
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 specifics 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-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 tumors 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 acutemyloid 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). Coincidently, 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 αoLDL-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).

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

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Target gene</th>
<th>Biological function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder urothelial carcinoma (BUC)</td>
<td>transcription factors (PAX3, PAX7, HOXA10, FOXO1, E2F1, ETF7, YY1, MYC)</td>
<td>cell cycle, apoptosis</td>
<td>(Xu et al., 2013b)</td>
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<tr>
<td>Breast carcinoma</td>
<td>DNMT3b</td>
<td>DNA methylation</td>
<td>(Sandhu et al., 2014)</td>
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<tr>
<td></td>
<td>MMP-2</td>
<td>invasion and metastasis</td>
<td>(Zhao et al., 2012)</td>
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<tr>
<td>Colorectal carcinoma (CRC)</td>
<td>CIQTNF6, SPARC, COL4A2</td>
<td>onset and migration</td>
<td>(Tian et al., 2013)</td>
</tr>
<tr>
<td></td>
<td>MMP-2</td>
<td>metastasis</td>
<td>(Pekarsky et al., 2006)</td>
</tr>
<tr>
<td></td>
<td>Tiam1</td>
<td>proliferation, metastasis</td>
<td>(Wang et al., 2014)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>IFN-γ, STAT-1</td>
<td>regulation of immune</td>
<td>(Schmitt et al., 2012)</td>
</tr>
<tr>
<td>Endometrial adenocarcinoma</td>
<td>insulin growth factor 1 (IGF1)</td>
<td>invasion</td>
<td>(Hiroki et al., 2010)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>~</td>
<td>~</td>
<td>Espinosa-Parrilla et al., 2014</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>~</td>
<td>~</td>
<td>Zheng et al., 2013</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>Snail, TGF-β, MEK/ERK, SPARC</td>
<td>angiogenesis, invasion, cell-cycle, cell-cycle proliferation</td>
<td>(Grant et al., 2014)</td>
</tr>
<tr>
<td></td>
<td>Src, inhibitor of DNA binding/differentiation 1 (ID1)</td>
<td>invasion, metastasis</td>
<td>(Rothschild et al., 2012)</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>TGFIβ1, ID1</td>
<td>apoptosis, DNA methylation</td>
<td>(Wang et al., 2012b)</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>PTEF, MAPK4, IGF1</td>
<td>apoptosis</td>
<td>(Dai et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>MUC1, DNMT1, DNMT3a, DNMT3b</td>
<td>apoptosis</td>
<td>(Dai et al., 2012)</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>ZNF217, IP07, VEGF-A, hnRNP-K</td>
<td>apoptosis, RNA metabolism</td>
<td>(Szczurek et al., 2013)</td>
</tr>
<tr>
<td></td>
<td>Snail</td>
<td>invasion, metastasis</td>
<td>(Ru et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>MMP-2</td>
<td>invasion, metastasis</td>
<td>(Steele et al., 2010)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>NF-xB, YY1</td>
<td>cell differentiation</td>
<td>(Wang et al., 2008)</td>
</tr>
<tr>
<td>Cholangiocysts/cholangiocarcinoma</td>
<td>McI-1</td>
<td>apoptosis</td>
<td>(Mort et al., 2007)</td>
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<td>Renal cell carcinoma</td>
<td>~</td>
<td>~</td>
<td>(Wotschofsky et al., 2012)</td>
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<td>Head and neck carcinoma</td>
<td>~</td>
<td>~</td>
<td>(Nurul-Syakima et al., 2011)</td>
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<td>Thyroid carcinoma</td>
<td>SMAD3</td>
<td>proliferation and differentiation</td>
<td>(Leone et al., 2012)</td>
</tr>
<tr>
<td>Uterine leiomyoma</td>
<td>~</td>
<td>~</td>
<td>(Qiang et al., 2014)</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>McI-1</td>
<td>apoptosis</td>
<td>(Sengupta et al., 2008)</td>
</tr>
<tr>
<td>Hypopharynx cancer</td>
<td>~</td>
<td>apoptosis</td>
<td>(Xu et al., 2013a)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>McI-1</td>
<td>apoptosis</td>
<td>(Aladaz et al., 2013)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia (CML)</td>
<td>~</td>
<td>apoptosis</td>
<td>(Cortez et al., 2010)</td>
</tr>
<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>ABL1, BCR/ABL1</td>
<td>Proliferation, apoptosis</td>
<td>(Li et al., 2013)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>~</td>
<td>apoptosis</td>
<td>(Garzon et al., 2009)</td>
</tr>
<tr>
<td></td>
<td>NMTI1, DNMT3A, DNMT3B, SP1</td>
<td>apoptosis</td>
<td>(Mims et al., 2013)</td>
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</table>

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

Proliferation is related to the cell cycle control. As we know, CDK6 is an important cycle regulator 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...
of PDPN and inhibit invasion, apoptosis, and proliferation of glioblastomas (Cortez et al., 2010). The miR-29b has 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 cysteiny1 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 cholangiocytic/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). Futhermore, miR29b upregulated p53 expression and promoted apoptosis by directly controlling MCL1 and repressing PIK3R1 (p85a) 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 sites 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 TGFβ1-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 microRNA-29b: an Emerging Player in Human Cancer

Inhibiting Tumor Invasion and Metastasis

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which offers the possibility of using synthetic miR-29b therapy by interfering with the expression of miR-29b, current studies show the promising targets for tumor tissues and circulating blood, miR-29b might be served as predictive biomarkers associated with tumor prognosis. On the base of the facts that miRNAs exist in 29b is associated with tumor stage, tumor metastasis and many different types of cancer, and the dysregulatedmiR-

### 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 dysregulatedmiR-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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