Local Anti-miR Delivery
The Latest in the Arsenal of Drug-Eluting Stents
Kathryn J. Moore, Katey J. Rayner

MicroRNA-specific regulation of gene expression has now been implicated in the development of several pathophysiologic processes that underlie diseases of the cardiovascular system. As such, miRNAs have become attractive targets for the design of potential therapies aimed at atherosclerosis, myocardial infarction, and cardiomyopathy. However, their ability to control multiple pathways in different tissue types leads to the possibility that their inhibition will result in unwanted effects. One challenge has therefore been the development of tissue- or cell-specific miRNA therapeutic approaches that avoid these off-target effects. In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Wang et al report the targeted delivery of miR-21 inhibitors for the treatment of arterial in-stent restenosis (ISR) and demonstrate how using an anti-miR-21–coated stent approach overcomes untoward side effects of systemic anti-miR-21 delivery (Figure).

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Despite advances in the prevention and management of coronary artery disease risk factors, a substantial number of patients still require revascularization therapy to open obstructed vessels. Conventionally, metal stents were deployed in diseased coronary arteries to dilate the lumen and restore blood flow that is otherwise blocked by large atherosclerotic lesion(s). However, the risk of restenosis of the diseased vessel caused by the proliferation of vascular smooth muscle cells and increased synthesis of extracellular matrix is high with this approach, and stents that elute antiproliferative drugs are now widely used to prevent ISR because of myointimal hyperplasia. Current drug-eluting stents use small molecules that broadly inhibit the cell cycle to block proliferation, but do not specifically target the underlying mechanisms that accompany ISR, nor do they address mechanisms that prevail at later stages after stent implantation. To address this challenge, Wang et al investigated the regulatory role of microRNAs in ISR, using a humanized animal model in which balloon-injured human internal mammary arteries (hMA), with and without stenting, are transplanted into RNU nude rats. The authors identified miR-21 as being highly upregulated in stented hMA in this model and confirmed the increase of miR-21 expression in human ISR tissue samples compared with coronary artery disease specimens. Indeed, this miRNA has previously been associated with increased cell proliferation and decreased apoptosis in the vessel wall and was also found to be upregulated in murine, pig, and human vein graft failure models. Furthermore, genetic deletion of miR-21 or antisense-mediated inhibition of miR-21 using pluronic gel limited the proliferative response and reduced myointima formation in murine models, further underscoring its promise as a therapeutic target for ISR.

Wang et al first attempted to inhibit miR-21 systemically in the hMA-RNU rat model by delivering a single intravenous dose of a fluorescently labeled anti-miR-21 locked nucleic acid one day after hMA implantation. The retrieval of the stented vessels 28 days later showed that systemic miR-21 inhibition markedly reduced luminal obliteration compared with that in untreated mice, demonstrating the effectiveness of miR-21 inhibition in reducing smooth muscle cell proliferation. However, despite these promising effects on myointimal hyperplasia, systemic anti-miR-21 locked nucleic acid delivery also resulted in significant reductions of miR-21 expression in liver, heart, lung, and kidneys and was accompanied by an increase in serum creatinine levels, suggesting a negative impact on renal function. To overcome these unwanted side effects, the investigators next tried a targeted approach in which stents were coated with the anti-miR-21 locked nucleic acid to permit local delivery to the hMA vessels. After 28 days, vessels retrieved from the RNU rats showed that compared with otherwise identical bare metal stents, the anti-miR-21–coated stents markedly reduced ISR. Furthermore, no accumulation of the locked nucleic acid was observed in the kidney, and anti-miR-21 did not delay vessel re-endothelialization, a side effect of current drug-eluting stent medications, such as rapamycin, which is believed to be a major contributor to stent thrombosis and late ISR.

Although previous studies have suggested that miR-21 may regulate endothelial cell proliferation, anti-miR-21 treatment was not found to alter endothelial cell proliferation in the current study, which the authors suggest may be because of low endogenous miR-21 expression in the endothelium compared with the vascular smooth muscle cells that predominate in the myointimal response to injury.

An emerging risk after the placement of current-generation drug-eluting stents in diseased arteries is the development of late thrombosis and neoatherosclerosis, which is believed to result from a different mechanism than the initial proliferative response of early-phase ISR. Although the antiproliferative

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drugs currently used in drug-eluting stents are unlikely to combat this problem, a study of genetic miR-21 ablation in mice reported that reductions in neointimal formation after stent implantation were accompanied by a decrease in macrophage inflammatory activation.\textsuperscript{11} Although more work needs to be done to address this possibility, these data suggest that anti-miR-21–eluting stents may offer anti-inflammatory and antiproliferative effects that would be advantageous for combating late thrombosis in ISR.

This study is the first to use anti-miRs for the treatment of ISR and opens the door to the incorporation of anti-miRs into the arsenal of drugs available for use with drug-eluting stents. With the continuing discovery of miRNAs that modulate the vascular response to stent implantation, the potential for anti-miR combinations and time release formulations will no doubt offer interesting possibilities for the future. Finally, although this study represents an advance in targeting miRNAs in coronary arteries, we will need similarly creative solutions that allow anti-miR–based therapeutic modulation in a tissue- or cell-specific manner for the treatment of other disease conditions.

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Disclosures

None.

References


Figure. Anti-miR-21–coated stents prevent myointimal hyperplasia. In a stented artery (top), stent deployment compresses an existing plaque to open up the arterial lumen. Twenty-eight days later, significant myointimal hyperplasia occurs with a bare metal stent (left), resulting in restenosis and renarrowing of the vessel lumen. With an anti-miR-21–coated stent (right), there is reduced smooth muscle cell (SMC) proliferation, increased expression of miR-21 target genes, and reduced myointimal hyperplasia resulting in a preservation of lumen diameter.
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