abundant miRNAs.[101-103] Owing to the protective function of EVs or exosomes against degradation by RNAse enzymes, exosomal miRNAs are stable in blood or other body fluids, making them ideal candidates for biomarkers in cancers. Pfeffer SR *et al.* showed that exosomal miR-149-5p was expressed at significantly higher levels in patients with metastatic sporadic melanoma compared to that in familial melanoma patients or unaffected control subjects, suggesting that miR-149-5p could be a poor prognostic factor in melanoma.[104] As we mentioned above, miR-149-5p was found to have targeting activity towards GPC1 in endothelial cells. Similarly, miR-149-5p decreased GPC1 expression in colorectal cancer cell lines. Moreover, miR-149-5p was significantly decreased in GPC^+ exosomes from tumor tissues and plasma of colorectal cancer patients compared to that in peritumoural tissues and plasma of healthy controls.[105]

Conclusions

miR-149-5p or miR-149-3p plays dual roles in the proliferation and apoptosis of various tumors (Figure 2). In cancer metastasis, miR-149-5p is found to be an important tumor suppressor, and its expression was downregulated (Figure 3). Currently, both miR-149-5p and miR-149-3p are confirmed to increase drug sensitivity according to most of the literature (Figure 4). In tumor microenvironment, miR-149-5p regulated FAP expression on CAFs via targeting IL-6, leading to fibroblast activation inhibition and its expression was downregulated in gastric cancer. Overexpression of miR-149-5p or miR-149-3p alleviated FGF2 signaling in endothelial cells and

reduced neovascularization (Figure 5). miR-149-5p gene polymorphisms contribute to alter susceptibility to cancers. Therefore, it can be suggested that miR-149 could serve as biomarkers and therapeutic targets in numerous cancers.

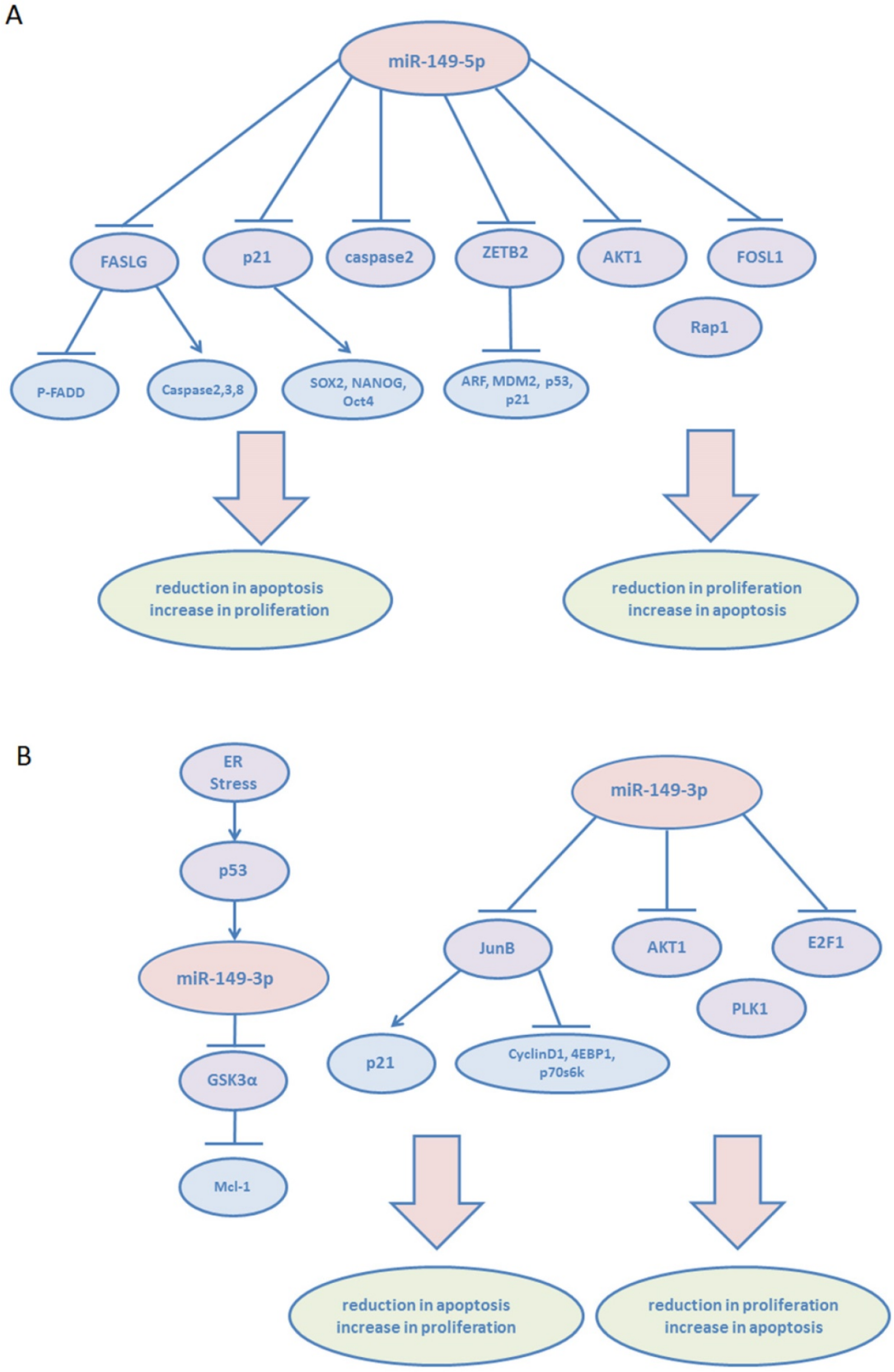

Figure 2. Dual roles of miR-149-5p and miR-149-3p in proliferation and apoptosis. (A): miR-149-5p. (B): miR-149-3p.

