

MINI-REVIEW

microRNA-29b: an Emerging Player in Human Cancer

Hao Liu, Bin Wang, Jie Lin, Liang Zhao*

Abstract

MicroRNAs (miRNAs) are ubiquitously expressed small, non-coding RNAs that negatively regulate gene expression at a post transcriptional/translational level. They have emerging as playing crucial roles in cancer at all stages ranging from initiation to metastasis. As a tumor suppressor miRNA, aberrant expression of microRNA-29b (miR-29b) has been detected in various types of cancer, and its disturbance is related with tumor development and progression. In this review, we summarize the latest findings with regard to the tumor suppressor signature of miR-29b and its regulatory mechanisms. Our review highlights the diverse relationships between miR-29b and its target genes in malignant tumors.

Keywords: microRNAs - gene expression - tumor suppressor - gene therapy

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Introduction

MicroRNAs (miRNAs) are a class of single-stranded small molecule RNA with about 22 nucleotides in length (Bartel, 2009). These short RNA molecules are able to bind to specific sites typically present in the three prime untranslated region (3'-UTR) of their target genes and mediate either mRNA decay with perfect base pairing or translational blockade with imperfect base pairing (Pillai et al., 2007). So far, there are about 1424 miRNAs in human, 720 in mouse, and 408 in rat which were confirmed by miRBase database (Kozomara and Griffiths-Jones, 2011). It is known that hundreds of miRNAs participate in various biological phenomena, such as cell proliferation, development, differentiation and metabolism (Kavitha et al., 2014). As a special one among them, the miR-29b has unexceptionally become a hot topic. The miR-29b contains miR-29b-1 and miR-29b-2. The structure, function, and regulation of miR-29b are in high degree in human, mouse and rat. miR-29b-1 is transcribed into the same primary transcript from a locus at chromosome 7q32 and separated by 652 bases, which coincides with the common fragile site (FRA7H) (Pillai et al., 2007). miR-29b-2 is from the same transcript located in 1q32 separated by 507 bases (Garzon et al., 2009). In this review, the research progress on the miR-29b and its target genes in malignant tumor will be summarized.

Expression of miR-29b in Malignant Tumors

Nowadays, a large body of surveys reported that miR-29b was highly expressed in normal tissues and down-regulated in different types of cancer. The miR-29b

promoter region contains putative E-box Myc binding site and increased expression of c-Myc repressed the promoter activity of miR-29b by 50% in cholangiocarcinoma cells (Mott et al., 2010). Consistent with this finding, a hedgehog signaling component Gli was identified as a putative binding site in the human miR-29b promoter sequence and resulted in down-regulation of miR-29b expression (Mott et al., 2010). CCAAT/enhancer-binding protein- α (CEBPA) was recently found to directly regulate miR-29b expression in acute myeloid leukemia (AML) (Eyholzer et al., 2010). Rothschild et al showed that miR-29b was identified as an important mediator of the Src-ID1 pathway, controlling lung cancer cell invasion. (Rothschild et al., 2012).

It was observed that the expression of miR-29b was down-regulated in a variety of tumor tissues including gastric cancer, prostate cancer, breast cancer, lung cancer, etc (Table 1).

The Regulation of miR-29b

The regulation of miR-29b expression occurs in several different levels: (1) at the chromosome level, tumor genesis was commonly accompanied with abnormalities of chromosomes including deletion, amplification and translocation. In acute myelocytic leukemia (AML) patients, miR-29b suppression is due to loss of chromosome 7q or CCAAT-enhancer binding protein-alpha (CEBPA) deficiency (Eyholzer et al., 2010). Coincidentally, miR-29b is also correlated with Mcl-1 and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in cholangiocarcinoma cells, and regulates Tcl-1 in chronic lymphatic leukemia (CML) cells by 11q

deletion (Pekarsky et al., 2006).

