Asian Biomedicine Vol. 7 No. 1 February 2013; 3-14 DOI: 10.5372/1905-7415.0701.145

Review article

MicroRNAs: potential regulators of airway smooth muscle cell plasticity involved in asthma-induced airway remodeling

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Background: Airway remodeling, which is fundamentally disordered in asthma, is related to the severity of asthma and poor response to current therapies. During airway remodeling, airway smooth muscle cells are not simply target cells, but participate actively in enhancing airway remodeling through changes induced by cellular plasticity.
Objective: We indicated that microRNAs, a class of regulatory non-coding RNAs, could regulate cellular plasticity at the posttranscriptional level. Here, we discuss the roles of microRNAs as regulators of plasticity in airway smooth muscle cells and possible mechanisms by which microRNAs modulate airway.
Methods: We conducted a literature search using the MEDLINE (PubMed) databases using the keywords "asthma", "microRNAs", "airway remodeling", and "cellular plasticity". Only articles published in English were included in the review.
Results: MicroRNAs, which regulated cellular plasticity in airway smooth muscle cells, was shown to modulate airway remodeling in asthma through different mechanisms.
Conclusion: MicroRNAs can be expected to be developed into a novel treatment strategy for reversing airway remodeling in patients with asthma.

Keywords: Airway remodeling, asthma, cellular plasticity, gene regulation, MicroRNA

Abbreviations
ASM = airway smooth muscle
AGO = Argonaute
C19MC = chromosome 19 miRNA cluster
DGCR8 = DiGeorge syndrome critical region gene 8
hnRNP A1 = heteronuclear ribonucleoprotein A1
miRNAs = microRNAs
PACT = RNA-dependent protein kinase
pre-miRNA = precursor miRNA
pri-miRNAs = primary miRNAs
RISC = RNA-induced silencing complex
SMC = smooth muscle cell
SM-MHC = smooth muscle myosin heavy chain
snoRNA = small nucleolar RNA
TRBP = trans-activator RNA binding protein
TDP-43 = TAR DNA-binding protein-43
3′-UTR = 3′-untranslated region

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Airway remodeling, a key feature of asthma, involves a complex array of changes in the composition and organization of the airway wall [1, 2]. It is related to the severity of asthma and responds poorly to current therapies. The pathologic features of airway remodeling include sub-epithelial fibrosis, airway smooth muscle (ASM) hypertrophy/hyperplasia, angiogenesis, and edema, among others [3]. Airway remodeling is fundamentally disordered in asthma, but the exact mechanisms leading to the disorder are not clear. While extensive studies have shown that some aspects of airway remodeling in asthma are a consequence of persistent inflammation [4, 5], this is not considered the only cause of airway remodeling. Further studies have indicated that the induction of cellular plasticity in ASM cells contributes actively to enhancing airway remodeling and the difficulty in the control of severe asthma [1, 6-8]. Pharmacological reversion of ASM cell plasticity is beneficial for the treatment of airway remodeling in cell culture models of asthma, as well, further indicating that plasticity in ASM cells is critically involved in asthma-induced airway remodeling [9].

Cellular plasticity refers to the alterations in function and phenotype mediated by changes in the expression of phenotype-specific proteins in response to unique environmental conditions. The initial investigations of the mechanisms regulating cellular plasticity focused mainly on kinases and transcription factors. In recent years, however, basic studies have revealed that microRNAs (miRNAs) are key regulators of gene expression, exhibiting a level of molecular control that differs from the well-accepted regulatory role of signaling pathways mediated by kinases and transcription factors [10, 11]. In some cell types, the activity of a single miRNA appears to dominate over other miRNAs, determining the complex characteristics developed by the cells during cellular development [12]. Recent studies have suggested that miRNAs are involved in regulating ASM cell plasticity and airway remodeling. Thus, to better understand airway remodeling in asthma, we will focus on the contributions of miRNAs in ASM cell plasticity and discuss their roles in airway remodeling of asthma in this review.

A general overview of human MiRNAs

MiRNAs are small, single-stranded, non-protein-coding RNA molecules that regulate gene expression at the posttranscriptional level [13]. Lee and colleagues discovered the first miRNA gene, lin-4, in nematodes, and ascertained its function in regulating target mRNA translation via an antisense RNA-RNA interaction [14]. To date, 1921 mature human miRNAs are listed in the miRNA registry (miRBase18.0, November 2011; http://www.mirbase.org). It is estimated that up to 60% of all protein-encoding genes are regulated by these miRNAs [15].

