Journal of Pulmonary & Respiratory Medicine
Guo et al., J Pulm Respir Med 2014, 4:1
DOI: 10.4172/2161-105X.1000168
Mini Review Open Access

MicroRNAs and Smooth Muscle Cells Phenotypic Switching in PAH

Dongqing Guo, Lida Wu and Yuchun Gu*

Molecular Pharmacology Laboratory, Institute of Molecular Medicine, Peking University, Beijing, China

Abstract

Smooth muscle cells undergo a switching from contractile phenotype to synthetic phenotype in pulmonary hypertension characterized by excessive proliferation and migration of smooth muscle cells. MicroRNAs are small non-coding RNAs that can negatively regulate gene expression by directly binding with the 3'-UTR of mRNA. Numerous microRNAs have been reported to modulate the smooth muscle cells phenotypic switching and been urged to become possible therapeutic targets for pulmonary hypertension. This review will focus on the roles of microRNAs in regulating smooth muscle cellular phenotypic switching in PAH.

Keywords: microRNAs; Smooth muscle cells; Phenotypic switching; PAH

Pulmonary Arterial Hypertension (PAH) is a progressive fatal disorder with a poor prognosis characterized by elevated pulmonary arterial pressures leading to right ventricular failure and death [1,2]. Abnormal switching from a contractile phenotype to a synthetic phenotype [3], are pivotal events in the development structural remodeling of vasculatures associated with PAH [4]. In response to a variety of environmental cues including growth factors, cell-cell contacts and altered mechanical load, circulating hormones, smooth muscle cells experience a phenotypic switching [5].

MicroRNAs (miRNAs) are a novel class of endogenous, small and non-coding RNAs that function in transcriptional and post-transcriptional regulation of gene expression by directly binding with the 3'-UTR of mRNA [6-8]. miRNAs can directly regulate about 30% of the genes in a cell [9], therefore it is not surprising that miRNAs are involved in the regulation of almost all major cellular function, including developmental timing, cell death, cell proliferation [10,11], fat storage [12], haematopoiesis [13-18] and patterning of the nervous system [19-22]. Recent studies have revealed that many non-coding miRNAs can be as novel phenotypic markers and modulators of Vascular Smooth Muscle Cells (VSMCs). These findings display extensive implications for the diagnosis and therapy of a variety of proliferative vascular diseases [23], including PAH. The review will focus on the roles of microRNAs in regulating smooth muscle cellular phenotypic switching in pulmonary hypertension.

There are two classic pulmonary hypertension animal models apart induced by monocrotaline (MCT) and hypoxia [24]. In pulmonary hypertension induced by MCT, it usually occurs that endothelial cells damage accompanied with the increasing release of growth factors. PDGF is one of the most common growth factors in PAH and released primarily by vascular endothelial cells and platelets at the sites of vascular injury [25]. Indeed, an increased expression of signaling proteins in the PDGF pathway has been demonstrated in several cardiovascular disorders [26]. Activation of PDGF inhibits smooth muscle cell (SMC)-specific gene expression (SM22α, SM α-actin and calponin) and increases the rate of proliferation and migration, leading to dedifferentiation of VSMCs. Many miRNAs have been demonstrated to play important roles in the stimulation of PDGF with indistinct mechanisms.

MiR-15b is shown to be induced by PDGF in pulmonary artery smooth muscle cells and it is critical for the repression of SMC-specific contractile genes [27]. MiR-638 is abundantly expressed in SMCs and markedly down-regulated in the PDGF stimulation. In differentiation medium, miR-638 expression is significantly up-regulated to inhibit SMC proliferation by targeting the orphan nuclear receptor NOR1 [25]. MiR-24 also functions in the process and directly down-regulates Tribbles like protein-3 (Trb3) expression which results in decreased Smad protein levels and VSMC contractile genes expression [28]. Non-coding small miR-221/222 are novel regulators of vascular neointimal lesion formation during PDGF pathway via their target genes p27 (Kip1) and p57 (Kip2) [29]. PDGF stimulation could inhibit the expression of miR-221, leading to down-regulation of the targets p27 (Kip1) and c-Kit. Down-regulation of p27 (Kip1) is critical for PDGF-mediated induction of cell proliferation. Decreased c-Kit causes inhibition of SMC-specific contractile gene transcription by reducing the expression of myocardin (myocd), a potent SMC-specific nuclear coactivator [30]. Additionally, Davis BN et al. also found myocardin reduced SMC migration by increasing expression of miR-24/29a, resulting in down-regulation of platelet-derived growth factor receptor β (PDGFRB) expression [31]. Meanwhile, another report shows that overexpression of myocardin leads to significant induction of miR-1 expression and inhibition of SMC proliferation by targeting Pim-1, a serine/threonine kinase [32].

