Basic Science for Clinicians

Vascular Smooth Muscle Cell Proliferation in Restenosis

Steven O. Marx, MD; Hana Totary-Jain, PhD; Andrew R. Marks, MD

Current therapeutic approaches to restore blood flow in stenotic blood vessels involve the use of percutaneous devices and coronary bypass surgery. In all procedures that disrupt the normal integrity of the blood vessels, there is an increased incidence of vessel luminal narrowing, termed restenosis. Restenosis, arbitrarily defined as greater than 50% narrowing of vessel diameter compared with the reference vessel, is modulated by genetic background and diseases that affect the cardiovascular system, including diabetes, hypertension, and hypercholesterolemia. In the 1970s, Andreas Gruntzig pioneered the use of transluminal dilatation of coronary arteries for symptomatic coronary artery disease and reported a 19% rate of restenosis (6 of 32 patients). Subsequent studies demonstrated a restenosis rate of approximately 33%. More than 25 years later, despite pharmacological and mechanical approaches to reduce the incidence of restenosis, it remains a significant problem, especially in high-risk patient groups, limiting overall success.

Restenosis after percutaneous intervention is characterized by platelet aggregation, release of growth factors, inflammatory cell infiltration, medial smooth muscle cell proliferation and migration, and extracellular matrix remodeling. The vascular response to injury depends not only on the cells within the vessels but is also modulated by circulating bone marrow–derived cells. Understanding the molecular mechanisms underlying the physiological healing response and the pathological restenosis response has been the focus of extensive investigations, which have led to the development of novel approaches to control the pathological formation of the neointima. In this review, we will focus on some of the molecular mechanisms responsible for the abnormal neointimal hyperplasia, specifically focusing on cell cycle and microRNA (miRNA) in the vascular smooth muscle.

Pathophysiology of Restenosis

Acute occlusion at the percutaneous intervention site within hours to days after the procedure is usually caused by an intimal flap, thrombus formation, subintimal hemorrhage extending into the media, or elastic recoil of the overstretched vessel wall. The incidence of acute occlusion after percutaneous intervention has been minimized by the use of intravascular stents and aggressive anticoagulation/antiplatelet treatment during the perioperative period. Nevertheless, the overall rate of restenosis with bare-metal stents is approximately 20%. Drug-eluting stents have reduced the rate of restenosis, in most studies to <10%.

Animal models and human postmortem studies have shown that the mechanism of intimal hyperplasia is similar to wound healing. The wound-healing process can be divided into 3 phases: inflammatory phase (hours to days), granulation or cellular proliferation phase (days to weeks), and an extracellular matrix remodeling phase (months). After injury, there is deposition of platelets that release platelet-derived growth factor (PDGF) and other mitogenic factors that penetrate the vascular wall and trigger medial vascular smooth muscle cell proliferation and migration. The platelets also release chemokines, which initiate an inflammatory response. Over the first 2 weeks after injury, the vascular smooth muscle cells multiply 3 to 5 times, accounting for 90% of the ultimate intimal proliferation.

Endothelial Cells in Restenosis

A normal functioning endothelium is very important because it promotes vasodilatation and suppresses intimal hyperplasia by inhibiting thrombus formation, inflammation, and smooth muscle proliferation and migration. The endothelium provides a selectively permeable barrier that protects against circulating growth factors. Endothelial denudation and medial wall injury are the initial effects of balloon- and/or stent-induced injury and are important triggers of the wound “healing” program.

Vascular Smooth Muscle Cells

Vascular smooth muscle cells retain remarkable plasticity during postnatal development and can undergo dedifferentiation to a synthetic phenotype. This probably represents a survival advantage because it enables the efficient repair of the vasculature after injury. As in many evolutionarily conserved processes, these properties can be disadvantageous and can predispose to abnormal responses after injury, contributing to restenosis. Vascular smooth muscle progenitor cells have been identified in the bone marrow (multipotent vascular stem cell progenitors and mesenchymal stem cells), in the circulation (circulating progenitor cells), in the vessel wall (resident progenitors cells and mesangioblasts), and in extravascular sites.