MiRNA genes have been identified in all human chromosomes except the Y chromosome, and the loci of human miRNA genes are often located at chromosomal regions susceptible to deletions, translocations, and amplifications [16]. The biosynthesis of miRNA results from both canonical and non-canonical pathways, which illustrates unexpected complexity and flexibility in the miRNA processing pathways (**Figure 1**). Most human miRNAs are synthesized by canonical pathways, which require the RNase III enzyme Drosha, in a complex with DiGeorge syndrome critical region gene 8 (DGCR8) in the nucleus, as well as a cytoplasmic RNase III enzyme, Dicer. In contrast, the non-canonical miRNA pathways bypass Drosha or Dicer, using alternative cleavage mechanisms [17-19]. During miRNA processing, miRNA genes synthesized by the canonical or non-canonical pathways are initially transcribed by RNA polymerases into primary miRNAs (pri-miRNAs). The pri-miRNAs range from hundreds to thousands of nucleotides in length, have 5′ 7-methylguanosine caps and 3′ poly (A) tails [20, 21]. RNA polymerase II is mainly responsible for pri-miRNA transcription [21], although a relatively small percent of miRNA genes, such as a human chromosome 19 miRNA cluster (C19MC), are transcribed by RNA polymerase III [22]. In addition, the position of miRNA genes in the genome influences the mode of transcription. Intergenic miRNAs, which are clustered in the genome and expressed as polycistronic transcripts, are transcribed from their own promoters [23, 24]. Intronic miRNAs, which are positioned within a protein-coding gene, are transcribed with their host genes from the host transcriptional start sites [25-27].

In canonical pathways, the long pri-miRNAs are subsequently cleaved by the nuclear RNase III enzyme Drosha, in combination with its binding partner DGCR8, to form a hairpin RNA of 60-70 nucleotides that is referred to as the precursor miRNA (pre-miRNA) [17, 18]. The yielded pre-miRNAs are stem-loop structures consisting of a 22-nucleotide stretch of complementary double-stranded RNA and a 2-nucleotide overhang at the 3′ end [17]. The pre-miRNAs are exported to the cytoplasm by the nuclear Exportin 5 in a Ras-related nuclear protein-guanosine triphosphate-dependent manner [28, 29]. Once in the cytoplasm, the pre-miRNAs are further cleaved by a different RNase III enzyme, Dicer, along with its RNA-binding partner trans-activator RNA binding protein (TRBP) and an activator of the RNA-dependent protein kinase (PACT), at sites close to the loop to form double-stranded duplexes (miRNA: miRNA*) [28, 30, 31]. The double-stranded RNA molecules are quickly dissociated, and the miRNA* strand is often degraded, while the selected miRNA strand becomes a mature miRNA. The mature miRNA with Dicer, TRBP, and PACT is incorporated with members of the Argonaute (AGO) family and target protein coding mRNA to produce the RNA-induced silencing complex (RISC), which alters protein expression of the targeted mRNA by different mechanisms. Occasionally, both strands give rise to functional miRNAs, though. For example, miR-155 and miR-155* cooperatively regulate type I interferon

production in human plasmacytoid dendritic cells [32]. In addition, the miRNA strand can be secreted out of the cells to mediate cell-to-cell communication [33].

The non-canonical pathways include several alternative pathways (**Figure 1**). In one of these pathways, miRNAs referred to as "mirtrons" bypass Drosha cleavage and are processed by a splicing and debranching mechanism. In this process, the mirtrons, along with transcribed protein-coding genes, form the splicing complex, which liberates short hairpin introns. The short hairpin introns are subsequently linearized by the debranching enzyme, DBR1, allowing the

