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Review Article

miR-145-mediated suppression of cell growth, invasion and metastasis

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Abstract: MicroRNAs are a large group of negative gene regulators that work through a posttranscriptional repression mechanism. Evidence indicates that microRNAs play a fundamental role in a wide range of biological functions such as cellular proliferation, differentiation and apoptosis. In cancer, microRNAs may function as tumor suppressors and oncogenes, and therefore, they are referred to as 'oncomiRs'. In support of this notion, we have shown that miR-145 is underexpressed in tumor tissues and is capable of inhibiting tumor cell growth and invasion by targeting several genes such as c-Myc and mucin 1. This unique feature of miR-145-mediaed gene silencing may suggest that miR-145 is a potential cancer biomarker and serves as a novel target for cancer therapy.

Keywords: miR-145, microRNAs, negative gene regulators, suppression, repression, cancer, cell growth, invasion, metastasis

Introduction

It is well known that gene expression is tightly controlled to exert a variety of cellular functions. Evidence has indicated the importance of epigenetic and post-translational modifications in controlling gene expression [1]. Moreover, newly discovered microRNAs have added another layer of control to this complex gene regulatory network. With their discovery back in 1993 in *C. elegans* [2], and later in humans [3], microRNAs have been shown to regulate diverse cellular processes. It has been estimated that 30% of the human genes are under regulation of microRNAs, making them most abundant class of regulatory molecules [4].

MicroRNAs are small non-coding RNA molecules, 20-22 nucleotides; they are generally transcribed by RNA polymerase (Pol II) as primary transcripts, i.e., pri-microRNAs, which are then cleaved to produce stem-loop structured precursors (pre-microRNAs) of ~100 nucleotides (nt) in length by the nuclear RNase III enzyme Drosha [5]. The pre-microRNAs are then exported to the cytoplasm by exportin-5 [6], where the RNase III enzyme Dicer further processes them into mature microRNAs (~22 nt). One strand of the microRNA duplex is subsequently incorporated into the RNA-induced silencing complex (RISC) that mediates gene suppression through mRNA degradation or translation repression [7].

As master gene regulators, microRNAs have been shown to be involved in regulating various cellular processes, such as cell cycle [8; 9], proliferation [10], apoptosis [11, 12], differentiation [13, 14] and development [15] by targeting multiple protein-coding genes through partial base pairing to the 3'-UTR of the target gene [16, 17]. Deregulation of microRNA expression has been reported in a variety of human diseases, in particular cancer. The first report in cancer came from the profiling studies on chronic lymphocytic leukemia patients [18]. Both miR-15 and miR-16 were downregulated in patients with B-cell chronic lymphocytic leuke-

mia due to specific deletions on chromosome 13q14 [19]. Further studies indicate that those microRNAs are frequently located at cancer-associated chromosomal fragile sites. It has also been shown that the let-7 family negatively regulates the Ras oncogene [20], and its clinical significance was demonstrated recently by reduction of lung tumors in mice after injecting let -7 through intranasal route [21]. Of particular interest, the tumor suppressor p53 has been shown to transcriptionally activate a number of microRNAs such as miR-34 family and miR-145 [22-24].

On the other hand, several groups have reported the overexpression or amplification of microRNAs that can target tumor suppressor genes, thus functioning as oncogenes. For instance, the miR-17~92 cluster, regulated by c-Myc, serves as an oncogene in lymphoma and lung cancer [25-27]. Another microRNA, miR-155, has been linked to c-Myc overexpression in B-cell cancers and was later shown to be significantly upregulated in pediatric Burkitt lymphoma [25]. Finally, we and others have reported that miR-21 serves as an oncogene; suppression of miR-21 inhibits cell growth and metastasis [28-33].

miR-145 gene organization and its regulation

miR-145 was first identified in mice from heart tissue using small RNA cloning techniques [3] and then later reported in human [34], revealing a unique seed sequence that is conserved in Xenopus and mammals. Human miR-145 (hsa-miR-145) is enriched in germline and mesoderm-derived tissues, such as uterus, ovary, testis, prostate, spleen, and heart [35]. miR-145 is located on chromosome 5 (5q32-33) within a 4.09 kb region (http://microrna.sanger.ac.uk). Although the pri-microRNA structure has not been identified, it is suggested to be co-transcribed with miR-143 [36].