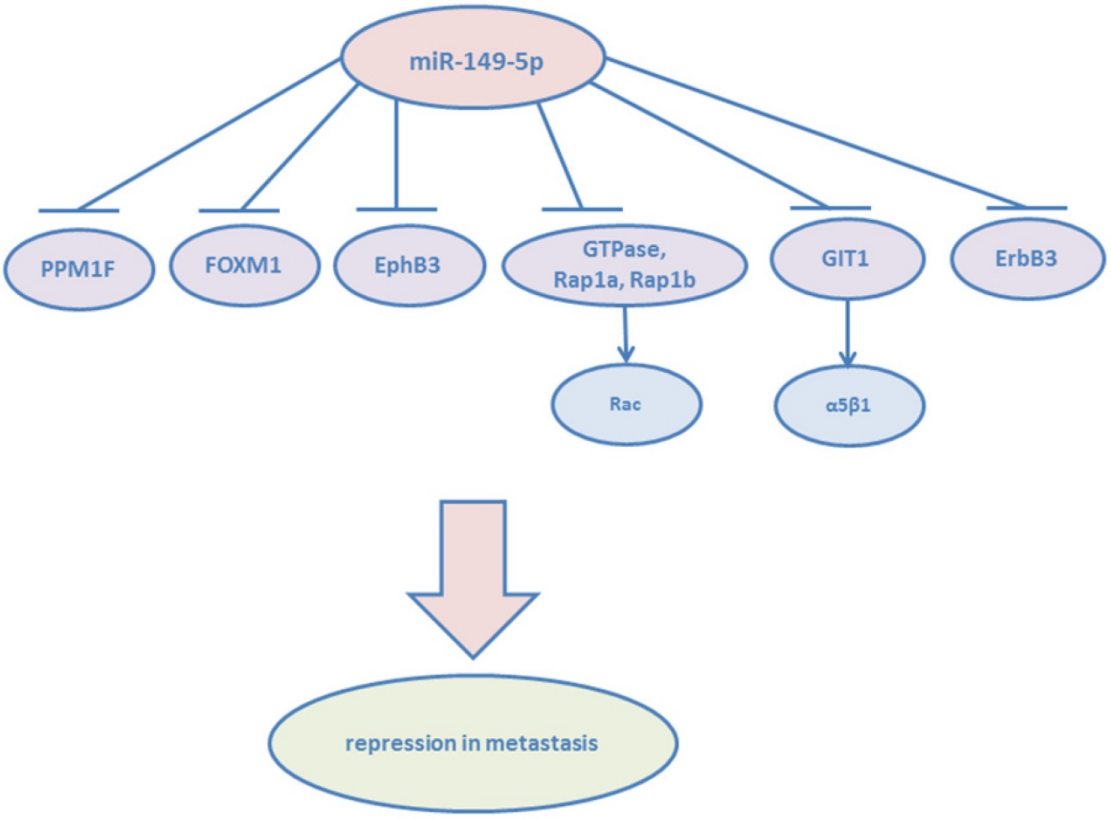

Figure 3. miR-149-5p found to be an important tumor suppressor of metastasis.

