The miR-29 family: genomics, cell biology, and relevance to renal and cardiovascular injury

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Submitted 29 September 2011; accepted in final form 28 December 2011

Kriegel AJ, Fang YL, Ding X, Liang M. The miR-29 family: genomics, cell biology, and relevance to renal and cardiovascular injury. Physiol Genomics 44: 237–244, 2012. First published January 3, 2012; doi:10.1152/physiolgenomics.00141.2011.—The human miR-29 family of microRNAs has three mature members, miR-29a, miR-29b, and miR-29c. miR-29s are encoded by two gene clusters. Binding sites for several transcriptional factors have been identified in the promoter regions of miR-29 genes. The miR-29 family members share a common seed region sequence and are predicted to target largely overlapping sets of genes. However, the miR-29 family members exhibit differential regulation in several cases and different subcellular distribution, suggesting their functional relevance may not be identical. miR-29s directly target at least 16 extracellular matrix genes, providing a dramatic example of a single microRNA targeting a large group of functionally related genes. Strong antifibrotic effects of miR-29s have been demonstrated in heart, kidney, and other organs. miR-29s have also been shown to be proapoptotic and involved in the regulation of cell differentiation. It remains to be explored how various cellular effects of miR-29s determine functional relevance of miR-29s to specific diseases and how the miR-29 family members may function cooperatively or separately.

microRNA; kidney; heart

GENOMIC ORGANIZATION

The gene encoding the precursors of miR-29b-1 and miR-29a is located on chr. 7q32.3 in human, while the gene encoding miR-29b-2 and miR-29c is on chr. 1q32.2. The sequences encoding the two microRNAs in each cluster are separated by <1 kb (11, 21, 61). RACE and RT-PCR analyses have confirmed that miR-29b-1 and miR-29a are transcribed together as a polycistronic primary transcript (11, 61). Likewise, miR-29b-2 and miR-29c are transcribed together (Fig. 1B). Both primary transcripts are transcribed from the [+] strand, with miR-29b-1 and miR-29b-2 being upstream of miR-29a and miR-29c, respectively.

Human miR-29b-2 and miR-29c are encoded by the last exon of the miR-29b-2/c primary transcript (GenBank accession numbers: EU154351 and EU154352) (11). In contrast, the precursors of miR-29b-1 and miR-29a are processed from the last intron of the primary transcript EU154353 (11) (Fig. 1B). A study informed by an expressed sequence tag (BI768447) identified a new splice variant indicating that the precursors of miR-29b-1 and miR-29a can be generated from the last exon of a different primary transcript (GU321462) (61). Cell type and other factors may determine which splicing pattern dominates. While both intronic and exon coding will eventually yield mature miR-29b and miR-29a, the alternative splicing may influence the regulation of the expression of these microRNAs.

The genomic organization of miR-29 genes in rodents is less well characterized but appears to share many characteristics of the human genes, including the gene clusters. For example, rat...
REGULATION OF MIR-29 EXPRESSION

Transcriptional Regulation

Like most microRNAs and mRNAs, miR-29s are transcribed by RNA polymerase II. Recent studies have identified several critical cis elements in the proximal region of miR-29 gene promoters (Fig. 2A). Chromatin immunoprecipitation analysis has identified strong myc binding in the vicinity of the transcription start site of both miR-29b-1/a and miR-29b-2/c clusters (11, 61). Other studies have confirmed additional transcriptional factor binding sites including a Gli binding site at -561, 110, and +134 in the human miR-29b-1/a promoter (61); a Smad3 binding site in a highly conserved region -22 kb upstream of miR-29b-2 (72); at least one Yin-Yang-1 (YY1) binding site in the miR-29b-2/c promoter (92); a CEBP binding site located at +15 to +29 bp immediately downstream of the miR-29b-1/a transcription start site (21); and two TCF/LEF binding site within the proximal promoter of miR-29b-1/a (33).