Of interest, 5q31.1 is a well-known fragile site in human genome (http://www.genenames.org/) and is deleted in 11% of sporadic breast cancer; this could in part explain the downregulation of miR-145 in some breast tumors. Furthermore, miR-145 and miR-143 are localized close to each other at chromosome 5q32 which is often deleted (e.g., in myelodysplastic syndromes) [37]. A recent report supports this notion in patients with 5-q syndrome [38] because deletion of chromosome 5q correlates with loss of two microRNAs (miR-145 and miR-146a) that are frequent in hematopoietic stem/progenitor cells (HSPCs). To determine the effect of genetic alterations on microRNA expression, Harber *et al.*, sequenced 90 cancer cell lines and scrutinized for mutations in microRNA sequences [39]. They found no mutation in mature microRNA sequence although there are several mutations in pre- and pri-microRNA sequences. For example, OVCAR8 (ovary) and NCI-H727 (lung) cells harbored a mutation in pri-miR-145, i.e., C-133A/pri microRNA/homozygous and G-5R (G/A)/pri-microRNA/heterozygous, respectively. However, this mutation does not seem to have any effect on microRNA processing and thus low expression of miR-145 may not be attributed to genetic aberrations.

Transcriptional and posttranscriptional regulation could play an important role in miR-145 expression. We are the first group to demonstrate the transcriptional induction of miR-145 by p53 in response to stress such as serum starvation or anticancer drugs [24]. Further study indicates that p53 bind to the putative p53 response element in the miR-145 promoter. Similar reports from two different groups [40; 41] confirm this finding in breast and colon cancer cell lines. Interestingly, Suzuki *et al.,* [40] showed that p53-mediated induction of miR-145 is dependent on RNA processing, providing a novel mechanism of posttranscriptional regulation of miR-145. p53 interacts with Drosha processing complex through association with p68 and facilitates the processing of primary transcript of miR-145. Using RNA CHIP analysis, they demonstrated that wild type p53, but not mutant p53, associates between p68 and miR-145, suggesting the possible role of this mechanism in clinical settings. This would shed some light on the downregulation of miR-145 in tumors carrying null or mutant p53. In addition, the miR-145-mediated pro-apoptotic effect appears to be dependent on p53 activation, and p53 activation can, in turn, stimulate miR-145 expression [41]. This may provide a clue as to why expression of miR-145 is low in tumors where p53 is also lost. However, this mechanism cannot explain why miR-145 is downregulated in tumors or cancer cell lines carrying wild type p53, implying other mechanisms involved. In support of this notion, we found that MCF10A cells express a much higher level of miR-145

Table 1. Expression profile of miR-145 in various tumors

Cancer type	expression	Technique used for detection	Fold (p-value)	Authors
Breast	Low	Microarray, Northern blot,	~2.5 (=0.0040)	Iorio *et al.*., 2005
		In-situ hybridization,	-	Sempere *et al.*., 208
		RT-PCR	~ 3 fold(<0.01)	Sachdeva *et al.*., 2009.
Colon	Low	Small RNA cloning,	-	Michael *et al.*.,2003,
		Northern blot,	~4 fold	Bandres etal.,2006,
		RT-PCR	~5 fold(<0.01)	Schepler *et al.*., 2008, Sachdeva *et al.*., 2009.
Prostate	Low	RT-PCR	(=0.003)	Ozen *et al.*., 2008 [48]
Lung	Low	Northern blot, RT-PCR		Lin xi *et al.*., Izzoti *et al.*., 2009
Liver	Low	Microarray, northern blot, RT-PCR	~2fold(0.0126)	Gramantieri *et al.*., 2007 [49]
Bladder	Low	RT-PCR	~20 fold	Ichimi *et al.*., 2009 [50]
Pituatory	Low	RT-PCR	2 fold(=0.04)	Amaral *et al.*., 2009 [51]
B-cell	Low	RT-PCR	-	Akao *et al.*., 2007
Ovary	Low	Microarray, Northern blot, RT-PCR	-	Iorio *et al.*., 2007, Nam *et al.*., 2008 [52]

than MCF-7 cells although both cell lines express wild type p53.