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Correspondence to Andrew R. Marks, MD, Department of Physiology and Cellular Biophysics, Russ Berrie Medical Sciences Pavilion, Room 520, 1150, St Nicholas Ave, New York, NY 10032. E-mail arm42@columbia.edu
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Mechanisms of Smooth Muscle Cell Proliferation: The Cell Cycle

Smooth muscle cells progress through DNA replication and mitosis in a regulated series of cell-cycle events. Under normal conditions, quiescent smooth muscle cells are maintained in a nonproliferative phase (G0) (Figure 1). After vessel injury, smooth muscle cells enter a gap phase (G1), at which time factors necessary for DNA replication in the subsequent synthetic phase (S) are produced. After S phase, the cells enter another gap phase (G2), when proteins are synthesized for mitosis (M phase). Restriction points (R) at the G1-to-S and G2-to-M junctions ensure orderly progression through the cell cycle.

Growth factors, such as PDGF, basic fibroblast growth factor, and insulin-like growth factor-1, stimulate cells to enter the cell cycle and propel them to reach the R point in the late G1 phase. Beyond this, cell cycle progression from the G2 phase to the M phase does not require further growth factor stimulation. On binding to their respective cell surface tyrosine kinase receptors, growth factors trigger cell cycle entry by transactivating nuclear factors such as c-fos and c-myc. These nuclear factors act as transcriptional factors and increase the expression of various cell cycle regulatory proteins.

The cell cycle is coordinated by the expression and activities of regulatory proteins. Cyclins and their respective cyclin-dependent kinases (CDKs) form distinct complexes and are positive regulators of cell cycle progression. CDK phosphorylation of the retinoblastoma gene product (Rb) at the R point at G1-S junction is an important step in the progression through the cell cycle. Rb ordinarily binds to and inactivates the transcription factor E2F to maintain the cell in a quiescent state. Phosphorylation of Rb in late G1 releases E2F, which in turn enhances the expression of genes encoding regulatory proteins necessary for cell cycle progression through S, G2, and M.

The CDK inhibitors (CDKIs) are critical negative regulators of the cell cycle. The CDKIs are structurally divided into 2 different families: the INK4 family (p14, p15, p16, p18, and p19) and the KIP/CIP family (p21, p27, and p57). For example, p27Kip1, which binds to and inhibits phase G1 cyclin/CDK complexes, is maintained at high levels in quiescent cells and declines to permit cell cycle progression. In the later phases of arterial healing, p27Kip1 is upregulated, which is associated with inhibition of cellular proliferation. Another CDKI, p21Cip1, is present at low levels in G0, accumulates in late G1, and provides counterbalance to increased cyclin/CDK activities. Apart from CDKIs, other indirect cell cycle inhibitors also contribute to the regulation of mitosis.

Overexpression of p27Kip1 results in cell cycle arrest in the G1 phase. Gene transfer of p27Kip1 or p21Cip1 into balloon-injured vessels significantly reduced vascular smooth muscle cell proliferation and neointimal formation. Conversely, a reduction in p27Kip1 levels (caused by gene deletion in mice) resulted in increased neointimal formation and inflammatory cell accumulation after mechanical vascular injury.

Mechanisms of Smooth Muscle Cell Migration

In the uninjured vessel, vascular smooth muscle cells are nonmigratory because of a combination of several factors including the relative absence of stimulatory factors, their quiescence from a proliferative standpoint, and because the matrix is highly adhesive. There are many promigratory and antimigratory molecules, including small biogenic amines, peptides growth factors, cytokines, and extracellular matrix components. Blood flow, shear stress, and matrix stiffness

Figure 1. Schematic of cell cycle. Cell cycle progression is dependent on the regulated expression and activation of a set of kinases (cyclin-dependent kinases, cdks) and cyclins, which phosphorylate proteins that regulate cell growth including the retinoblastoma protein (pRb indicates unphosphorylated; ppRb, phosphorylated form) at the restriction point (R) at the G1/S junction. Cdk inhibitors p27Kip1 and p21Cip1 delay cell cycle progression by inhibiting cdk activity.

