

Micrornucleic acids and vascular restenosis

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ABSTRACT

يعتبر ميكرو حمض ربيي نووي أو ميكرو رنا (miRNAs) مجموعة صغيرة من الحمض الريبوزي النووي الغير مشفر والذي يتحكم بوظائف الخلوية إما عن طريق تفكك المركب أو تثبيط هدف الرسول من ترجمة معلومات الرنا. ويرتبط التعبير الرائع للحمض ربيي النووي بالأمراض التي تصيب الإنسان بما في ذلك الحال الوظيفي في مرض قلبي وعائي. تلخص هذه المراجعة أحدث الأفكار في تحديد الأوعية الدموية للميكرو حمض ربيي وتحديد الآليات لأدوارها في عودة التضيق الوعائي والذي غالباً يكون بالتأثير على تكاثر وهجرة خلايا العضلات الوعائية. نناقش هنا العقاقير ميكرو حمض ربيي والعلاج الجيني في عودة التضيق الوعائي.

Micrornucleic acids (miRNAs) are small non-coding RNAs, which control diverse cellular functions by either promoting degradation, or inhibiting target messenger RNA translation. An aberrant expression profile of miRNAs has been linked to human diseases, including cardiovascular dysfunction. This review summarizes the latest insights in the identification of vascular-specific miRNAs and the underlying mechanisms for their roles in vascular restenosis, mainly by influencing the proliferation and migration of vascular smooth muscle cell. Here, we discuss miRNA-based drug and gene therapy in vascular restenosis.

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Vascular stenosis is a common pathological characteristic of vascular restenosis after angioplasty and other cardiovascular diseases that will ultimately affect the function of the target organs.¹ So far, there are no satisfying therapies to this kind of disease.² Restenosis has greatly limited the benefits of angioplasty and other therapeutics. Micrornucleic acids (miRNAs) are short, non-coding RNAs that negatively regulate the expression of proteins by binding to specific sequences on the 3' region of target mRNAs.³⁻⁵ Bioinformatics analysis predicts that each miRNA may regulate hundreds of targets, suggesting that miRNAs may play important roles in almost every biological pathway and process, including those in the cardiovascular system. Recent studies⁶⁻⁸ have identified that miRNAs play important roles in vascular restenosis. To explore the role of miRNAs in vascular restenosis, we review recent progress regarding the involvement of miRNAs in vascular restenosis (Table 1), and their usage as a new therapeutic approach for vascular restenosis.

Source and function of miRNA. Micrornucleic acids genes are located in the intron, non-coding exon, and intergenic regions of genomes, and are initially transcribed by polymerase II into primary miRNAs (pri-miRNAs). The pri-miRNAs are subsequently cleaved in the nucleus by a microprocessor complex composed of Drosha and Pasha into a stem-loop pre-cursormiRNA (pre-miRNA) that has a length of approximately 70 nucleotides (nt). Pre-miRNAs are in turn transported by exportin-5 into the cytoplasm where they are cleaved by Dicer, an RNase III family member into mature miRNAs with 22-nt. The mature miRNAs are able to be incorporated into the RNA-induced silencing complex (RISC). Ribonucleic acids-induced silencing complex functions to degrade mRNA or block protein translation by either binding mRNA through a perfect complementary match or through an imperfect match in the 3' untranslated region (UTR).³⁻⁵ In the past several years, miRNA has been extensively investigated, and it is now recognized that miRNA plays a key role in regulating fundamental cellular processes, including cell proliferation, apoptosis, differentiation, and migration.⁹⁻¹²

Table 1 - The role of micrornucleic acids (miRNAs) in vascular restenosis.