What's more, the damaged endothelial cells also could secret miRNAs to promote the SMC phenomenon switching via vesicles mediated intercellular communication [33,34]. Vesicle-mediated miRNAs has been proved in atherosclerosis while the research is very few in PAH, and it will become a new research hotspot. MiR-126 is an endothelial cell-restricted microRNA and highly expressed in endothelial cells [35]. Targeted deletion of miR-126 in mice causes leaky vessels, hemorrhaging and partial embryonic lethality, due to loss of vascular integrity and defects in endothelial cell proliferation, migration and angiogenesis [36]. Apoptotic endothelial cells at atherosclerotic plaques release microvesicles known as apoptotic bodies which are enrich in miR-126 into the circulation, and these microvesicles shuttle miR-126 to recipient neighboring vascular cells, their abundance correlates with negative indicators of the disease [37], suggesting possible intercellular communication or intercellular signal transduction mediated by miR-126 between EC and SMC. So we believe that in pulmonary hypertension, vesicles mediated miR-126 from ECs may also stimulate

***Corresponding author**: Yuchun Gu, Molecular Pharmacology Laboratory, Institute of Molecular Medicine, Peking University, Beijing, 100871, China, Tel: +86-10-8254-5679; E-mail: ycgu@pku.edu.cn

Received December 30, 2013; **Accepted** January 21, 2014; **Published** January 24, 2014

Citation: Guo D, Wu L, Gu Y (2014) MicroRNAs and Smooth Muscle Cells Phenotypic Switching in PAH. J Pulm Respir Med 4: 168. doi:10.4172/2161-105X.1000168

the proliferation of SMC. Besides, extracellular vesicles secreted by KLF2-transduced or shear-stress-stimulated HUVECs are enriched in miR-143/145 and control target gene expression in co-cultured SMCs [34]. Several reports suggested that miR-143 and miR-145 play critical roles in phenotype remodeling of VSMCs. Deficiency of miR-143 and miR-145 leads to VSMCs phenotypic switching from a contractile to synthetic phenotype [38], MiR-145 is down-regulated in PAH mouse models which can protect against the development of PAH. Besides, miR-145 is expressed in remodeled vessels in patient samples of heritable PAH and idiopathic PAH [39].

Apart from vesicle mediated microRNAs, recently Zhou et al. demonstrated that EC-secreted miR-126 and RNA-protein complexes (miRNAs and Ago2) regulate SMC gene expression (Forkhead Box O3, B cell Lymphoma 2 and Insulin Receptor substrate 1) and cellular functions via paracrine effects [40]. They also detected the association between Ago2 and miR-21, miR-221, miR-155, miR-143 and 145 and the results supporting the hypothesis that Ago-mediated miRNAs transmission is a general mechanism regulating intercellular communications [34].

Chronic hypoxia causes pulmonary vascular remodeling and leads to Pulmonary Hypertension (PAH) and right ventricle hypertrophy [41,42]. The remodeling process encompasses concentric medial thickening of small arterioles, muscularization of previously capillary-like vessels, and structural wall changes in larger pulmonary arteries [43]. The pulmonary arterial muscularization is characterized by the proliferation and phenotypic switching of smooth muscle cells. In hypoxic pulmonary hypertension, misexpression of miRNAs has been implicated in the pathologies.