The normally quiescent smooth muscle cells within the medial layer of the vessel wall are activated to migrate and proliferate in response to increased stimulatory growth factors and cytokines (PDGF, interleukin-1, interleukin-6, and tumor necrosis factor-α) and reduced endothelium-derived inhibitory factors (nitric oxide, heparin sulfate proteoglycan). Some of the neointimal smooth muscle cells may also originate from the adventitial fibroblasts, which migrate to the intima and differentiate in myofibroblasts. Recent studies have challenged the concept that neointimal formation is dependent on the proliferation and migration of local endothelial and smooth muscle cells. It has been proposed that in models of postangioplasty restenosis, graft vasculopathy, and hyperlipidemia-induced atherosclerosis, smooth muscle progenitor cells are mobilized from the bone marrow and home to sites of vascular injury, differentiating into smooth muscle cells. In these studies, a bone marrow or circulating cell marker has been found to colocalize with vascular smooth muscle cell markers in vascular lesions after arterial injury or atherosclerosis. Based on the species, type of injury, and the method of labeling, the percentage of bone marrow–derived cells within the neointima is between 20% and 66%. Although the selective control of vascular smooth muscle progenitors in the vessel wall may be an attractive therapeutic target, the concept is controversial, and more studies are required to define the role of progenitor cells in mediating vascular diseases.
can also affect the migration of vascular smooth muscle.
Vascular smooth muscle cell migration begins with the
stimulation of cell surface receptors that activate signal
transduction pathways, which trigger remodeling of
the cytoskeleton, changes in the adhesiveness of the smooth
muscle cell to the matrix, and activation of the motor
proteins. Vascular smooth muscle cells extend lamellipodia
toward the stimulus through actin polymerization. Focal
contacts form just behind the leading edge to increase
adhesion of the cell membrane to the matrix. Vascular smooth
muscle cells also must degrade the focal contacts in the
trailing edge. The actin cytoskeleton is regulated by numer-
ous signaling pathways and molecules, including trimeric G
proteins, small G proteins, lipid kinases, Ca2+-dependent
kinases, Rho kinase,28 and mitogen-activated protein ki-
nases.27,29 Promigratory stimuli that increase myoplasmic
Ca2+ concentration activate myosin light chain kinase and
myosin II.30

Vascular smooth muscle cell migration is also linked to the
cell cycle and proliferation. Smooth muscle cells can migrate
when in the G1 phase but not in later phases of the cell
cycle.31 p21Cip1 and p27Kip1 are not only negative regulators
of the cell cycles but also have important inhibitory effects on
vascular smooth muscle migration. Overexpression of
p27Kip1 and p21Cip1 reduced human vein endothelial cell and
vascular smooth muscle cell migration in vitro.32,33 p27Kip1
inhibits the cellular changes such as lamellipodia formation
and reorganization of actin filaments and focal adhesions that
are associated with vascular smooth muscle cell migration.34
A p27Kip1 mutant that lacks CDK inhibitory activity failed to
inhibit the proliferation and migration of vascular smooth
muscle cells.34 p27Kip1 also affects the sensitivity to rapam-
ycin’s antimigratory effects in both vascular smooth muscle
and endothelial cells (see below).

Role of MicroRNAs in Regulation of Vascular
Smooth Muscle Cell Differentiation
Recent studies have demonstrated that microRNAs (miRNAs) are
expressed in the vascular system and are involved in control
of proliferation and differentiation of vascular smooth muscle
cells.35 Each miRNA is able to regulate the expression of
multiple target genes, frequently involved in the same cellular
pathway. Conversely, target genes may be affected by more
than 1 miRNA. It is presumed that thousands of human genes
are targeted by miRNAs.36

Mature miRNAs are short, noncoding ribonucleic acid
molecules, typically 22 nucleotides long, which bind to
complementary sequences in the 3’ untranslated regions of
target mRNA transcripts. PremiRNAs are exported from the
nucleus to the cytoplasm, where they are processed by an
RNase II enzyme, Dicer. They are then bound to
the miRNA-induced silencing complex, which contains 2 key
proteins, argonaute 2 and transactivation-responsive RNA-
binding protein, to form mature miRNA.37 The mature
miRNA and miRNA-induced silencing complex binds to
complementary sites in the mRNA transcripts and negatively
regulate gene expression. MiRNA binding leads to either
mRNA degradation or inhibition of translation, depending
on whether the miRNAs bind to their mRNA targets with
perfect complementarity or imperfect complementarity, re-
spectively.38,39 An important characteristic of miRNA expres-
sion is tissue- and cell-specific expression patterns.40