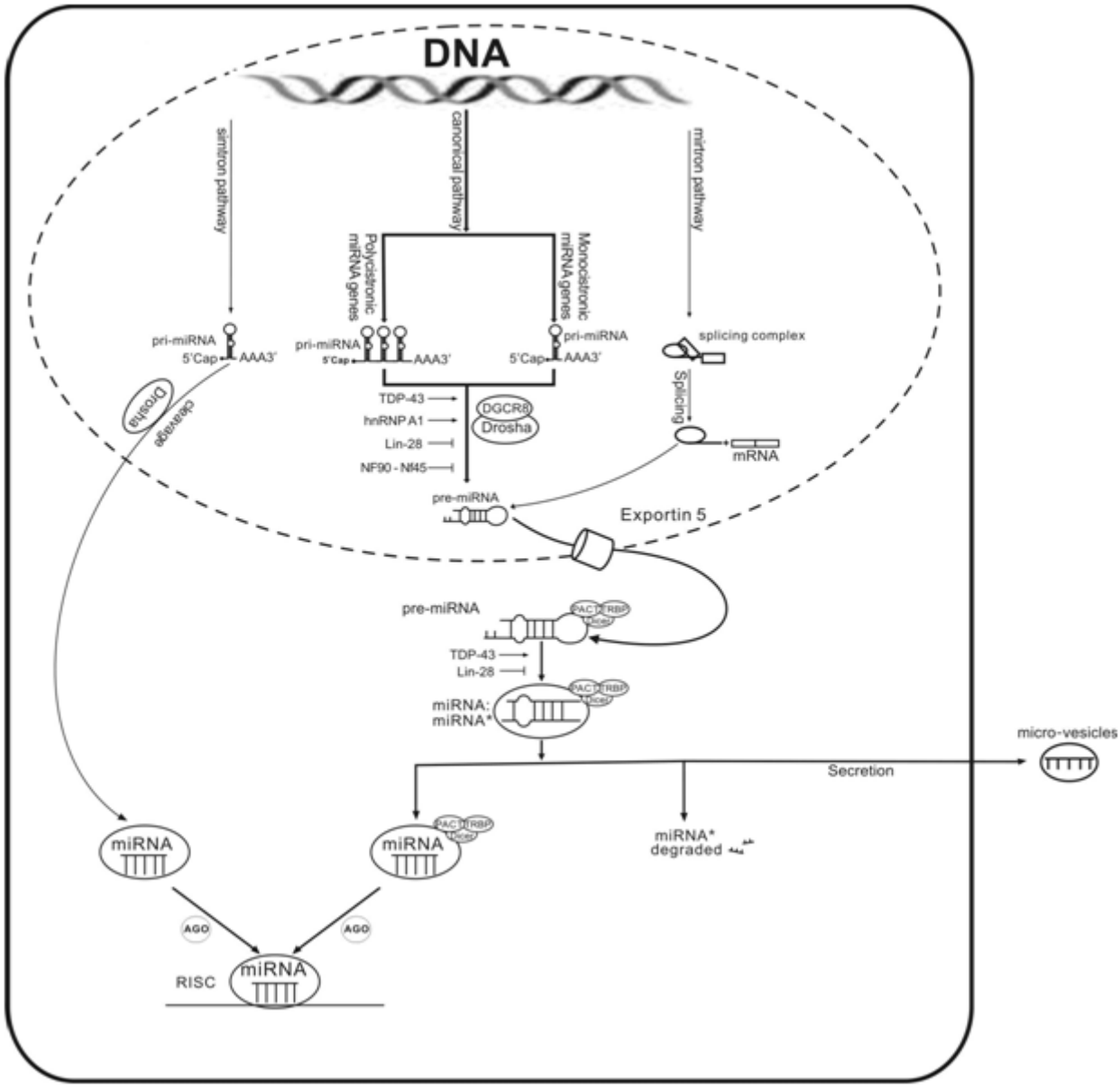

Figure 1. An overview of human miRNA synthesis by canonical and non-canonical processing pathways. In the initial steps of miRNA biosynthesis by canonical and non-canonical pathways, the miRNA-encoded genes are first transcribed by RNA polymerase. In the canonical pathway, the pri-miRNA is subsequently processed into pre-miRNA by a complex including Drosha and DGCR8. In the mirtron pathway, mirtrons bypass Drosha/DGCR8 processing, and are spliced and debranched into a short hairpin pre-miRNA mimics. The pre-miRNA is exported from the nucleus to the cytoplasm by Exportin 5, cleaved by Dicer, and enters the RISC complex. In the simtron pathway, simtrons are processed by Drosha and unknown factors, exported into the cytoplasm, and enter the RISC complex with AGO, but are not cleaved by Dicer. During the miRNA processing, positive or negative regulators can influence miRNA biosynthesis at the posttranscriptional level.