Downregulation of miR-145 in tumors

Deregulation of microRNAs has been reported in many types of human disorders including cancers. For instance, let-7 has been found to be underexpressed in lung cancer [21] and miR-15/miR-16 in chronic lymphocytic leukemia [42]. In contrast, other microRNAs such as miR-21 are upregulated in variety of tumors [31, 32]. The first report for deregulation of miR-145 in tumors came from a study by Michael *et al.* [34]. Using the small RNA cloning approach, they showed that the total number of clones sequenced for miR-145 were 2 from patients having colon adenocarcinomas compared to 8 from normal tissue, which was confirmed by northern blot analysis. Interestingly, they also found a decreased level of miR-145 in pre-cancerous adenometous polyps, suggesting a possible role in tumor initiation. In addition, there is a general downregulation trend of miR-145 in various colon cancer cell lines. The same trend was also reported in 15 colorectal cancer cell lines [43]. Downregulation of miR-145 in different tumor types are listed in **Table 1**.

In situ hybridization detected accumulation of miR-145 in normal colon epithelia with no signal from adenocarcinomas cells[44; 45]. Consistent with these reports, we found that miR-145 is underexpressed in both breast and colon cancer specimens, compared to matched normal tissue samples [24]. Of interest, this downregulation of miR-145 seems to depend on the type of tissue. For example, we found that the downregulation is more prominent in colon cancer than in breast cancer [24]. Furthermore, miR-145 was progressively downregulated from normal breast to cancer with high proliferative index (p=0.013) [46]. A recent work by Chen *et al.,* also found a ten-fold decrease in miR-145 expression in 13 nasopharyngeal carcinoma patient samples when compared to 9 normal adjacent tissues [47].

miR-145 as a tumor growth inhibitor

The functions of microRNAs in regulating cell growth and proliferation have been well estab-

lished in recent years because they can target genes involved in cell proliferation. Downregulation of miR-145 in different types of tumors suggests its role in controlling cell proliferation, serving as a tumor suppressor. The first report suggesting the tumor suppressive role of miR-145 in colon cancer came from a study by Shi *et al.* [53, 54]. They demonstrated that miR-145 has a profound inhibitory effect on two colon cancer cell lines in vitro model by suppressing insulin receptor substrate-(IRS-1) through binding to its 3'-UTR. Consistent with this finding, miR-145 can also significantly reduce cell growth in B-cell lymphoma cell lines [55].

We demonstrated the tumor suppressive role of miR-145 in colon cancer in a xenograft mouse model [24]. Overexpression of miR-145 not only inhibits growth in both breast and colon cancer cell lines, but also can inhibit tumor growth significantly in orthotopic mouse model. After injecting lentiviral infected stably expressing miR-145 HCT-116 cells subcutaneously in mice, we found that miR-145 bearing tumors grow much slowly compared to vector control, which is more significant than in vitro inhibition. Moreover, flow cytometry analysis revealed that miR-145 can cause the cell cycle arrest at G0-G1 phase and also have a decrease in S-phase, suggesting that the miR-145 expressing cells are less proliferative. This miR-145-mediated inhibition of cell proliferation is likely due to through direct targeting c-Myc oncogene by directly binding to its 3'-UTR. We further confirmed that miR-145 is able to down regulate some of the c-Myc target genes such as cyclin D1 and eIF4E which are involved in cell cycle regulation. In consistent with our results, Akoe *et al.,* also found that the level of miR-145 was inversely correlated to level of c-Myc in B-lymphoma cell lines [55]. Similar results regarding the tumor suppressive role of miR-145 in breast cancer were reported by two different groups. Firstly, Wang *et al.*, have shown that overexpression of miR-145 in MCF-7, a tumorigenic cell line, can cause growth inhibition by inducing apoptosis compared to non-tumorigenic MCF10A which expresses a high level of miR-145 [56]. Secondly, miR-145 can cause a significant inhibition of different breast cancer cell lines expressing wild type p53 [41], which is associated with PARP cleavage and apoptotic death. Moreover, ectopic expressed miR-145 in breast cancer cells can cause upregulation of p53-regulated genes such as PUMA and p21.