In addition to the presence of these binding sites, miR-29 expression has been shown to be regulated by various transcriptional regulators and signaling pathways. Kapinas et al. (33) reported that miR-29a transcription was regulated by Wnt signaling, which is important in human osteoblast differentiation. aberrant expression of miR-29s, resulting from dysregulation of signaling pathways, contributes to the development of disease processes. For example, NF-κB plays a central role in the regulation of myoblasts proliferation and differentiation in part by regulating the YY1-miR-29 negative regulatory circuit. Constitutive activation of NF-κB-YY1 pathway in rhabdomyosarcoma suppresses miR-29b/c. As a result, the uncontrolled YY1 level promotes tumor development (92). In cholangiocarcinoma cells, activation of c-myc, hedgehog, and TLR/NF-κB signaling pathways suppresses the miR-29b-1/a promoter activity (61). Other factors, such as CCAAT/enhancer binding protein alpha (CEBPA), may activate miR-29 expression. Loss of the activation by CEBPA in acute myeloid leukemia leads to silencing of miR-29b (21). Developmental changes and cell type-specific distribution of miR-29 expression, such as that reported in the murine lung (18), further support the presence of dynamic regulation of miR-29 expression.

Posttranscriptional Regulation

It appears that the three mature miR-29s may be regulated by distinct mechanisms in some cases, even though they are cotranscribed in two primary transcripts. For example, miR-29a is constitutively expressed in HeLa cells, while miR-29b exhibits low-level expression, with rapid degradation, except for during mitosis (29). miR-29c is not expressed at any
significant level. In the renal medulla of the Dahl salt-sensitive (SS) rat and a consomic rat strain derived from it, miR-29a appears to be more abundant than miR-29b and miR-29c and the three miR-29s respond differently to 3 days of a high-salt diet (53).

The molecular mechanism underlying differential regulation of miR-29 family members remains to be further explored. Posttranscriptional processing or stability of mature miR-29s may contribute importantly to the observed differential regulation. Utilization of alternative promoters could also play a role. Pulse-chase analysis in HeLa cells indicated that miR-29b and miR-29c mimics were degraded faster than miR-29a mimic. Mutational analysis suggested that the rapid decay of miR-29b might involve uracil at nucleotide positions 9–11 (102).

Subcellular Distribution: Nucleus vs. Cytoplasm

In an elegant study by Hwang et al. (29), it was discovered that in HeLa cells different miR-29s have distinctly different subcellular localization. miR-29a is primarily localized to the cytosol with some nuclear presence. In contrast, miR-29b is significantly enriched in the nucleus (29). The six nucleotides on the 3′-end of miR-29b were found to be required for nuclear localization. Mutations within this region impaired nuclear localization of exogenously delivered miR-29b oligonucleotides, while other internal deletion mutations do not prevent nuclear localization. Furthermore, the importance of this six-nucleotide sequence was evident when addition to the 3′-end of an unrelated siRNA induced its nuclear enrichment (29).

The nuclear localization of miR-29b is intriguing, but not unique. Recently deep sequencing of small RNAs in nuclear and cytoplasmic fractions of human nasopharyngeal carcinoma cells found that most mature miRNAs are imported into the nucleus to some degree (51). However, it is also clear that several miRNAs, including miR-29b, are actually enriched in the nucleus. In this analysis miR-29b had a 4.54-fold higher abundance in the nucleus than in the cytoplasm. Only miR-32 and miR-148 were enriched to a greater extent. This analysis also detected miR-29c, finding that it was enriched 2.84-fold in the nucleus (51). Cytosolic and nuclear miRNAs may interact with different proteins and elicit different biological effects that remain to be elucidated.

CELLULAR EFFECTS

Regulation of Extracellular Matrix

An exciting possibility that we and others have postulated is that a microRNA may have significant impact on a functional phenotype by regulating multiple genes that fall into the same or related pathways (47). The regulation of extracellular matrix by the miR-29 family is a dramatic example of a single microRNA family regulating a large set of functionally related genes. Our laboratory and other investigators have collectively shown that miR-29 family members target at least 16 genes related to extracellular matrix. These genes code for several of the key proteins involved in the physiological or pathological formation of extracellular matrix, including a large number of collagen isoforms, laminin γ1, fibrillin 1, elastin, matrix metalloproteinase 2, and integrin β1 (46, 53, 78, 88) (Fig. 2B).

The interaction between miR-29s and mRNAs encoding these extracellular matrix genes has been shown in many cases to be mediated by seed region binding in the 3′-untranslated region (UTR) (53). Bioinformatic analyses, primarily using TargetScan with support from PicTar and in some cases miRanda, indicate that the 3′-UTRs of 20 collagen genes contain predicted, conserved binding sites for miR-29s (53). The large number of collagen isoforms as predicted targets of miR-29s is not because of any extensive sequence homology among 3′-UTRs of collagen isoforms. Instead, the phenomenon is unique to miR-29s because no other miRNA was predicted to target more than 11 of the 20 collagen genes (53). Targeting by miR-29s often results in decreases of mRNA abundance of extracellular matrix genes, suggesting the effect of miR-29s on these target genes is at least in part mediated by decreasing mRNA stability. Analysis of target mRNA abundance is a viable approach for studying cellular effects of miR-29s in this case. Analysis of target proteins or proteomes (37, 86) would be physiologically more relevant but technically more challenging.

