Editorial

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The Role of MicroRNAs in Vascular Diseases; Smooth Muscle Cell Differentiation and De-Differentiation

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Refer to the page 255-263

Vascular smooth muscle cells (VSMCs) undergo two important physiological processes such as differentiation (contractile state) and dedifferentiation (proliferative state) during vascular diseases. In general, a prerequisite for pathological and physiological vascular remodeling processes such as atherosclerosis, hypertension, and restenosis after angioplasty is the phenotype alteration of VSMCs. Dedifferentiation of VSMCs is known to trigger vascular injury and lesion formation,[1] and is associated with changes in various gene expressions that are commanded by epigenetic and transcriptional control mechanisms via DNA-binding transcription factors.[2] For instance, serum response factor (SRF) binding to CArG boxes triggers expression of VSMC differentiation marker genes in the association with its cofactors, myocardin (MyoCD) and Elk-1 (ETS domain-containing protein).[1][3][4] In contrast, Kruppel-like factor 4 (KLF4) binds to transforming growth factor beta (TGF-β) and prevents the VSMC differentiation marker genes, smooth muscle α-actin (SMA and *ACTA2*) and SM-22α (*TAGLN*) by the repression of MyoCD expression and SRF/MyoCD activity.[5] Moreover, the VSMC differentiation is affected by histone modifications such as histone methylation and acetylation.[6][7] KLF4 recruits histone H4 deacetylase activity to VSMC genes liberating the association of SRF to the methylated histone and CArG box chromatin for the repression of VSMC gene expression. As mentioned above, understanding the mechanisms involved in the regulation of the VSMC differentiation in proliferation-based pathology such as restenosis and neointima formation after angioplasty is important in developing new therapeutic approaches for the treatment of vascular diseases.

Nowadays, microRNAs (miRNAs) have emerged as a promising therapeutic tool as they target genes and/or proteins via posttranscriptional regulation in response to diverse environmental and metabolic changes in vascular cell differentiation, migration, proliferation, and apoptosis.[8-10] miRNAs, single-stranded and noncoding small RNAs, are engendered from primary RNA precursors via two cleavage steps composed by two endoribunucleases, Drosha and Dicer. miRNAs regulate the post-transcription level to orchestrate the fine-tuning of transcription networks.[11] Several miRNAs have been studied for their roles in the VSMC function and plasticity—for instance, miR-1, miR-21, miR-221/miR-222, and miR-cluster miR-143/miR-145 and miR-663.[12-14] MiR-143/miR-145 is downregulated, whereas miR-21, miR-146, and miR-221/222 are induced upon vascular injury.[12] Among them, miR-143/miR-145 is significantly sufficient to regulate the VSMC contractile state.[15][16] miR-663 has been revealed as a novel modulator of human VSMC phenotypic switching by targeting JUNB. Overexpression of miR-663 suppresses the expression of JUNB and MYL9 that are induced by platelet-derived growth factor-BB (PDGF-BB) and ultimately attenuates VSMC migration and neointima formation.[14]

Kee et al.[17] proposed that miR-18a-5p is a novel miRNA that regulates VSMC differentiation by targeting syndecan-4, and it promotes vascular smooth muscle cell differentiation by regulation of the VSMC marker genes, smooth muscle α-actin and SM22α. Moreover, the expression of miR-18a-5p is increased in the early time frame of carotid injury models. The level of miR-18a-5p was upregulated in VSMC differentiation and downregulated in VSMC dedifferentiation, which were each induced by the treatment of medium and PDGF-bb, respectively. According to this

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study, miR-18a-5p regulates both mRNA and protein levels of syndecan-4, which are induced in neointimal VSMCs after the vascular injury.[18] Syndecan-4 also regulates smad-2 expression as a downstream target. Overexpression of syndecan-4 reduced the expression of smad2, whereas silencing of syndecan-4 induced the expression of smad-2. Interestingly, syndecan-4 does not seem to affect the VSMC differentiation.

Even though some aspects of miR-18a-5p were revealed, this study has a range of limitations that need be resolved for any clinical significance. This study claims that syndecan-4 and smad-2 express opposite patterns upon miR-18a-5p transfection. However, mRNA levels of both syndecan-4 and smad-2 were increased seven days after the carotid injury; moreover, smad 2 mRNA and protein expression show no change in VSMCs overexpressed with miR-18a-5p. Moreover, syndecan-4 does not seem to affect the VSMC phenotype switching. Another questionable aspect of the study is that the VSMC differentiation markers showed an increase after the balloon carotid injury, whereas it is well established that VSMCs switch to their proliferative (dedifferentiation) state upon such phenomena.

The regulation of the VSMC differentiation using miRNAs is vital and imperative as a therapeutic approach for the treatment of atherosclerosis and restenosis. This study does not produce enough data and explanation to support all its overall claims. Further study and clarification of the mechanisms introduced may allow an improved hypothesis and a higher clinical significance. However, this study identifies a novel miRNA, miR-18a-5p, in the regulation of the VSMC differentiation and thus offers some significance to the understanding and development of the treatment for atherosclerosis. It also implicates an investigative view of possible mechanisms that needs further elucidation and reiterates the significant outlook of miRNAs in the decryption of cardiovascular diseases.

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