Further studies indicate that miR-145 inhibits cell growth in EGFR mutant lung adenocarcinomas [57, 58]. Compared to non-mutant lung adenocarcinomas cells, the EGFR mutant cells revealed 44% and 16% inhibition, respectively, and 45% apoptosis of the miR-145-transfected cancer cells may be correlated with EGFR mutation. Also, in lung cancer cells, miR-145 can suppress cell growth by inhibiting Akt activation [58]. In addition, miR-145 can also sensitize the tumor cells to chemotherapeutic agents such as gifitinib. Tumor suppressive role of miR-145 was also reported in urothelial carcinoma and colon carcinoma respectively [59, 60]. In this regard, miR-145 induces cell death in both caspase-dependent and caspase-independent fashion. These studies identify several miR-145 targets including PPP3CA, CBFB, YES and STAT1, suggesting the function of miR-145 as a tumor suppressor by regulating multiple oncogenesis related genes.

Finally, animal model studies also support the suppressive role of miR-145 in cancer. For example, microRNA microarray analysis from lung cancer models from mice suggests the role of miR-145 in lung cancer because miR-145 was significantly repressed in the cyclin-E transgenic mice compared to normal lungs [45]. Using a rat model, Izzoti *et al.*, reported that rat lungs exposed to environmental cigarette smoke for 28 days can decrease the level of miR-145, implying a role of miR-145 in pathogenecity of smoke-associated cancer [61].

Role of miR-145 in cell invasion and metastasis

It is well known that microRNAs can also impact cell invasion and metastasis. For example, miR-10b indirectly activates the pro-metastatic gene RHOC by suppressing HOXD10 [62], thus leading to tumor invasion and metastasis. Similarly, miR-373 and miR-520c promote tumor invasion and metastasis, at least in part by regulating the gene CD44 [63]. Like many other microRNAs, miR-145 can also impact cell migration and invasion. For example, miR-145 is specifically expressed in pericytes in microvasculature and it inhibits migration of microvascular cells in response to growth factor gradients by directly targeting a transcription factor Fli-1 [64]. To better understand the role of miR-145 in cell invasion and metastasis, we profiled the expres-

sion of miR-145 in different metastatic breast cancer cell lines compared to non-metastatic cell lines, and found that there is an inverse correlation between the miR-145 level and invasiveness. Of interest, miR-145 appears to impact cell growth in a cell type-specific manner. For example, miR-145 suppresses cell growth in non-metastatic MCF-7 cells, however, it has no significant growth inhibitory effect in two metastatic cell lines MDA-MB-231 and LM2-4142; instead, it suppresses their cell invasion ability [65]. This miR-145-mediated suppression of cell invasion is in part due to the silencing of the metastasis gene mucin 1 (MUC1). This finding was supported by luciferase reporters carrying the 3′-UTR of MUC1, Western blot and immunofluorescence staining. We also confirmed by ectopic expression and siRNA knockdown, the ability of MUC1 to promote cell invasion which can be reversed by miR-145. Of interest, suppression of MUC1 by miR-145 causes a reduction of β-catenin as well as the oncogenic cadherin-11. Finally, suppression of MUC1 by RNAi mimics the miR-145 action in suppression of invasion, which is associated with downregulation of β-catenin and cadherin-11. In addition to MUC1, our unpublished data suggest that miR-145 can also target multiple metastasis-related genes including MMP-11 and ADAM-17.