intron to form short hairpin pre-miRNA mimics. Subsequently, the pre-miRNA mimics are exported into the cytoplasm and assembled into RISC in a manner that is similar to the canonical pathways [19, 34]. Furthermore, a novel miRNA processing pathway that does not require Dicer has also been reported [35]. In this pathway, miRNA termed "simtrons" (splicing-independent mirtron-like miRNAs) are processed by Drosha with an unknown binding partner, before entering the RISC. The components in canonical miRNA biogenesis, including DGCR8, Dicer, and Exportin 5, are not required. In addition, a class of small RNAs originating from the small nucleolar RNA (snoRNA) ACA45, which require Dicer activity but are synthesized independently of Drosha/DGCR8, can interact with AGO to function as miRNAs in regulating gene expression [36].

Multiple proteins that modulate the processing of specific miRNAs at the posttranscriptional level have been identified, as well. Positive regulators, including TAR DNA-binding protein-43 (TDP-43) and heteronuclear ribonucleoprotein A1 (hnRNP A1), or negative regulators, including Lin-28 and nuclear factor complex (NF90 and NF45), are involved at the Drosha or Dicer processing steps, or both (**Figure 1**) [37-40]. For instance, Lin-28 inhibits let-7 miRNA biogenesis by blocking both Drosha- and Dicer-mediated cleavage and accelerating decay of let-7 precursors in human small cell lung cancer [40]. Research regarding the exact role of these regulators in controlling the synthesis of lung-related miRNAs is lacking, and may provide valuable information for the development of new strategies for disease therapy.

The molecular mechanisms of MiRNA-mediated gene regulation

Mature miRNAs in the cytoplasm can exert different effects on gene expression at multiple levels (**Figure 2**) [41]. Customarily, the mature miRNAs recognize and bind to the 3′ -untranslated region (3′ -UTR) of specific target protein coding mRNAs following the base-pairing rules of Watson and Crick [42]. The miRNA-mRNA duplexes with Dicer, TRBP, PACT and AGO proteins are assembled into RISC [31]. RISC is the functional unit capable of executing miRNA-mediated post-transcriptional repression of gene expression by virtue of two different mechanisms: promoting mRNA cleavage and blocking mRNA translation, including inhibition of translational initiation or elongation, degradation of the target mRNA, and sequestration of targets into cytoplasmic P bodies [41, 43, 44]. However, Vasudevan et al. also found that miRNAs could promote gene expression by stimulating mRNA translation in rare cases [45, 46]. These findings indicate that miRNA-mediated gene regulation may be much more complicated than originally perceived. In humans, translational repression is likely to be the major control mechanism [47]. According to experimental and bioinformatics analyses, the extent of base pairing between miRNAs and miRNA-repressible mRNAs not only determines miRNA target specificity, but also decides the ultimate fate of the target mRNA. If the target mRNA has perfect complementarity to the miRNA, the target mRNA will be cleaved [48]. However, if the target mRNA has imperfect complementarity, the miRNA will inhibit target mRNA translation [41]. Furthermore, the miRNA-mRNA interactions appear to follow a common set of rules [41, 49-51]. First, the base pairing between residues 2–8 at the 5′-miRNA end (representing the seed region) and the 3′ -UTR of the target mRNA must be perfectly complementary and contiguous. Second, bulges or mismatches must be present in the central region of the miRNA–mRNA duplex to preclude the AGO-mediated endonucleolytic cleavage of mRNA. In addition, the presence of an A residue at position 1 and an A or U at position 9 on the mRNA improves the efficiency of binding, but these nucleotides do not need to base pair with the miRNA nucleotides. However, there must be good base pairing between the miRNA-mRNA duplex at nucleotides 13 to 16 to stabilize the reciprocal interaction (**Figure 2**).