(2) At the epigenetic level, silencing of tumor suppressor genes frequently occurs and may account for their inactivation in cancer cells. A previous study demonstrated that miR-29b can suppress cytokine signaling-1 (SOCS-1) expression by inducing promoter demethylation of SOCS-1 (Amodio et al., 2013). The miR-29b can also revert the aberrant methylation by targeting the DNA (cytosine-5)-methyltransferase 3a (DNMT3a) and DNMT3b genes (Fabbri et al., 2007). miR-29b plays an important role in oxLDL-mediated methylation of matrix metalloproteinase-2 (MMP-2)/MMP-9 genes (Chen et al., 2011). (3) At the transcriptional level, the miR-29b cluster is involved in the group of interferon (IFN)- and signal transducers and activators of transcription (STAT)-regulated genes (Schmitt et al., 2012). The miR-29b promoter contains three GATA3-binding sites. GATA3 increased the activity of the miR29b promoter, and deletion of the GATA sites diminished GATA3-mediated reporter induction, demonstrating that these sites are necessary for the expression of miR-29b (Chou et al., 2013). In addition, miR-29b sensitizes multiple myeloma cells to bortezomib-induced apoptosis through the activation of a feedback loop with the transcription factor Sp1 (Amodio et al., 2012a).

Functions and Mechanism of miR-29b in Tumorigenesis and Suppressing Tumor Proliferation

Proliferation is related to the cell cycle control. As we known, CDK6 is an important cycle regulators which may contribute cell death and proliferation. Gene expression analysis of miR-29b-overexpressing AML cells showed the suppressive effect on cell cycle regulatory factor CDK6 (Garzon et al., 2009). Down-regulation of miR-29b targets CDK6 directly and leads to up-regulation of CDK6 in mantle cell lymphoma (MCL). Overexpression of cyclin D1 was always found in MCL, which leads to the acceleration of G1-S cell-cycle progression. Cyclin D1 overexpression is a primary event and exerts its function through activation of CDK4/CDK6. miR-29b further attenuates cell-cycle progression and suppresses tumor cell proliferation, which demonstrated the cooperation between CDK6 and cyclin D1 (Zhao et al., 2010). Wang et al. reported that the tumor-suppressive role of miR-29b was associated with its promyogenic function by targeting YY1. Its overexpression inhibited cell proliferation and induced differentiation of RH30 rhabdomyosarcoma cells (Wang et al., 2008). In Cortez's study, they demonstrated that miR-29b directly targeted the 3' untranslated region