Wang *et al.*, profiled 13,935 coding genes and 273 microRNAs from 62 prostate cancer patients with aggressive phenotype (Gleason grade ≥ 8) and 63 prostate cancer patients with nonaggressive phenotype (Gleason grade ≤ 5) and reported that miR-145 expression was significantly low in samples with aggressive phenotype, suggesting its possible involvement in aggressive phenotype in prostate cancer [66]. miR-145 causes cell growth inhibition and apoptosis, which is possibly through targeting cyclin A2, a gene involved in cell cycle regulation. Interestingly, downregulation of the miR-145 in aggressive prostate cancer is consistent with upregulation of c-Myc in the same sample set which is consistent with our finding that c-Myc is a major target for miR-145.

In contrast, a study from Arndt *et al.*, suggests an oncogenic role of miR-145 in metastatic colon cancer [67]. Although they found a decrease level of miR-145 along with miR-143 in tumor specimens compared to normal tissues, in a metastatic cell line SW620, ectopic expression of miR-145 causes a mesenchymal-like phenotype and ~50% increase in cell proliferation specifically in serum-free medium. It remains to be determined whether this is cell-type specific. However, since the oncogenic effect of miR-145 was observed when cells were grown in serum-free medium, this may suggest that growth factors can affect the miR-145 targeting specificity or efficiency.

miR-145 affects the p53-mediated cell cycle arrest

As discussed above, miR-145 functions a tumor suppressor in cell growth and invasion. This feature may be related to the fact that miR-145 is regulated by p53. It is well known that p53 regulates many pathways; two important pathways are cell cycle arrest and apoptosis. Although our results suggest that suppression of miR-145 alters the p53-mediated cell cycle arrest, which is likely in part through silencing of c-Myc, miR-145 does not seem to have a significant effect on apoptosis in our system. For example, c-Myc knockdown has no effect on Bax level, but p21 level is increased, which is likely due to the fact that c-Myc can suppress p21 by partnering with Miz1 [68]; when c-Myc is reduced, p21 is increased [24]. These results suggest that a lack of miR-145 impairs the p53-induced cell cycle arrest, but has little effect on other p53 activities such as apoptosis, and induction of Bax. Thus, identification of c-Myc as a miR-145 target may explain why miR-145 can synergize the effect of p53-mediated induction of p21 because in addition to its direct effect on the p21 promoter activity, suppression of c-Myc by p53-indcued miR-145 will further relieve the c-Myc repression on p21. More importantly, miR-145 provides a specific control point such that p53 can regulate different pathways depending on the cellular content.

Based these findings, we propose a working model regarding the role of miR-145 (**Figure 1**). Akt controls mitogenic growth pathways. We have shown that while growth factors activate Akt, stress such as serum starvation or PI-3K inhibition suppresses its activity, leading to activation of p53. Similarly, DNA damaging agents such as Doxo can also activate p53 through ATM. As a result, the activated p53 induces miR-145, which subsequently silences c-Myc and its downstream targets including miR-17 and eIF4E, leading to protein synthesis, cell proliferation and tumorigenesis. Although p53 can

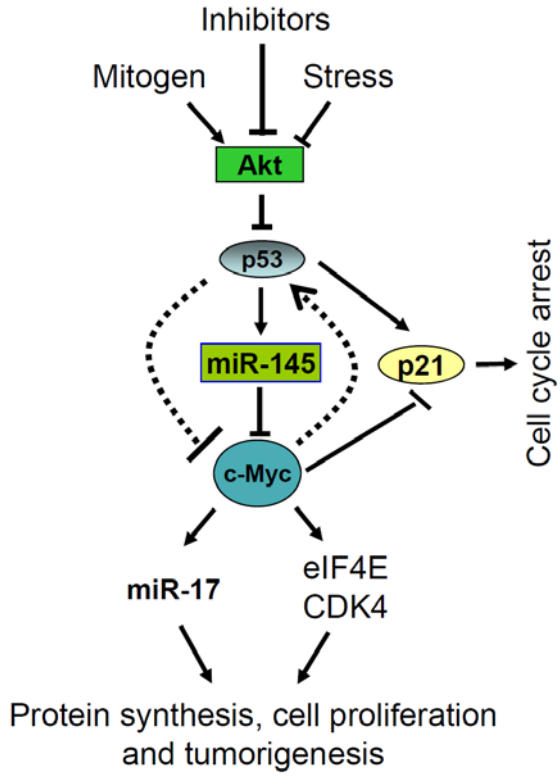

Figure 1. A simplified working model for miR-145 and its function as a tumor suppressor.