The regulation of extracellular matrix by miR-29s has been implicated in the development of fibrosis in many organs including heart (88), kidney (53, 72), lung (67), and liver (75, 77), as well as systemic sclerosis (59). Interestingly, it has been suggested that miR-29b can also prevent liver fibrosis by blocking activation of hepatic stellate cells through cell arresting mechanisms (77). Transforming growth factor (TGF)-β, an important transcriptional stimulator of many extracellular matrix genes (40, 44, 63, 85), may be an important factor that downregulates miR-29s in fibrotic conditions including in renal epithelial cells (20, 72), human fetal lung fibroblasts (18), and human trabecular meshwork cells (57). The relevance of miR-29 regulation of extracellular matrix to tissue fibrosis will be discussed in detail later in this article.

Regulation of Cell Proliferation, Differentiation, and Apoptosis

The importance of miR-29s in the regulation of cell proliferation, differentiation, and apoptosis is best illustrated by the role of miR-29s in cancer. miR-29s apparently serve as tumor suppressors in several cases, although they could be oncogenic in some cases. Downregulation of miR-29 family members has been correlated with many types of cancer including leukemia (9, 25, 26, 71), melanoma (64), and liver (96), colon (17), cervical (45), and lung (99) cancer. In many studies downregulation of miR-29 correlated with more aggressive forms of cancer or relapse (9, 71, 104), suggesting therapeutic restoration of miR-29 may improve disease prognosis. A beneficial effect of exogenous miR-29a and miR-29b treatment has been demonstrated experimentally in acute myeloid leukemia. Induced expression of miR-29a and miR-29b slowed cell growth and induced apoptosis of leukemia cells in vitro and exogenous delivery of miR-29b to xenografted K562 cell tumors was effective in reducing their size (26).

One of the mechanisms by which miR-29s suppress tumor growth is by relieving the suppression of p53. The p53 transcription factor is important in controlling expression of genes that regulate cell growth, senescence, apoptosis, and genome integrity in response to stress (2, 39, 74, 90, 91). Suppression or inactivation of p53 is a common characteristic in many types
of cancer (28, 66, 84, 93). All three miR-29 family members can target p85α and CDC42, genes that normally suppress p53 expression (68) (Fig. 2B).

Several miR-29 targets are oncogenes or anti-apoptotic genes (Fig. 2B). It has been suggested that loss of miR-29 regulation of Tcf1-1 facilitates the upregulation of Tcf1-1 observed in aggressive B-chronic lymphocytic leukemia (71). The Tcf1-1 proto- oncogene is an important coactivator of Akt, mediating antiapoptotic signaling in B and T cells (41, 70). Another important miR-29 family target, whose regulation would impact malignant cell survival, is the Gcl-2 family member, Mcl-1 (60, 96). Mcl-1 is an antiapoptotic protein that is overexpressed in acute myeloid leukemia (35). Expression of the oncogene CDK6, targeted by all miR-29 family members, is required for cell cycle to progress into S-phase (104). Other mechanisms possibly underlying the tumor-suppressive effect of miR-29s include regulation of aberrant DNA methylation by targeting DNA methyltransferases 3A and 3B (22, 26), promotion of proper myoblast differentiation but not rhabdomyosarcomaogenesis by targeting YY1 (92), modulation of immunomodulatory molecule B7-H3 to suppress the immune escape by solid tumors (97), suppression of interferon γ (58), and targeting B-Myb that is involved with cell proliferation and apoptosis (1, 31). In HPV-mediated cervical cancer restoration of miR-29a and miR-29b expression might aid in preventing malignant transformation of cervical cells by blocking the cell cycle at G1 and facilitating apoptosis through regulation of YY1 and CDK6 (45). Interestingly, loss of the regulation of extracellular matrix by miR-29s, besides its major effect on fibrosis, may also contribute to cancer cell migration and metastasis. For example, the downregulation of miR-29c in nasopharyngeal carcinomas might contribute to the metastatic tumor invasion through reduced regulation of extracellular matrix targets or related proteins (78).