Overexpression of miR-145 or miR-143 is sufficient to
promote differentiation and inhibit proliferation of cultured
vascular smooth muscle cells.51,42 Deficiency of miR-145 or
miR-143 promoted the synthetic phenotype of vascular smooth
muscle, with increased migration to PDGF,43,44 miR-221 and
miR-222, expression of which can be transcriptionally in-
duced by PDGF, are also implicated in vascular smooth
muscle cell differentiation.55,46 Overexpression of miR-221
reduced differentiation and increased proliferation and migra-
tion of vascular smooth muscle. Reduction of miR-221
increased expression of smooth muscle differentiation mark-
ers and blocked the effects of PDGF on proliferation and
migration. miR-221 targets the 3’ untranslated regions of
C-Kit and p27Kip1 mRNA.

In response to vascular injury, the expression of miRNA is
dynamically regulated. At 7 days after balloon injury of the
rat carotid artery, 113 of 140 artery miRNAs were differenti-
tially expressed; 60 were upregulated and 53 were downregu-
lated.47 At 14 days after injury, 110 of 140 miRNAs were
differentially expressed and at 28 days after injury, 102 of the
140 artery miRNAs were differentially expressed. In partic-
ular, miR-21 had more than 5-fold increase compared with
control. Depletion of miR-21 caused decreased cell prolif-
eration and increased cell apoptosis. Local delivery of an
antisense oligonucleotide to knockdown miR-21 inhibited
neointima formation in rat carotid artery after angioplasty.47
Adenoviral-mediated gene transfer of miR-145, which is
downregulated after injury,47 inhibited neointimal lesion for-
mation in injured rat carotid arteries.42 Surprisingly, neointi-
mal formation was significantly impaired in miR-143 knock-
out, mir-145 knockout, or double knockout mice, which is
congruent with other reports.48 Knockdown of miR-221 and
miR-222, which are both increased in proliferative vascular
smooth muscle, inhibits vascular smooth muscle cell prolif-
eration and neointimal formation in rat carotid artery after
injury.45

In endothelial cells, miR-126 has been shown to be
required for migration and proliferation of human umbilical
vein endothelial cells in response to vascular endothelial
growth factor stimulation.49 miR-126 functions in part by
directly repressing negative regulators of the vascular endo-
thelial growth factor pathway, including the Sprouty-related
protein SAGED1 and phosphoinositol-3 kinase regulatory
subunit 2 (PIK3R2/p85-beta),49 and by regulating vascular
cell adhesion molecule 1 expression, which mediates leuko-
cyte adherence to endothelial cells.50

Current Therapies Targeting Vascular
Smooth Muscle Proliferation and Migration
Currently available drug-eluting stent formulations deliver
high concentrations of rapamycin, rapamycin analogues, or
paclitaxel into the vessel wall (Figure 2). We will briefly
review the mechanism of action of each.

Rapamycin
Rapamycin (AY-22,989, USAN name Sirolimus; Rapamune)
is a macrocyclic triene antibiotic produced by the filamentous
bacterium (*Streptomyces hygroscopius*). Rapamycin was isolated from a soil sample from Easter Island (Rapa Nui). At Ayerst Research Laboratories, rapamycin was found to have antifungal properties. However, the immunosuppressive activity of rapamycin precluded its development as an anti-biotic/antifungal agent. Subsequently, rapamycin was shown to have potent antitumor activity as well. Because it is extremely lipophilic, it easily passes through cell membranes.

The receptor for rapamycin in all eukaryotes is a 12 000-Dalton cytosolic protein, known as FKBP12 (FK506 binding protein, 12 kDa), which is a member of the immunophilin family of proteins possessing peptidyl-prolyl cis-trans isomerase activity (PPIase). A rapamycin-FKBP12 “gain of function” complex interacts with the target of rapamycin (TOR) proteins to potently inhibit signaling to downstream targets (Figure 2). A mammalian homologue has been cloned from several species and has been termed mTOR, FRAP (FKBP12 and rapamycin associated protein), RAFT (rapamycin and FKBP12 target), SEP (sirolimus effector protein), or RAPT (rapamycin target). The mTOR complex 1 (mTORC1) regulates growth through effectors such as S6K1 and 4E-BP1. The mTOR complex 2 (mTORC2) regulates the prosurvival kinase Akt/ PKB by phosphorylating it on Ser473, which is necessary for full activation of Akt, along with PDK1 phosphorylation of Thr308. Rapamycin binds to the intracellular protein FKBP12 to generate a drug-receptor complex that binds to and inhibits mTORC1. FKBP12-rapamycin does not bind to mTORC2, suggesting that mTORC2 is not directly inhibited by rapamycin. Rapamycin suppresses the assembly and function of mTORC2, which inhibits the phosphorylation of Akt Ser473. Thus, rapamycin and its analogues are universal inhibitors of mTORC1 and S6K1 and cell-type specific inhibitors of mTORC2 and Akt. Akt stands at the crossroads of growth factor and metabolic signaling and is strongly activated by insulin.