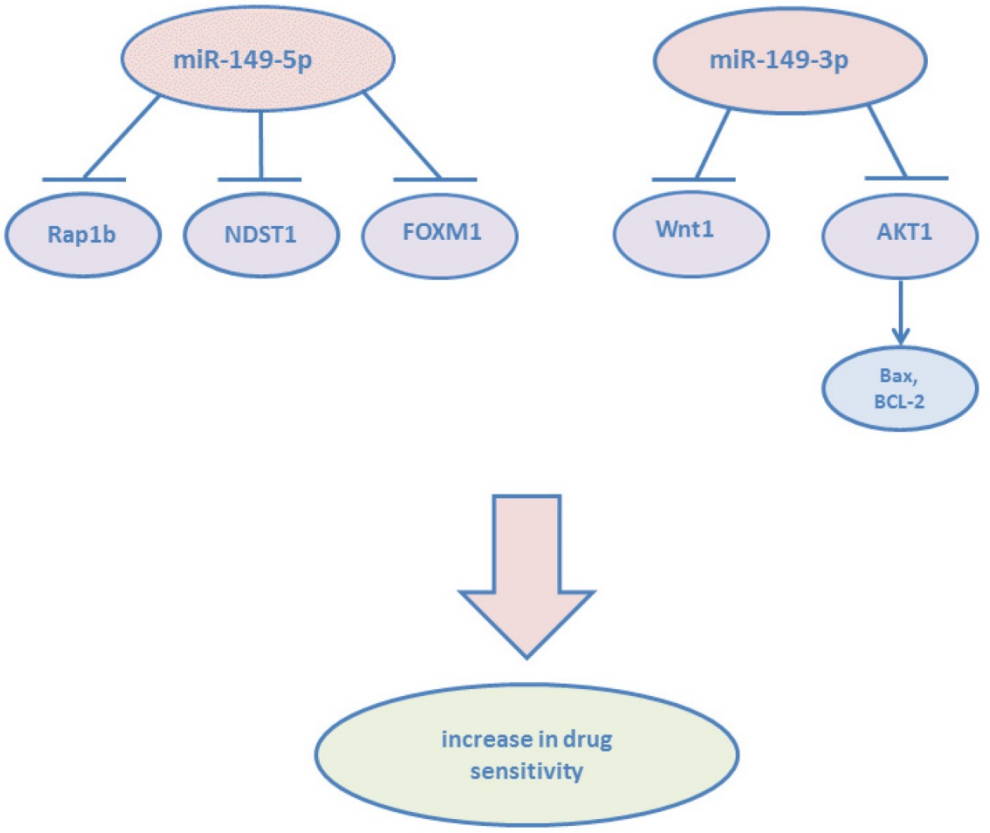

Figure 4. miR-149-5p and miR-149-3p confirmed to increase drug sensitivity.

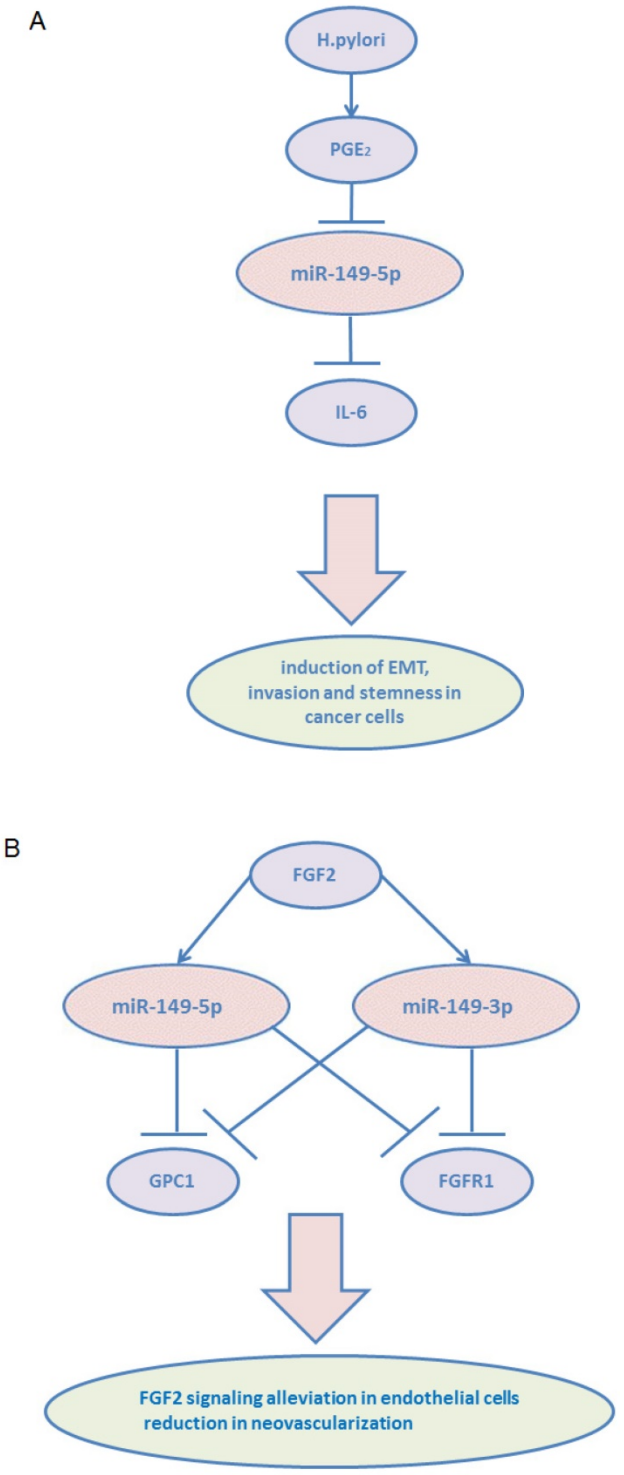

Figure 5. miR-149-3p and miR-149-5p participate in tumor microenvironment. (A) miR-149-5p mediates the crosstalk between tumor cells and CAFs: H. pylori infection leads to induce PGE2 signaling and result in reduction of miR-149-5p in CAFs and increase IL-6 secretion. (B) Overexpression of miR-149-5p or miR-149-3p alleviated FGF2 signaling in endothelial cells and reduced neovascularization via targeting GPC1 and FGFR1.

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Competing Interests

The authors have declared that no competing interest exists.

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