Different miRNAs	Role of miRNAs
<i>Inhibitors</i>	
miRNA-143/145 ¹⁸⁻²⁵	miRNA-1 ³⁰
miRNA-195 ²⁶	miRNA-133 ³¹
miRNA-503 ²⁷	miRNA-31 ³²
Let-7d ²⁸	miRNA-132 ³³
miRNA-424/322 ²⁹	
<i>Promoters</i>	
miRNA-221/222 ³⁵⁻³⁷	miRNA-142-5p ⁴⁵
miRNA-21 ³⁸⁻³⁹	miRNA-663 ⁴⁶
miRNA-146a ⁴⁰⁻⁴²	miRNA-638 ⁴⁷
miRNA-24-2 ⁴³	miRNA-15b ⁴⁸
miRNA-26a ⁴⁴	
VSMC - vascular smooth muscle cell	

The mechanism of vascular restenosis. The pathogenesis of vascular restenosis is very complex, it may be related to endothelial dysfunction and injury, platelet aggregation and thrombosis, VSMC proliferation, synthesis of extracellular matrix (ECM), and other related factors.¹³ The formation of restenosis mainly includes 3 steps:¹⁴ 1) vessel recoil: intervention vessel such as angioplasty can cause rapid vascular elastic recoil in one hour. 2) vessel remodeling: the chronic contracture of vascular elastic layer 6 months after vascular injury. 3) neointima hyperplasia: the proliferation and migration of VSMC and the formation of ECM. Among these steps, the proliferation, migration of VSMCs, and secretion of ECM plays an important role in restenosis.¹⁵ Normally, the VSMC is quiescent and specialized for contractile function. This is referred to as the contractile or differentiated phenotype. However, under certain circumstances, such as in vascular injury, the VSMCs undergo phenotypic modulation and start to proliferate and migrate out of the vascular media.¹⁶ This process is important for the vascular repair process, but can also be detrimental such as in restenosis following angioplasty when the vessel is partially or completely occluded by proliferating VSMCs.^{1,2} In recent years, miRNAs have been implicated in the regulation of VSMC phenotype and closely related to vascular restenosis.^{6-8,17} We overview

the current knowledge on individual miRNAs that plays an important role in vascular restenosis by regulating VSMC phenotype (Figure 1).

Micrornucleic acids, which inhibit the proliferation and migration of VSMCs. **1) Micrornucleic acid-143/145.** The nonhomologous clustered miRNAs miR-143 and miR-145, which originate from the same transcriptional unit, are well known for their crucial role in VSMC differentiation and vascular pathogenesis.¹⁸ In VSMCs, miR-145 targets many transcription factors to promote differentiation and simultaneously represses proliferation of VSMCs by the coincidence of serum response factor dependent (SRF-dependent) co-activators and co-repressors. On one hand, miR-145 mediates phenotypic modulation from a contractile, quiescent phenotype to a synthetic, proliferative phenotype by repression of its target genes krüppel-like factor 4 (KLF4), a transcription factor involved in pluripotency.¹⁹ On the other hand, by targeting krüppel-like factor 5 (KLF5), miR-145 in turn can increase the expression of its downstream signal molecule myocardin that interacts with SRF to activate most genes associated with contractile VSMC phenotype.^{20,21} Unlike miR-145, miR-143 targets Elk-1, which acts as an activator of VSMC proliferation by displacing myocardin from SRF.²² Micrornucleic acids-143 inhibits VSMC proliferation by inhibiting Elk-1. Further, miR-143 target genes include protein kinase C-ε and PDGF receptor-α participating in cell migration and proliferation.^{23,24} In addition, the expression level of miR-143/145 would be down regulated in some vascular diseases,²² including injured or atherosclerotic vessels. Further, loss of the miR-143/145 cluster could promote neointima formation.^{18,22,25}

2) Micrornucleic acid-195. Wang et al²⁶ found that miR-195 reduced VSMC proliferation, migration, and synthesis of IL-1b, IL-6, and IL-8. Using bioinformatics prediction and experimental studies, they showed that miR-195 could repress the expression of CDC42, CCND1, and FGF1 genes. Using a rat model, they found that the miR-195 gene, introduced by adenovirus, substantially reduced neointimal formation in a balloon-injured carotid artery.