The functions of miRNAs are not necessarily restricted to single targets or single cells. MiRNAs have numerous high- and low-affinity targets, and it is estimated that each miRNA family has an average of 300 conserved targets [42]. This property indicates that each miRNA can bind to multiple targets and many miRNAs can bind to the same target mRNA. Therefore, miRNAs can regulate many genes in a pathway or physiological process at the same time, and a slight change in miRNA levels can significantly modulate cell physiology [52]. In addition to regulating downstream mRNA targets directly, miRNAs have been reported to act by indirect means through global effects on methylation or targeting of transcription factors [53, 54]. Recently, it was reported that miRNAs secreted from cells could be delivered to recipient cells by circulating plasma microvesicles,

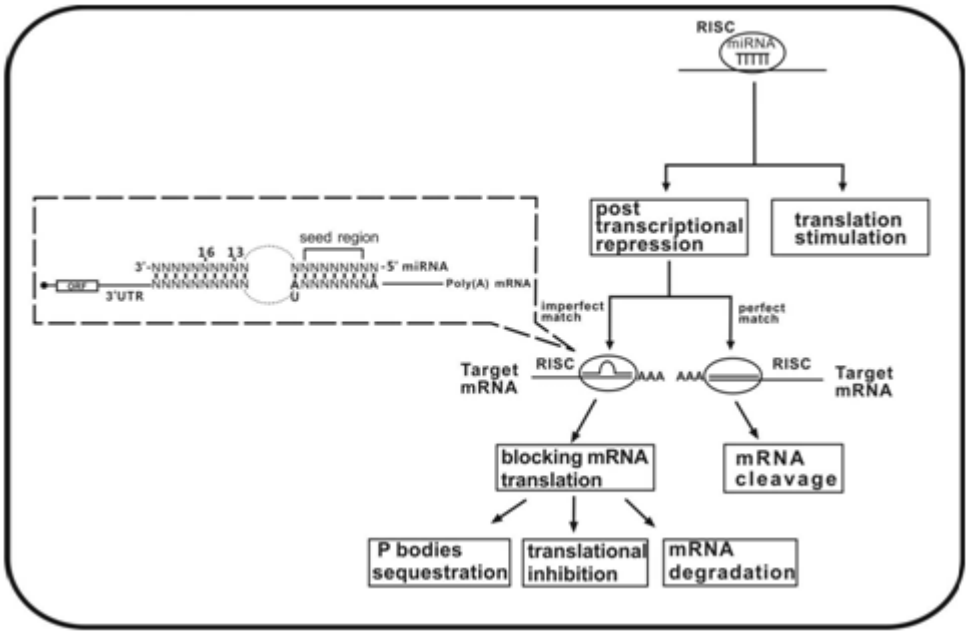

Figure 2. The molecular mechanisms of miRNA-mediated gene regulation.

indicating that exogenous miRNAs can mediate cell-to-cell communication and regulate recipient cell function [33, 55]. These discoveries support the idea that miRNAs do not simply act as "switches" to turn genes on or off, but may directly or indirectly "tune'' the expression levels of target genes. Thus, further investigation is needed to map the interconnected regulatory miRNA network.

Lung MiRNA expression profiling in physiological processes and asthma

The time- and spatial-specific expression of miRNAs can control cellular phenotype and function by regulating the expression of known and unknown critical genes [13, 56]. In order to identify miRNAs active during lung development, high throughput experiments have been executed with the lung tissue from humans and BALB/c mice. These experiments revealed remarkable similarities in the miRNA expression profiles of normal BALB/c mice and humans. The increased expression of eight miRNAs (miR-134, -154, -214, -296, -299, -323, -337, and -370) was detected in both neonatal mouse and human fetal lung, and upregulation of five miRNAs (miR-26b, -29a, -29b, -142-3p and -187) was detected in adult mouse and human lung [57]. These results suggest these miRNAs are evolutionarily conserved and mediate important regulatory functions in both species. The overall miRNA expression profiles in adult lung were also similar in normal BALB/c mice and humans. Of the 156 miRNAs analyzed from both species, the most highly expressed miRNAs included miR-26a and members of the miR-29, miR-30, and let-7 families. These finding are similar to the results of lung miRNA expression profiling performed by Babak and Sempere [58, 59]. Some of these miRNAs have been shown to have a significant role in asthma. For example, increased expression of let-7 has been associated with allergic inflammation of lung, and inhibition of let-7 in vivo profoundly inhibited the production of interleukin (IL)-13, a cytokine essential for expression of allergic lung disease [60]. In addition, other high-throughput experiments with different probe designs and labeling methods have identified unique lung-specific miRNAs in different species. MiR-195 and miR-200c were identified as lung-specific miRNAs in Sprague Dawley rats, while miR-18, -19a, -24, -32, -130, -213 were identified as lung-specific miRNAs in C57BL/6 mice [59, 61]. Although the functional roles of these identified lung-specific miRNAs are not completely understood, they likely play unique roles in controlling the fate specification of cells during lung development in different species.