Table 1. Target Genes for miR-29b and Role in Cancer Etiology

Cancer type	Target gene	Biological function	Reference
Bladder urothelial carcinoma (BUC)	transcription factors (PAX3, PAX7, HOXA10, FOXO1, E2F1, ETF7, YY1, MYC)	proliferation, cell cycle, apoptosis	(Xu et al., 2013b)
Breast carcinoma	DNMT3b MMP-2	DNA methylation invasion and metastasis	(Sandhu et al., 2014) (Zhu et al., 2012)
Colorectal carcinoma (CRC)	C1QTNF6, SPARC, COL4A2 ~ MMP-2 Tiam1 ~	invasion invasion onset and migration metastasis proliferation, metastasis	(Wang et al., 2012a) (Tan et al., 2013) (Poudyal et al., 2013) (Wang et al., 2014) (Svoboda et al., 2012)
Melanoma	IFN- γ , STAT-1	~ regulation of immune	(Schmitt et al., 2012)
Endometrial adenocarcinoma	insulin growth factor 1 (IGF1)	invasion	(Hiroki et al., 2010)
Gastric carcinoma	~	~	(Espinosa-Parrilla et al., 2014)
Hepatocellular carcinoma	~ MMP-2	~ angiogenesis, invasion and metastasis	(Zheng et al., 2013) (Fang et al., 2011)
Lung carcinoma	Snail, TGF- β , MEK/ERK, SPARC Src, inhibitor of DNA binding/differentiation 1 (ID1)	invasion, metastasis, cell-cycle, proliferation invasion, metastasis	(Grant et al., 2014) (Rothschild et al., 2012)
Ovarian carcinoma	TGF β 1, ID1 PTEN, MAPK4, IGF1 MUC1, DNMT1, DNMT3a, DNMT3b	invasion, metastasis apoptosis	(Teng et al., 2014) (Dai et al., 2013)
Pancreatic carcinoma	PTEN	apoptosis, DNA methylation	(Dai et al., 2012)
Prostate carcinoma	ZNF217, IPO7, VEGF-A, hnRNP-K Snail MMP-2	methylation apoptosis, RNA metabolism invasion, metastasis invasion, metastasis	(Wang et al., 2012b) (Szczyrba et al., 2013) (Ru et al., 2012) (Steele et al., 2010)
Rhabdomyosarcoma	NF- κ B, YY1	cell differentiation	(Wang et al., 2008)
Cholangiocytes/cholangiocarcinoma	Mcl-1	apoptosis	(Mott et al., 2007)
Renal cell carcinoma	~	~	(Wotchofsky et al., 2012)
Head and neck carcinoma	~	~	(Nurul-Syakima et al., 2011)
Thyroid carcinoma	SMAD3	proliferation and differentiation	(Leone et al., 2012)
Uterine leiomyoma	~	~	(Qiang et al., 2014)
Nasopharyngeal carcinoma	Mcl-1	apoptosis	(Sengupta et al., 2008)
Hypopharynx cancer	~	~	(Xu et al., 2013a)
Glioblastoma	Mcl-1 PDPN	apoptosis invasion, apoptosis, proliferation	(Aldaz et al., 2013) (Cortez et al., 2010)
Chronic lymphocytic leukemia (CML)	~ Tel-1	~ apoptosis	(Papakonstantinou et al., 2013) (Pekarsky et al., 2006; Calin et al., 2007)
Acute myeloid leukemia (AML)	ABL1, BCR/ABL1 Mcl-1	Proliferation, apoptosis apoptosis	(Li et al., 2013) (Garzon et al., 2009)
Multiple myeloma	NMT1, DNMT3A, DNMT3B, SP1 ~ DNMT3A, DNMT3B Mcl-1	apoptosis, DNA methylation ~ DNA methylation apoptosis	(Mims et al., 2013) (Rossi et al., 2013) (Amodio et al., 2012b) (Zhang et al., 2011)

of PDPN and inhibit invasion, apoptosis, and proliferation of glioblastomas (Cortez et al., 2010). The miR-29b has been shown to be correlated with good prognosis in patients with acute myeloid leukemia (AML), and functions as a tumor suppressor in leukemic blasts by targeting proliferation pathways, apoptosis and cell cycle (Garzon et al., 2008). In bladder urothelial cancer (BUC), miR-29b may be also functionally associated with tumor proliferation (Xu et al., 2013b).

Promoting Tumor Apoptosis

Aspartate-specific cysteinyl proteases (Caspases) play an important role in apoptosis. Caspases represent two central class of molecules that are either involved with the stimulation of the apoptotic cascade (initiator caspases), or the various sequential biological pathways required for its execution (effector caspases) (Alenzi et al., 2010). miR-29b treated cells inhibited apoptosis with activating Caspase3, fragmenting poly-ADP-ribose polymerase (PARP), increasing BAX and decreasing BCL-2 (Li et al., 2013). In cholangiocytes/cholangiocarcinoma, miR-29b targeted MCL1, which encoding the Bcl2 family protein, and sensitized tumor cells treated with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) to apoptosis (Mott et al., 2007). miR-29b combined with MUC1 DNA aptamer which is named MUC1 aptamer-miR-29b chimera (Chi-29b) significantly induced cell apoptosis in paclitaxel-resistant OVCAR-3 cells and inhibited growth of xenograft OVCAR-3-Taxol tumors which is associated with the activation of PTEN signaling and downregulation of MAPK 4 & 10 and IGF1 expression. Chi-29 also can inhibit the proliferation of paclitaxel-resistant OVCAR-3 cells and the growth of xenograft paclitaxel-resistant ovarian OVCAR-3 tumors through reducing Aldehyde dehydrogenase 1 (ALDH1) positive cells by activating the PTEN-Akt-Bax apoptosis pathway and down-regulating the miR-29b-targeted gene expression (Dai et al., 2013). Furthermore, miR29b upregulated p53 expression and promoted apoptosis by directly controlling MCL1 and repressing PIK3R1 (p85 α) and CDC42, both of which negatively regulate p53 (Park et al., 2009).