repress c-Myc by a transcriptional mechanism [69, 70], our results suggest that miR-145 may play a more important role in this aspect because anti-miR-145 can rescue the vast majority of the p53-mediated repression. In addition to p53-mediated repression, c-Myc can enhance p53 expression through $p19^{Arf}$ [71], which make a feedback loop. Another important function of miR-145 in this regulatory network is to enhance the p53 effect on p21, through which p53 can directly and indirectly induce p21 expression. Therefore, this is complex regulatory system that the cell may use to balance the "yin" and "yang" effect. Interruption of this balance, such as the down-regulation of miR-145, could lead to cell malignancy [72].

miR-145 as a biomarker

Given that microRNAs are often deregulated, they may serve as potential cancer biomarkers. In particular, miR-145 seems to be downregulated in precancerous tissues [34], it may prove to be a biomarker for early detection of cancer. Current diagnosis and staging of various cancers are mainly based on histological examination and radiological imaging, which involves an invasive needle or surgical biopsy. However, recent studies have demonstrated that tumor derived-microRNAs can be detected in blood or serum and are well protected from endogenous RNases [73], and thus, open a new avenue for biomarker discovery. Further studies suggested that more than 100 microRNAs are differentially expressed between normal and tumor patients in blood and their level is sufficient to detect as biomarkers [74; 75]. In support of this notion, Zhu *et al.,* reported that miR-145 can be easily detected in serum samples using qRT-PCR [76] although they did not find any change in expression of miR-145 in their set of breast cancer samples compared to normal samples. It would be interesting to determine whether the circulating miR-145 level changes over the period of cancer development and progression, in particular, along with other relevant circulating microRNAs serves as a microRNA signature for cancer diagnosis.

Of considerable interest, miR-145 may serve a biomarker for other disorders. For example, in blood samples miR-145 level was found highly deregulated in polycythemia Vera [77] and multiple sclerosis (MS) [78]. Moreover, miR-145 is the best single microRNA marker that allows discriminating MS from controls with a specificity of 89.5%, a sensitivity of 90.0%, and an accuracy of 89.7% from blood. Analyzing human bone marrow samples with myelodysplastic syndrome, Starczynowski *et al.* have reported that loss of two hematopoietic stem/progenitor cells specific microRNAs, i.e., miR-145 and miR-146a, strongly correlates with the disease [38]. Although these studies are promising, it is evident that more studies are needed to further evaluate miR-145 as a novel biomarker.

miR-145 in stem cells and differentiation

Although the focus of this review is on cancer, we will also briefly touch on the role of miR-145 in other cellular functions, in particular in stem cell and differentiation which are also linked to cancer development. Pluripotency and self renewal are the two important attributes of embryonic stem (ES) cells which are maintained by group of transcription factors, such as Lin-28, c-Myc, OCT4, SOX2, NANOG and KLF4. A recent

study [79] has shown that miR-145 is induced during differentiation, and it directly silences the stem cell self renewal and pluripotency program. For example, ectopic expression of miR-145 in human ES cells blocks self-renewal while blockade of miR-145 with antisense oligonucleotides increases the self-renewal. Importantly, miR-145 seems to control this process by suppressing multiple targets such as OCT4, SOX2 and KLF4. The downregulation of miR-145 in various cancers as well as the finding that miR-145 suppresses differentiation suggests that miR-145 functions as a pro-differentiation factor. In contrast, Starczynowski *et al.* have found that miR-145 is highly expressed in primitive lin-(mouse) and CD34+ (human) bone marrow cells than committed cells and stable knockdown of miR-145 in these cells in mouse marrow results in 5-q syndrome [38]. It remains to be determined whether this is due to different conditions under which cells were collected and cultured.