Upregulation of miR-29s has also been shown to occur in some types of cancer. In breast cancer the miR-29a upregulation may induce malignancy by suppression of tristetraprolin (27). Moreover, miR-29 transgenic mice develop an indolent B-cell chronic lymphocytic leukemia phenotype (69, 76).

miR-29s may also contribute to normal tissue differentiation (Fig. 2B). In a cell model of myogenic differentiation, upregulation of miR-29a can attenuate the inhibitory action of TGF-β on myogenesis through targeting HDAC4, a key inhibitor of muscle differentiation (95). Derepression of miR-29 was shown to accelerate skeletal myogenesis by targeting its repressor YY1 (92). miR-29s regulate osteoblast differentiation targeting antiosteogenic factors and extracellular matrix proteins (46) as well as Wnt signaling antagonists (33).

RELEVANCE TO CARDIOVASCULAR AND RENAL PHYSIOLOGY AND DISEASE

Heart

In 2008, van Rooij et al. (88) reported a reduction in expression of all three miR-29 isoforms in the areas bordering the infarcted myocardium in mice and miR-29b in human samples. Upon further analysis it was determined that cardiac fibroblasts were the primary cell type responsible for miR-29 expression in the heart. Additionally, treatment of isolated mouse cardiac fibroblasts with TGF-β reduced expression of miR29a, miR-29b, and miR-29c (88). It has been known for some time that TGF-β is important for stimulating cardiac fibrosis (6). Knockdown of miR-29 family members relieves the suppression of many targeted extracellular matrix genes involved with fibrogenesis both in vivo and in vitro (88, 100). Cardiac pressure overloading and chronic calcineurin signaling have also been shown to reduce miR-29c expression in animal models (88, 89), while miR-29b is downregulated in end-stage dilated cardiomyopathy (62). In dilated cardiomyopathy the left ventricle is dilated and becomes more compliant while the activity of extracellular matrix degrading matrix metalloproteinase increases (7, 12, 82, 87). Matrix metalloproteinase 2 is a confirmed miR-29b target (53). In total, these studies indicate that expression of miR-29 family members may be important for regulating extracellular matrix expression during pathological remodeling in cardiac tissue.

Soci et al. (80) showed that an intensive exercise protocol upregulated miR-29c and reduced expression of several extracellular matrix genes. They found ventricular compliance was increased. This study suggests that expression of miRNAs can be altered beneficially under physiological conditions (80).

Other studies indicate that suppression of miR-29 genes may be ineffectual, or even cardioprotective, in some contexts. The miRNA expression patterns in response to treatment of adult cardiac fibroblasts with angiostatin II revealed an upregulation of miR-29b, which was mediated through the angiostatin II type 1 receptor (30). It would be interesting to see if the upregulation of miR-29b contributes to the injurious effects of angiostatin II or represents a compensatory response. Another study reported that in vivo suppression of miR-29a and miR-29c protected hearts from ischemia reperfusion injury (100, 101).

Kidney

An important role of miR-29b in renal injury was identified in our studies of the Dahl SS rat (53). The SS rat is a well-established model of human common, salt-sensitive forms of hypertension and renal injury (14, 15, 73). The consomic SS.13BN rat, in which chromosome 13 of the SS genome has been replaced by chromosome 13 from the Brown Norway (BN) rat, exhibits substantially attenuated hypertension and renal injury (16, 48, 50, 56). We found that miR-29b in the...
renal medulla was upregulated by 3 days of a high-salt diet much more in SS.13BN rats than in SS rats. In vivo knockdown experiments in SS.13BN rats using intravenous administration of locked nucleic acid-modified anti-miR and extensive in vitro experiments showed that miR-29b targeted several extracellular matrix genes (Col1a1, Col3a1, Col4a1, Col5a1, Col5a2, Col5a3, Col7a1, Col8a1, Mmp2, and Itgβ1) and likely contributed to the protection against interstitial fibrosis in the SS.13BN rat (53).

Further evidence for renoprotective effects of miR-29s in renal fibrosis was reported in a study of a mouse model of obstructive nephropathy (72). Severe tubulointerstitial fibrosis was associated with reduced expression of miR-29s. Overexpression of miR-29b attenuated renal fibrosis in this model. Study of cultured renal tubular cells showed that miR-29b was downregulated by TGF-β1 via Smad3 (42, 72). Studies in our laboratories showed that miR-29c was downregulated in a rat model of progressive renal failure and in patients with renal interstitial fibrosis and was restored by renoprotective treatments in the rat model (unpublished data).