3) Other anti-proliferative miRNAs. In VSMCs, augmented miR-503 expression leads to reduced proliferation, migration by the down regulation of the miR-503 target genes CCNE1 and CDC25A.²⁷ Let-7d, an earlier discovered miRNA in human beings, is an important regulator of cell cycle and proliferation that can reduce the proliferation of VSMCs by inhibiting KRAS gene.²⁸ Recently, Merlet et al²⁹ found that miR-424/322 can also regulate VSMC phenotype and

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neointimal formation in the rat by targeting proteins involved in Ca²⁺ signaling, which is a mechanism well-known to induce VSMC proliferation. Additional miRNAs such as miR-1 and miR-133 have also been shown to reduce smooth muscle proliferation in vitro, and loss of these miRNAs may thus be involved in the development of neointimal hyperplasia.^{30,31} Wang et al³² found that miRNA-31 controls phenotypic modulation of human VSMCs by regulating its target gene cellular repressor of E1A-stimulated genes. At the same time, Choe et al³³ also revealed that the miR-132 targets Lrrkip1 to block VSMC proliferation and neointimal hyperplasia.

Micrornonucleic acids, which promote the proliferation and migration of VSMCs. 1)

Micrornonucleic acids-221/222. In VSMCs, miR-221/222-mediated down regulation of c-kit reduces the expression level of the potent smooth muscle cell-specific coactivator myocardin, which can keep VSMC in contractile and quiescent phenotype.³⁴ Micrornonucleic acids-221/222 play an additional role in modulation of VSMC proliferation by targeting the cell cycle inhibitor p27 (Kip1) and p57 (Kip2).^{35,36} As we know, PDGF-mediated signaling in VSMCs induces migration and proliferation, while, miR-221 was identified as a positive regulator in this signaling pathway. Knockdown of miR-221 expression in VSMCs significantly inhibited PDGF-induced migration and proliferation.³⁷

2) Micrornonucleic acids-21. Micrornonucleic acids-21 is up regulated in the neointimal and is one of the important regulators in VSMC proliferation and apoptosis.³⁸ The high expression of miR-21 can promote the proliferation of VSMC by targeting genes PTEN and PDCD4. When pulmonary artery smooth muscle cells (PASMCs) are in hypoxia, miRNA-21 up-regulation and PASMCs proliferation.³⁹ Micrornonucleic acids-21 also may promotes PASMCs proliferation and migration.

3) Micrornonucleic acids-146a. Another miRNA that participates in the phenotypic control of VSMCs is miR-146a. This miRNA promotes VSMC proliferation and neointimal hyperplasia in vivo.⁴⁰ It has been reported that miR-146a was up regulated in balloon-injured carotid arteries of rats⁴¹ and infection of antisense miR-146a oligonucleotides considerably decreased neointimal hyperplasia in these arteries.⁴¹ On one hand, this effect could be associated with the miR-146a target gene KLF4 and the potent cyclin-dependent kinase inhibitor p2140 and 2 VSMC differentiation-related

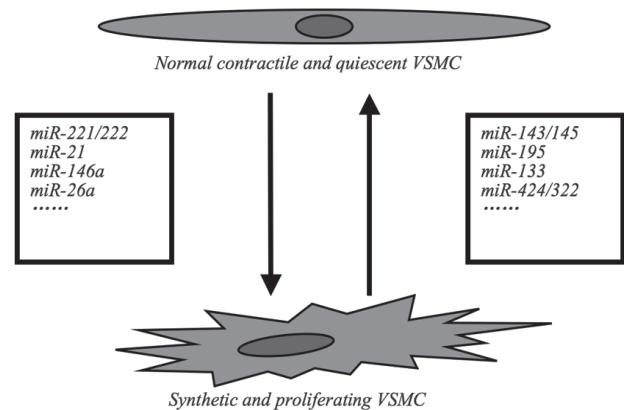


Figure 1 - Micrornonucleic acids are involved in the regulation of smooth muscle phenotype. Summary of highly expressed miRNAs (miR-143/145) in contractile vascular smooth muscle cell (VSMC) and miRNAs (miR-221/222) that are up regulated during phenotypic modulation of VSMCs into synthetic and proliferative cells in neointimal formation following vascular injury.

genes (smooth muscle-22α and α-smooth muscle actin). On the other hand, miRNA-146a also could regulate the maturation and differentiation of vascular smooth muscle cells by targeting NF-κB expression.⁴²