Inhibiting Tumor Invasion and Metastasis

The epithelial-mesenchymal transition (EMT) is a process by which epithelial cells lose their cell polarity (marker: e.g., E-cadherin) and cell-cell adhesion, and gain migratory and invasive properties to become mesenchymal stem cells (marker: e.g., N-cadherin), it refers to the cancer progression in which epithelial cells acquire mesenchymal features with high abilities of invasiveness and metastasis under various factors. Emerging evidence has shown associations of miRNAs with crucial cell processes such as the EMT (Orang et al., 2014). The suppression of EMT by miR-29b has been reported in various human cancers (Table 1). In accord with these data, miR-29b directly targets site in the 3'UTR of snail to inhibit tumor metastasis in prostate cancer cells. Consistently, exogenous expression of miR-29b inhibits Mcl-1 and MMP-2 protein

expression, and affects metastatic cascade including tumor invasion, motility, cellular survival, and proliferation (Ru et al., 2012). Tiam1, overexpressed in CRC, was validated as a target of miR-29b by binding directly in the Tiam1 3'UTR. The previous studies have reported that lentivirus-mediated RNAi resulted in the effective inhibition of in vitro cell growth and of the invasive ability of CRC cells (Liu et al., 2006). Tiam1 transgenic mice, which developed larger and more aggressive neoplasm than wt mice, suggesting its causal role in CRC metastasis (Yu et al., 2013). Tiam1 introduction can rescue miR-29b mediated biological behaviors, suggesting that the inhibitory effect of miR-29b is mediated in part through the repression of Tiam1 expression (Wang et al., 2014). GATA3 induces the expression of miR-29b, which in turn represses a network of prometastatic microenvironmental components, including ANGPTL4, LOX, MMP9 and VEGF-A (Melo and Kalluri, 2013), suggesting GATA3-miR-29b regulatory axis can inhibiting tumor invasion and metastasis. Consistently, miR-29b can lead to a partial blocking of TGF β 1-induced EMT by repressing inhibitor of DNA binding 1 (Id-1), a novel marker of ovarian cancer progression (Teng et al., 2014).