Long et al. (54) found that miR-29c was upregulated in glomeruli from db/db mice and in kidney microvascular endothelial cells and podocytes cultured in high ambient glucose. Systemic treatment with 2′-O-methyl-modified antisense complementary to the mature miR-29c sequence reduced albuminuria and mesangial matrix accumulation in db/db mice. The injurious effect of miR-29c was associated with proapoptotic effects of miR-29c on cultured podocytes and targeting of Sprouty homolog 1. This is reminiscent of the well-established proapoptotic effect of miR-29s in cancer cells. In cultured HK-2 cells, a human kidney epithelial cell line, high glucose was reported to upregulate miR-29a, which might contribute to upregulation of collagen IV expression (20).

Vasculature and Circulation

Upregulation of miR-29 has been reported to play an important role in suppressing elastin and other extracellular matrix genes during aortic development in the mouse (65). The study further indicated that a change from TGF-β signaling to Wnt signaling during aortic development may be related to the changes in miRNA expression and mRNA expression that occur. miR-29 expression levels in the aorta continue to be important after development. An investigation of miRNA expression in human experiencing aortic dissection revealed a downregulation of miR-29a and miR-29c, which may play a role in pathological extracellular matrix expression and focal adhesion (52). Boon et al. (5) reported that the miR-29 family members were upregulated in the aorta in aged mice and mouse models of aortic aneurysms as well as in biopsies of human thoracic aortae. Knockdown of miR-29 attenuated angiotensin II-induced dilation of the aorta in mice. The anti-miR oligonucleotides used in this study matched nucleotide numbers 2–17 of miR-29b and miR-29c but had a mismatch with miR-29a at nucleotide number 10. However, all three miR-29s were shown to be efficiently knocked down by the anti-miR at the dosages used (5).

All three miR-29 family members have also been found to regulate the important clotting factor fibrinogen (24). Elevated fibrinogen levels have been associated with cardiovascular disease (19, 23, 32, 83, 94) and even reduced systolic function in otherwise healthy individuals (98). Fibrinogen is produced in the liver, where miR-29 family downregulation has been associated with fibrosis and disease (75). Perhaps the downregulation of miR-29 in the liver may impact the cardiovascular system indirectly by relieving the suppression of fibrinogen.

Patients with cirrhotic livers have lower miR-29 expression in the tissue, as well as lower circulating miR-29a (75). Levels of miR-29b have been found to be higher in the plasma of smokers (13). While it has not been determined if these circulating miRNAs would be capable of effecting gene expression in end organs, circulating miRNAs may have diagnostic or prognostic values.

FUTURE DIRECTIONS

Recent progress in the understanding of the miR-29 family is beginning to paint a clear picture in which miR-29s play potent antifibrotic and proapoptotic roles in several disease processes (Fig. 3). The antifibrotic effect of miR-29s fits the observation that miR-29 expression is downregulated by TGF-β1, a key profibrotic factor. This, however, does not rule out the possibility that miR-29s could participate in other biological pathways. In fact, members of the miR-29 family exhibit highly diverse characteristics in the regulation of their expression and subcellular localization, suggesting complex functions of miR-29s that are likely to be isoform and tissue specific.

Several important questions regarding the biology and disease relevance of miR-29s should be addressed in future studies (Fig. 3). It will be important to further explore the mechanisms underlying the differential regulation of expression and subcellular localization of miR-29 family members, as well as physiological and disease implications of such differential regulation. Strong evidence exists for antifibrotic and proapoptotic effects of miR-29s. It will be important to understand how these effects of miR-29s, and perhaps other cellular effects of miR-29s that are currently less appreciated, manifest in specific physiological or disease contexts. Finally, potential diagnostic and therapeutic values of miR-29s remain to be examined or established.

GRANTS

This work was supported by US National Institutes of Health Grants HL-085267, DK-084405, HL-082798, and HL-029587, a Clinical and Translational Science Institute grant (to M. Liang), and National Natural Science Foundation of China Grants 30871176 and 30971374 (to X. Ding).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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Physiol Genomics • doi:10.1152/physiolgenomics.00141.2011 • www.physiolgenomics.org


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