4) Other proliferative miRNAs. The miR-24-2 gene cluster located on human chromosome 19 encodes miR-24-2, miR-27a, and miR-23a. The 3 miRNAs are potent inducers of the synthetic, proliferative phenotype to VSMCs.⁴³ As a recently identified VSMC-specific miRNA, miR-26a promotes VSMC proliferation and migration through inhibiting apoptosis and differentiation by targeting SMAD-1 and SMAD-4; thereby, regulating the TGF-β signaling pathway.⁴⁴ At the same time, Kee et al⁴⁵ found that miR-142-5p promoted VSMC proliferation by down-regulating B cell translocation gene 3 (BTG3), which inhibited the expression of cell cycle regulatory genes and cell growth. Some researchers also found that the platelet-derived growth factor (PDGF) signaling pathway could regulate SMC-specific gene expression and cell proliferation by modulating the expression of miR-15b to induce a dedifferentiated state in the VSMCs.⁴⁶ Li et al^{47,48} proved that miR-638 and miR-663 are both key molecules in regulating human VSMC proliferation and migration by targeting different pathway. Micrornonucleic acids-638 regulated human VSMC proliferation and migration by targeting the NOR1/cyclin D pathway, while, miR-663 modulated VSMC phenotypic switch by targeting JunB/myosin light chain 9 expression. These findings suggest that targeting miR-663 and miR-638 or their specific downstream targets in human

VSMCs may represent an attractive approach for the treatment of proliferative vascular diseases.

In summary, the differentiation, migration, and proliferation of VSMC plays an important role in the formation of vascular restenosis. Micrornucleic acids, such as miR-143/145, miR-133, miR-195 or miR-221/222, and miR-21, are all involved in the regulation of the VSMC phenotype by targeting multiple genes; thus, it dysregulates the multiple cellular pathways and leads to vascular restenosis.

Micrornucleic acids-based drug and gene therapy in vascular restenosis. Micrornucleic acids are often up or down regulated in many diseases. The miRNA-based drugs have been designed to reduce or enhance miRNA expression for the particular therapeutic purpose. So far, anti-miR has been used to silence specific miRNA expression, whereas mimics of miRNA are used to increase the intracellular levels of specific miRNAs in vitro. The modified anti-miR drugs and mimics can be directly delivered into the target cells in vivo and have been shown to be very efficient, stable, and specific in regulating miRNA expression.⁴⁹⁻⁵² Recently, Jin et al⁵³ revealed that the expression of miR-21 in human umbilical vein endothelial cells (HUEVCs) was up regulated by rapamycin treatment, and treatment with a miR-21 inhibitor totally abolished the suppressive effects of rapamycin on endothelial proliferation and migration. It has been reported that the depletion of miR-21 could inhibit the proliferation of VSMCs and increase apoptosis.⁴¹ Treatment of VSMCs with anti-miR-221, anti-miR-222, and anti-miR-146a also represent a potential new strategy on vascular proliferative disorders. To harness miRNA's therapeutic potential, miRNA genes can be over expressed or silenced using delivery vectors (plasmid and viral vectors), which contain miRNA mimics or antagomir. However, miRNA-based gene therapy is just in its infancy. To date, the only gene therapy in clinical trial based on miRNA therapy is miR-122, which is a liver specific miRNA. The miR-122-based gene therapy is currently in phase 2 clinical trials.⁵⁴ It is a pity that miRNA-based drug and gene therapy in vascular restenosis are just developing, we still can see that vascular cell-specific miRNAs represent an important potential target for the treatment of vascular restenosis.

In conclusion, VSMCs have the ability to modulate their phenotype from a quiescent, contractile state to a proliferative, synthetic state in response to many stimuli, which participates in the formation of vascular restenosis.¹⁶ Micrornucleic acids play an important role in this process. Nowadays, miRNAs are considered

a promising clinical tool as therapeutic targets in vascular restenosis. However, miRNA-based drug and gene therapies in vascular restenosis is just in its infancy. To obtain knowledge of the potential target for the treatment of vascular restenosis, further study is required to ascertain the many functions of miRNAs in normal physiology and disease states.

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