Protecting Normal Cell by Regulating the Adaptive Immune System

Human immune system against tumors, and the

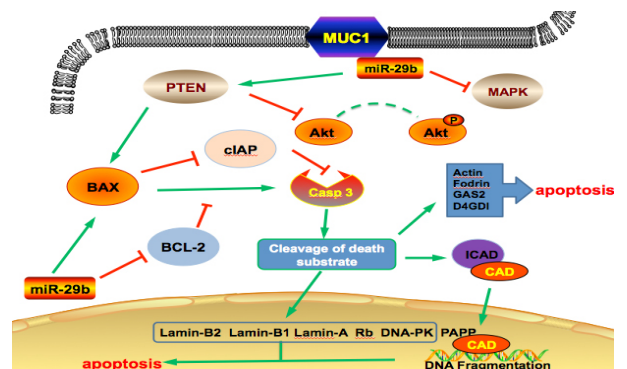


Figure 1. miR-29b Promotes Tumor Apoptosis through Death Receptors

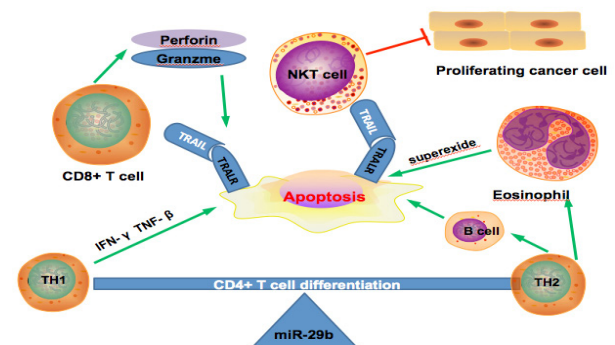


Figure 2. miR-29b Protects Normal Cell by Regulating the Adaptive Immune System. Through the expression of miR-29b, T cells are finely balanced in the Th1-Th2 cell fate decision. This fine balance allows external microenvironmental factors to influence the cell fate decision, allowing the adaptive immune response to be highly responsive to the context of infection

ability to detect tumor cells as non-self and destroy them is called immunosurveillance. Recent research has identified miR-29b as a critical regulator of key processes in adaptive immunity. miR-29b displayed three main functions in adaptive immunity: (1) controlling over thymic production of T cells by modulating the threshold for infection-associated thymic involution: the thymic involution results a >90% reduction in thymus size and a corresponding reduction in T cell generation. The type I interferons (IFN α and IFN β) is one of the key molecular mechanisms that underpin thymic involution. The thymic epithelium to respond to infections via type I IFN pathway by minimizing thymic function (Viral infection of the thymus). However, the exploitation of an evolutionarily conserved pathway creates the potential issue of perpetual thymic involution. The miR-29b tunes type I IFN signaling in thymic epithelial cells by inhibiting the production of IFNAR1 (Papadopoulos et al., 2011). The expression of miR-29b retains type I IFN in the point where involution does not occur in response to baseline or commensal production, but the capacity to appropriately respond to major infections is maintained. (2) Creating a threshold for T cell polarization: the expression of miR-29b in mature CD4 T cells is critical for setting the threshold for the Th1/Th2 cell fate decision. In CD4/CD8 T cell and NK cell lineages, both of these cell types reduce miR-29b following exposure to intracellular bacteria removes this counterbalancing force and initiates apposite feedback loop of enhanced IFN γ production and increased resistance to infection (Ma et al., 2011; Steiner et al., 2011). (3) Setting the threshold for lymphoid oncogenesis: thTe upregulation of miR-29b is likely to be a key event in malignant transformation. Transgenic mice overexpressing miR-29b in B cell show an expansion of CD5+CD19+IgM+ B cells which is same to the findings in indolent B cell chronic lymphocytic leukemia (B-CLL), suggesting its oncogenic function in B cell. In aggressive B-CLL, however, miR-29b may directly target several important oncogenes. Consistent with the findings in other types of cancer, miR-29b probably shows a tumor suppressive function in B cell (Santanam et al., 2010; Kincaid et al., 2012; Liston et al., 2012). Thus, miR-29b can protect normal cells by regulating tumor immunosurveillance.

Conclusion

Numerous studies have shown that the down-regulated expression of microRNA miR-29b could be detected in many different types of cancer, and the dysregulated miR-29b is associated with tumor stage, tumor metastasis and prognosis. On the base of the facts that miRNAs exist in tumor tissues and circulating blood, miR-29b might be served as predictive biomarkers associated with tumor diagnosis, chemoresistance and prognostic for survival in patients with cancer.

Focusing on the biological regulatory mechanism, current studies show the promising targets for tumor therapy by interfering with the expression of miR-29b, which offers the possibility of using synthetic miR-29b or its inhibitor as a novel treatment for cancer. Strong

evidence was needed by further exploring the mechanisms or miR-29b's biological function as well as their clinical implications in cancer.

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