In recent years, additional studies have investigated the differential expression patterns of miRNA using miRNA microarray technology in various models of asthma. MiRNA microarray analysis can also be used to characterize the global

miRNA expression patterns associated with different stages of asthma and identify potential therapeutic targets. In the doxycycline-induced IL-13 bitransgenic mouse model, which shares similar phenotypes with other mouse models of experimental asthma, Lu et al. found 21 lung miRNAs were differentially expressed compared with those in control mice that received no doxycycline. The highest upregulation was observed for miR-21, while the most substantial down-regulation was observed for miR-1. Up-regulation of miR-21 contributed to the polarization of Th cells toward a Th2 response by inhibiting IL-12p35 expression [62]. Furthermore, both miR-1 and miR-21 have been implicated as powerful regulators of cellular plasticity. MiR-1 can regulate plasticity of smooth muscle cells by repressing Kruppel-like factor 4 [63], while miR-21 regulates the phenotype switch from fibroblast to myofibroblast [64]. In a study of mouse models following short term (ST), intermediate term (IT), and long term (LT) exposure to allergen, dynamic miRNA expression accompanied a concomitant change from acute inflammation to the fibrotic process in asthma. Microarray analysis of 566 mature miRNAs indicated that 58, 66, and 75 miRNAs were significantly modulated following ST, IT, and LT allergen exposure, respectively. Alterations of at least 1.5-fold were observed in the expression levels of 20 miRNAs following ST exposure, 26 miRNAs following IT exposure, and 67 miRNAs following LT exposure [65]. Of note, some of these miRNAs have been identified in other asthma models, as well. Expression of miR-1 was shown to be repressed following ST exposure, consistent with the results of miRNA expression in doxycycline-induced IL-13 bitransgenic mice [62]. MiR-143 and miR-145 are upregulated following LT exposure, consistent with the results of miRNA expression in ASM cells exposed to IFN-β or IFN-γ [66]. Crucially, these alterations in miRNA expression correlated with the cellular phenotype switching associated with ASM plasticity (**Table 1**).

Although many studies have focused on determining the role of miRNAs in cancer, diabetes, and autoimmune diseases, only a handful of studies have investigated the precise functions of miRNAs in asthma-induced airway remodeling. A lack of readily available and specific high-throughput experimental techniques further complicates efforts to determine the precise functions of miRNAs, since each miRNA can have multiple mRNA targets regulating a diversity of cellular functions. At this time, the approaches used most frequently to identify miRNA targets are gain-of-function and loss-of-function studies, which only verify one suspected miRNA target at a time. Thus, it is likely that the identity and function of many miRNAs involved in ASM cell plasticity and asthma-induced airway remodeling remain to be determined.

Table 1. Selected miRNAs implicated in ASM cell plasticity

miRNA	Species	Condition or Treatment	Validated Target Genes	Function	References
miR-25	human	IL-1β, TNF-α and IFN-γ	KLF4	Promoting a more proliferative/synthetic phenotype of ASM cells that facilitate ECM turnover, airway remodeling and inflammation	[89]
miR-26a	human	mechanical stretch	GSK-3	Promoting a more proliferative ASM cells phenotype of that facilitate ASM cells hypertrophy	[90]
miR-133a	human/ mouse	IL-13/OVA	RhoA	Regulating the hyper-contractile phenotype switching of ASM cells	[93]
miR-143/145	human/ mouse	IFN-β/ IFN-γ/ house dust mite	ND	Regulation of ASM cell plasticity	[66,100]

ASM = airway smooth muscle, ND = not determined

MiRNAs involved in regulating ASM cell plasticity and asthma-induced airway remodeling