The role of miR-145 in differentiation of vascular smooth muscle cell (VSMC) has been recently investigated [36, 80, 81]. It is well known that the switch of VSMCs from a differentiated state to a dedifferentiated state plays an important role in the pathogenesis of atherosclerosis. However, the mechanism involved in these events was unclear. Cheng *et al.*, demonstrated that miR-145 is the most enriched microRNA in arteries and its expression is significantly downregulated in vascular walls with neointimal lesions formation [80]. They further demonstrated that miR-145 level decreases with differentiation of VSMCs, suggesting the role of miR-145 in the formation of atherosclerotic lesions. Finally, using *in vivo* in balloon-injured rat carotid arteries model they further verified the role of miR-145 in modulation of VSMCs. Similarly, Cordes *et al.*, found that miR-145 is highly expressed in multipotent murine cardiac progenitors and also in human stem cells. They demonstrated that miR-145 is necessary and sufficient to induce differentiation of multipotent neural crest stem cells into VSMCs. Using transgenic mouse model with miR-145 promoter fused to β -galactosidase gene, they found that miR-145 is cardiac-specific and smooth-muscle specific microRNA regulated by serum response factor, myocardin and Nkx2-5 (NK2 transcription factor related, locus 5). Gain of function or loss of function studies revealed that miR-145 can direct smooth muscle fate by regulating multiple transcription factors including KLF4, myocardin and elk1, thereby repressing the proliferation of smooth muscle cells and promoting its differentiation. These findings suggest the possible role of miR-145 in suppressing smooth muscle hyperplasia and in vascular injuries/ atherosclerosis. The mouse miR-143/145 cluster expression is confined to SMCs during development [82]. Of interest, miR-145 is required for VSMC acquisition of the contractile phenotype and VSMCs from miR-143/145-deficient mice have lost their contractile abilities, leading to neointimal lesion development which is supported by the evidence that miR-145 targets angiotensin-converting enzyme (ACE), because ACE might affect both the synthetic phenotype and contractile functions of VSMCs. Another line of evidence regarding the expression of miR-145 in smooth muscle cells comes from a study of the miR-43/miR-145 KO rats [83]. This microRNA cluster is expressed mostly in the SMC compartment in vessels and SMC-containing organs during development and postnatally and their loss induces structural modifications of the aorta, because of an incomplete differentiation of VSMCs.

In situ hybridization revealed that miR-145 is selectively expressed in pericytes in microvasculature of smooth muscles of various organs in mice [64]. In Zebrafish miR-145 is strongly expressed in smooth muscle in gut and regulates its development [84]. Loss of miR-145 results in defects of smooth muscle function as determined by increased expression of the embryonic smooth muscle markers sm22b and smoothelin. Furthermore, miR-145 directly represses gata6 *in vitro* and *in vivo* and therefore, plays a critical role in promoting the maturation of both layers of the gut during development through regulation of gata6.

In contrast, a recent study from Xin *et al.*, suggests a different regulation of smooth muscle cells by miR-145 [85]. miR-145 has no effect on proliferation and differentiation of smooth muscle cells, paradox to previous studies, however, in mice lacking miR-143 and miR-145, the formation of normal actin stress fibers is disturbed and SMCs do not form a neointima in response to injury. The miR-145 mutant mice display a significant reduction in blood pressure, which is likely due to their lack of a mature actin cytoskeleton, diminishing vascular rigidity in SMCs.

Perspective

MicroRNAs are a large group of negative gene regulators that have been shown to control a wide range of biological functions. Overwhelming evidence indicates that microRNAs are deregulated in many types of cancers, and they function as either oncogenes or tumor suppressors. We and others have shown that miR-145 is a tumor suppressor; it inhibits not only tumor growth, but also cell invasion and metastasis by targeting multiple cancer related genes. This unique feature of miR-145 targeting may suggest that miR-145 is a novel therapeutic target for cancer therapy. Given that efficient therapeutic can be achieved by injecting let-7 through intranasal route [21], it would be interesting to explore the similar approach for miR-145 as a therapeutic agent. In addition, microRNAs have been shown to serve as potential cancer biomarkers. In this regard, we expect that miR-145 as a tumor suppressor may prove to be a valuable biomarker for cancer diagnosis/prognosis.

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