Nuclear factor of activated T cells (NFAT) signaling pathway is linked to PASMC proliferation and phenotypic modulation in hypoxia. Down-regulation of miR-124 in hypoxia-treated PASMC is consistent with the activation of NFAT signaling pathway in hypoxia by targeting NFATc1, CAMTA1 and PTBP1 genes [44]. Fhl-1 is a member of the LIM family and acts as an early key protein in the mechanism of PAH [45]. It is regulated by HIF-1α in a feedback loop that serves to limit HIF-1α activity under conditions of prolonged hypoxia [46,47]. Hypoxia-induced down-regulation of miR-206 promotes PAH by targeting the HIF-1α/Fhl-1 pathway in PASMCs [46]. MiR-210 plays an anti-apoptotic role in HPASMC via interaction with transcription factor E2F3 [48]. MiR-138 has the similar effects in PAH by interaction with serine/threonine kinase Mst1 and preventing caspase activation and Bcl-2 signaling [4]. Hypoxia also could produce a significant inhibition of miRNA-328 expression, which is involved in PA vasoconstriction and remodeling by targeting at insulin growth factor 1 receptor and L-type calcium channel-α1C [49]. MiR-24 overexpression has detrimental effects on the SMC functional capacity inducing apoptosis, migration defects, enhanced autophagy and loss of contractile marker genes by targeting heme oxygenase 1 [50]. MiR-21 plays a significant role in hypoxia-mediated SMC phenotype by targeting PDCD4, SPRY2 and PPARα [51]. These miRNAs are potential regulators of hypoxia-mediated proliferation, apoptosis and differentiation of PASMCs. They are therefore recognized as novel treatment strategies in PAH [52].

Conclusion

MicroRNAs play an important role in the SMC phenotypic switching in pulmonary hypertension in response to different stimulus and they may become potential novel therapeutic agents in the cardiovascular diseases. However it still has a far way to go because of the little data in vivo in patients. The stability and safety of miRNA and targeted miRNA delivery should draw more attention in the future.

Acknowledgements

This work is supported by the research grants held by YG (NSF No. 81170236 and 973 Project No. 2013CB531206).

References

1. Sahara M, Sata M, Morita T, Hirata Y, Nagai R (2012) Nicorandil attenuates monocrotaline-induced vascular endothelial damage and pulmonary arterial hypertension. PLoS One 7: e33367.
2. Archer S, Rich S (2000) Primary pulmonary hypertension: a vascular biology and translational research “Work in progress”. Circulation 102: 2781-2791.
3. Owens GK, Kumar MS, Wamhoff BR (2004) Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol Rev 84: 767-801.
4. Li S, Ran Y, Zhang D, Chen J, Li S, et al. (2013) MicroRNA-138 plays a role in hypoxic pulmonary vascular remodelling by targeting Mst1. Biochem J 452: 281-291.
5. Cheng Y, Liu X, Yang J, Lin Y, Xu DZ, et al. (2009) MicroRNA-145, a novel smooth muscle cell phenotypic marker and modulator, controls vascular neointimal lesion formation. Circ Res 105: 158-166.
6. Zhang R, Su B (2009) Small but influential: the role of microRNAs on gene regulatory network and 3’UTR evolution. J Genet Genomics 36: 1-6.
7. van Rooij E, Olson EN (2007) MicroRNAs: powerful new regulators of heart disease and provocative therapeutic targets. J Clin Invest 117: 2369-2376.
8. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116: 281-297.
9. Lin Y, Liu X, Cheng Y, Yang J, Huo Y, et al. (2009) Involvement of MicroRNAs in hydrogen peroxide-mediated gene regulation and cellular injury response in vascular smooth muscle cells. J Biol Chem 284: 7903-7913.
10. Kloosterman WP, Plasterk RH (2006) The diverse functions of microRNAs in animal development and disease. Dev Cell 11: 441-450.
11. Ambros V (2004) The functions of animal microRNAs. Nature 431: 350-355.
12. Berezikov E, Guryev V, van de Belt J, Wienholds E, Plasterk RH, et al. (2005) Phylogenetic shadowing and computational identification of human microRNA genes. Cell 120: 21-24.
13. Li H, Zhao H, Wang D, Yang R (2011) microRNA regulation in megakaryocytopoiesis. Br J Haematol 155: 298-307.
14. Salaun B, Yamamoto T, Badran B, Tsunetsugu-Yokota Y, Roux A, et al. (2011) Differentiation associated regulation of microRNA expression in vivo in human CD8+ T cell subsets. J Transl Med 9: 44.
15. Hussein K, Büsche G, Muth M, Göhring G, Kreipe H, et al. (2011) Expression of myelopoiesis-associated microRNA in bone marrow cells of atypical chronic myeloid leukaemia and chronic myelomonocytic leukaemia. Ann Hematol 90: 307-313.
16. Guillon-Munos A, Dambrine G, Richerioux N, Coupeau D, Muylkens B, et al. (2010) The chicken miR-150 targets the avian orthologue of the functional zebrafish MYB 3’UTR target site. BMC Mol Biol 11: 67.
17. Faltejsková P, Slabý O, Hézová R, Michálek J (2010) [Role of microRNAs in the immune system]. Cas Lek Cesk 149: 10-15.
18. Hussein K, Theophile K, Büsche G, Schlegelberger B, Göhring G, et al. (2010) Aberrant microRNA expression pattern in myelodysplastic bone marrow cells. Leuk Res 34: 1169-1174.
19. Liu Q, He H, Zeng T, Huang Z, Fan T, et al. (2013) Neural-specific expression of miR-344-3p during mouse embryonic development. J Mol Histol.
20. Yu L, Liao Q, Chen X, Xu L, Zeng X, et al. (2014) Dynamic expression of miR-132, miR-212, and miR-146 in the brain of different hosts infected with Angiostrongylus cantonensis. Parasitol Res 113: 91-99.
21. Tan L, Yu JT, Liu QY, Tan MS, Zhang W, et al. (2014) Circulating miR-125b as a biomarker of Alzheimer’s disease. J Neurol Sci 336: 52-56.
22. Petri R1, Malmevik J1, Fasching L1, Akerblom M1, Jakobsson J2 (2014) miRNAs in brain development. Exp Cell Res 321: 84-89.
23. Zhang C (2009) MicroRNA-145 in vascular smooth muscle cell biology: a new therapeutic target for vascular disease. Cell Cycle 8: 3469-3473.