ASM cells are viewed as highly specialized cells dedicated to the regulation of airway caliber. ASM cells in normal airway show a contractile phenotype and retain an elongated, spindle-shaped appearance. These cells demonstrate a low rate of proliferation, appropriate contractility to contractile agonists, and few biosynthetic intracellular organelles [67]. They are characterized by a high density of contractile proteins and express smooth muscle cell (SMC)-specific genes, such as smooth muscle α-actin, smooth muscle myosin heavy chain (SM-MHC), SM22α, and calponin [68]. In asthma, ASM cells are regarded as primary determinants of airway remodeling [69]. Different functional and cellular phenotypes of ASM cell subpopulations contributing to airway remodeling were observed in response to physiological and pathological cues in the airways of asthmatics and in cultured primary ASM cells [70-72]. In this regard, ASM cells undergo abnormal switching to a more proliferative/synthetic phenotype, which is characterized by a decrease in SMC-specific contractile proteins and increased expression of intracellular organelles associated with synthesis [73-75]. These cells have abnormal proliferative, synthetic, and secretory potential, which can lead to increased smooth muscle mass and enhanced production of ECM proteins, chemokines, and cytokines that contribute to the pathology of airway remodeling and inflammation in asthma [74, 76]. The alterations in the ECM, in turn, modify the growth and synthetic function of ASM cells [77, 78]. The diminished abundance of SMC-specific contractile proteins is in line with a reduced responsiveness toward contractile agonists in vitro [79, 80]. However, data derived from in vivo studies revealed that ASM cells obtained from asthmatics exhibited a hyper-contractile phenotype when compared with ASM cells from non-asthmatics [72, 81]. This suggests that abnormal contractility of ASM cells resulted in increased ASM force generation and excessive airway narrowing [82, 83]. While these results indicate a paradox in the function of the hyper-contractile and proliferative/synthetic ASM phenotypes, it is also possible that ASM cells in vivo have an intermediate phenotype, retaining both contractile and synthetic properties depending on the stimulus. Such phenotypic modulation may result in the appearance of more proliferative/synthetic, as well as hyper-contractile SMCs with the overall effect of increasing the airway smooth muscle volume and contractility [84-86].

Although, the molecular mechanisms regulating this phenotypic plasticity are not well understood, recent studies have linked miRNAs with ASM cell plasticity by showing that miR-25, miR-26a and miR-133a regulate the cellular and functional phenotype of ASM cells. MiR-25 is 21 nucleotides in length and located on chromosome 7q22.1. It is down-regulated in cultured human ASM cells exposed to IL-1β, TNF-α and IFN-γ, which is similar to the environment found in symptomatic patients with asthma [87-89]. Inhibition of miR-25 with antagomir-25 can affect expression of in ammatory mediators by decreasing expression and secretion of RANTES and eotaxin, while increasing levels of TNF-α. Inhibition of miR-25 also affects the expression of a wide variety of ECM proteins that facilitate ECM turnover and airway remodeling. Moreover, inhibition of miR-25 down-regulates SMC-specific contractile proteins MHC and SM22 [89]. These findings suggest that miR-25 mediates its action on the proliferative/synthetic phenotype switching of ASM cells and promotes airway remodeling. Several recent reports demonstrate that miR-26a has a significant role in regulating the plasticity of ASM cells, as well [90, 91]. MiRNA microarray analyses indicated that, in response to mechanical stretch, miR-26a, miR-16, and miR-140 are highly expressed in cultured human ASM cells. Among these upregulated miRNAs, miR-26a has a broad role in regulating the proliferation, differentiation, migration, and apoptosis of smooth muscle cells [92], and stretch or enforced expression of miR-26a in vitro is sufficient to promote ASM cell hypertrophy. Furthermore, miR-26a knockdown can reverse this effect. Luciferase reporter assays demonstrate that GSK-3β, an anti-hypertrophic protein, is a target gene of miR-26a. Taken together, these results suggest that miR-26a is a hypertrophic gene that modulates the proliferative/synthetic phenotype of ASM cells [90]. MiR-133a was the first miRNA found to regulate the hyper-contractile phenotype switching of ASM cells. Chiba and colleagues reported miR-133a was down-regulated in human ASM cells treated with IL-13 and in bronchial tissue from sensitized BALB/c mice repeatedly challenged with ovalbumin [93]. The down-regulation of miR-133a resulted in augmentation of the contraction by upregulation of RhoA, a protein critically associated with the contraction of smooth muscle [82, 83, 93].

Potential therapeutic applications

The studies presented here provide compelling evidence that miRNAs have a pivotal role in regulating the plasticity of ASM cells and contribute to asthma-induced airway remodeling. As the reversion of ASM plasticity is helpful in treating the airway remodeling [9], pharmacologic or genetic manipulation of miRNAs involved in ASM plasticity may offer novel methods for the treatment or prevention of airway remodeling in asthma (**Figure 3**). Compared to conventional approaches, this miR-based approach has the potential for invoking sustained effects that could regulate multiple components of the same pathway or cellular process [94]. Corticosteroids, anti-inflammatory drugs commonly used for treating asthma, do not effectively reverse airway remodeling, possibly because these drugs do not regulate miRNA expression profiles in lung [95, 96]. Thus, additional regulation of miRNA expression may provide greater therapeutic benefits for asthma patients. The genetic approaches that modulate specific miRNA expression include overexpression by synthetic miRNA mimics and silencing by introduction of novel cholesterol-conjugated single-stranded RNA molecules, termed antagomirs, which are complementary to the mature target miRNA [97, 98]. MiR-145 may be a promising target for these approaches, since miR-145 is up-regulated in ASM cells exposed to IFN-β or IFN-γ, conditions which mimic the airway surroundings of subjects with asthma, especially after acute exacerbations [65, 99]. In the mouse model of house dust mite-induced asthma, silencing of miRNA-145 by antagomirs can inhibit airway inflammation, and the effect of antagomir-145 is comparable to glucocorticoid treatment [100]. Although these results suggest that miR-based approaches represent promising therapeutic strategies, the optimum target miRNAs involved in airway remodeling must be identified.

Conclusion

The cellular alterations associated with ASM cell plasticity are now recognized as critical mediators of airway remodeling in asthma, and recent studies indicate that specific miRNAs regulate this process. Thus, identification of these specific miRNAs and analyses of the functions of their mRNA targets will provide new insights necessary for the development of novel treatment strategies for reversing airway remodeling in patients with asthma.

Acknowledgements

This work was supported by a grant from the 2011 Graduate Students' Innovative Project of Hunan Province, China [No. CX2011B070]. The authors have no conflict of interest to report.

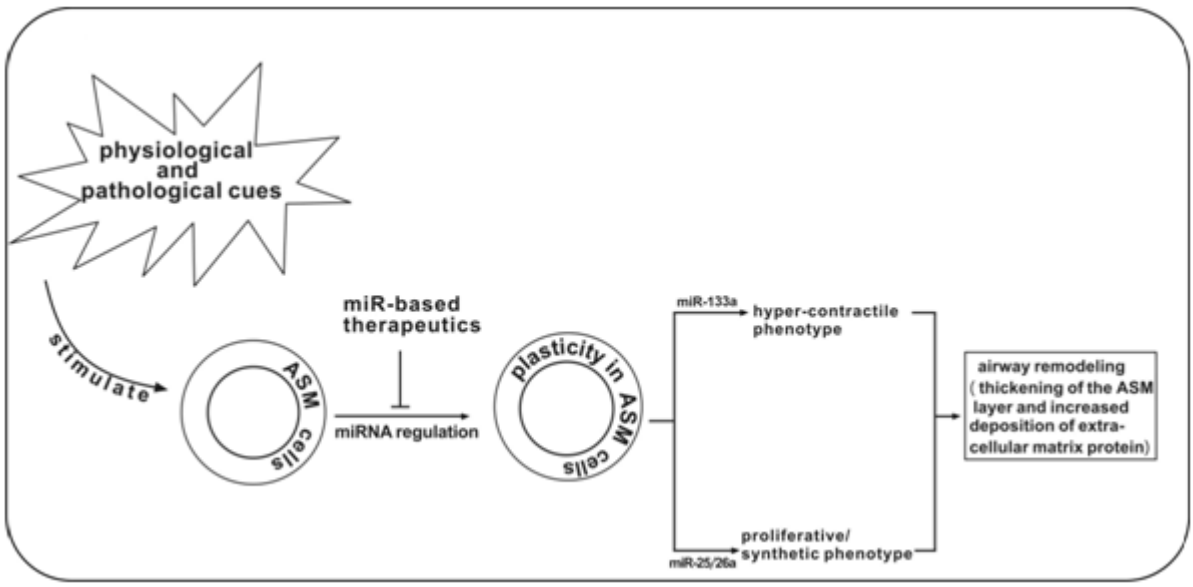

Figure 3. MiRNA-regulated ASM cell plasticity contributing to airway remodeling in asthma. In response to different pathologic and physiological stimuli, ASM cells show remarkable cellular plasticity under the regulation of miRNAs. Thus, miR-based therapeutics represents promising treatment strategies.

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