24. Stenmark KR, Meyrick B, Galie N, Mooi WJ, McMurtry IF (2009) Animal models of pulmonary arterial hypertension: the hope for etiological discovery and pharmacological cure. Am J Physiol Lung Cell Mol Physiol 297: L1013-1032.

25. Li P, Liu Y, Yi B, Wang G, You X, et al. (2013) MicroRNA-638 is highly expressed in human vascular smooth muscle cells and inhibits PDGF-BB-induced cell proliferation and migration through targeting orphan nuclear receptor NOR1. Cardiovasc Res 99: 185-193.

26. Andrae J, Gallini R, Betsholtz C (2008) Role of platelet-derived growth factors in physiology and medicine. Genes Dev 22: 1276-1312.

27. Kim S, Kang H (2013) miR-15b induced by platelet-derived growth factor signaling is required for vascular smooth muscle cell proliferation. BMB Rep 46: 550-554.

28. Chan MC, Hilyard AC, Wu C, Davis BN, Hill NS, et al. (2010) Molecular basis for antagonism between PDGF and the TGFbeta family of signalling pathways by control of miR-24 expression. EMBO J 29: 559-573.

29. Liu X, Cheng Y, Zhang S, Lin Y, Yang J, et al. (2009) A necessary role of miR-221 and miR-222 in vascular smooth muscle cell proliferation and neointimal hyperplasia. Circ Res 104: 476-487.

30. Davis BN, Hilyard AC, Nguyen PH, Lagna G, Hata A (2009) Induction of microRNA-221 by platelet-derived growth factor signaling is critical for modulation of vascular smooth muscle phenotype. J Biol Chem 284: 3728-3738.

31. Talasila A, Yu H, Ackers-Johnson M, Bot M, van Berkel T, et al. (2013) Myocardin regulates vascular response to injury through miR-24/-29a and platelet-derived growth factor receptor-β. Arterioscler Thromb Vasc Biol 33: 2355-2365.

32. Chen J, Yin H, Jiang Y, Radhakrishnan SK, Huang ZP, et al. (2011) Induction of microRNA-1 by myocardin in smooth muscle cells inhibits cell proliferation. Arterioscler Thromb Vasc Biol 31: 368-375.

33. Boon RA (2013) Endothelial microRNA tells smooth muscle cells to proliferate. Circ Res 113: 7-8.

34. Hergenreider E, Heydt S, Tréguer K, Boettger T, Horrevoets AJ, et al. (2012) Atheroprotective communication between endothelial cells and smooth muscle cells through miRNAs. Nat Cell Biol 14: 249-256.

35. Fish JE, Santoro MM, Morton SU, Yu S, Yeh RF, et al. (2008) miR-126 regulates angiogenic signaling and vascular integrity. Dev Cell 15: 272-284.

36. Wang S, Aurora AB, Johnson BA, Qi X, McAnally J, et al. (2008) The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. Dev Cell 15: 261-271.

37. Zernecke A, Bidzhekov K, Noels H, Shagdarsuren E, Gan L, et al. (2009) Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection. Sci Signal 2: ra81.

38. Song Z, Li G (2010) Role of specific microRNAs in regulation of vascular smooth muscle cell differentiation and the response to injury. J Cardiovasc Transl Res 3: 246-250.

39. Caruso P, Dempsie Y, Stevens HC, McDonald RA, Long L, et al. (2012) A role for miR-145 in pulmonary arterial hypertension: evidence from mouse models and patient samples. Circ Res 111: 290-300.

40. Zhou J, Li YS, Nguyen P, Wang KC, Weiss A, et al. (2013) Regulation of vascular smooth muscle cell turnover by endothelial cell-secreted microRNA-126: role of shear stress. Circ Res 113: 40-51.

41. Kim YM, Barnes EA, Alvira CM, Ying L, Reddy S, et al. (2013) Hypoxia-inducible factor-1α in pulmonary artery smooth muscle cells lowers vascular tone by decreasing myosin light chain phosphorylation. Circ Res 112: 1230-1233.

42. Zhang W, Cao Y, Zhang Y, Ma QS, Ma L, et al. (2006) [Effects of RNAi on hypoxia inducible factor-1alpha activity and proliferation of hypoxic pulmonary artery smooth muscle cells in rat]. Sheng Li Xue Bao 58: 71-76.

43. Aggarwal S, Gross CM, Sharma S, Fineman JR, Black SM (2013) Reactive oxygen species in pulmonary vascular remodeling. Compr Physiol 3: 1011-1034.

44. Kang K, Peng X, Zhang X, Wang Y, Zhang L, et al. (2013) MicroRNA-124 suppresses the transactivation of nuclear factor of activated T cells by targeting multiple genes and inhibits the proliferation of pulmonary artery smooth muscle cells. J Biol Chem 288: 25414-25427.

45. Kwapiszewska G, Wygrecka M, Marsh LM, Schmitt S, Trösser R, et al. (2008) Fhl-1, a new key protein in pulmonary hypertension. Circulation 118: 1183-1194.

46. Yue J, Guan J, Wang X, Zhang L, Yang Z, et al. (2013) MicroRNA-206 is involved in hypoxia-induced pulmonary hypertension through targeting of the HIF-1α/Fhl-1 pathway. Lab Invest 93: 748-759.

47. Hubbi ME, Gilkes DM, Baek JH, Semenza GL (2012) Four-and-a-half LIM domain proteins inhibit transactivation by hypoxia-inducible factor 1. J Biol Chem 287: 6139-6149.

48. Gou D, Ramchandran R, Peng X, Yao L, Kang K, et al. (2012) miR-210 has an antiapoptotic effect in pulmonary artery smooth muscle cells during hypoxia. Am J Physiol Lung Cell Mol Physiol 303: L682-691.

49. Guo L, Qiu Z, Wei L, Yu X, Gao X, et al. (2012) The microRNA-328 regulates hypoxic pulmonary hypertension by targeting at insulin growth factor 1 receptor and L-type calcium channel-α1C. Hypertension 59: 1006-1013.

50. Fiedler J, Stöhr A, Gupta SK, Hartmann D, Holzmann A, et al. (2013) Functional MicroRNA Library Screening Identifies the HypoxaMiR MiR-24 as a Potent Regulator of Smooth Muscle Cell Proliferation and Vascularization. Antioxid Redox Signal.

51. Sarkar J, Gou D, Turaka P, Viktorova E, Ramchandran R, et al. (2010) MicroRNA-21 plays a role in hypoxia-mediated pulmonary artery smooth muscle cell proliferation and migration. Am J Physiol Lung Cell Mol Physiol 299: L861-871.

52. Jalali S, Ramanathan GK, Parthasarathy PT, Aljubran S, Galam L, et al. (2012) Mir-206 regulates pulmonary artery smooth muscle cell proliferation and differentiation. PLoS One 7: e46808.