Rapamycin inhibits phosphorylation of the ribosomal S6 kinases (S6K1 and S6K2). S6Ks regulate translation of mRNAs possessing a 5′ terminal oligopyrimidine tract (5′TOP), a stretch of 4 to 14 pyrimidines found at the extreme 5′ terminus of some protein translation machinery mRNAs (reviewed in Reference 60). Rapamycin has also been shown to inhibit phosphorylation of 4E-BPs (eukaryotic initiation factor 4E binding protein), which then can compete with eIF4G proteins for binding with eIF4E. In addition, rapamycin can also modulate the phosphorylation of eIF4B and the translation elongation factor eEF2. Additional targets involved in translational control may also be downstream of TOR. Depletion of amino acids or glucose leads to rapid dephosphorylation of 4E-BP1 (PHAS-I) and p70 S6 kinase (S6K)-1.

Rapamycin also significantly reduces the kinase activity of the cyclin-dependent kinase (cdk) 4/cyclin D and cdk2/cyclinE complexes. This is achieved by increasing the cdk inhibitor p27^Kip1 in various cell lines. The cdk inhibitor p27^Kip1 inhibits cyclin E/cdk2 kinase activity by forming a complex (cyclinE/cdk2-p27^Kip1), leading to inhibition of phosphorylation of the retinoblastoma protein (pRB), as well as inhibition of the dissociation of the pRB:E2F complex. Loss of the ability to upregulate p27^Kip1 in BC3H1 myogenic cells is associated with rapamycin resistance and apoptosis on serum withdrawal.

Rapamycin inhibits intimal hyperplasia after both alloimmune and mechanical injury in rats. The mechanism of this inhibition was demonstrated to involve a direct effect of rapamycin on BC3H1 (myogenic cells) and smooth muscle cell proliferation and migration. The inhibition of cellular proliferation is associated with a reduction in the activity of CDKs and in retinoblastoma protein phosphorylation (pRB), leading to G1- to S-phase transition arrest. FK506 (tacrolimus) and FK520 (an analog of FK506) failed to inhibit either vascular smooth muscle cell proliferation or migration and in fact antagonize rapamycin’s antiproliferative and antimigratory properties through competition with FKBP12.

Mitogen-induced downregulation of p27^Kip1 is blocked by rapamycin. In p27^Kip1 null mice, we demonstrated relative rapamycin resistance in mixed embryonic fibroblasts (MEF) and splenic T-lymphocytes. In rapamycin-resistant myogenic cells (RR), constitutively low levels of p27^Kip1 were observed, which did not increase with serum withdrawal and rapamycin. The lack of p27^Kip1 reduces rapamycin-mediated inhibition of smooth muscle cell migration, which suggests an important role for p27^Kip1 in the signaling pathway(s) regulating smooth muscle cell migration. Silencing of p27^Kip1 also blocked the inhibitory effects of rapamycin on migration of endothelial cells. Decreased levels of p27^Kip1 in the vessel wall have been associated with markedly increased neointimal response after wire-injury. This study by the Nabel group demonstrated that the increased neointimal formation was due to lack of p27^Kip1 in cells within the vessel wall as well as bone marrow–derived cells. Thus, regulation of p27^Kip1 in nonvascular cells by rapamycin may be important in modulating the arterial response to injury. There is some controversy regarding the requirement for p27^Kip1 in mediating rapamycin’s inhibition of neointimal formation in vivo, with 1 study reporting that neointimal formation in p27^Kip1 null mice was not enhanced after wire injury and that rapamycin effectively reduced neointimal formation in p27^Kip1 null mice.

Systemic (intramuscular) administration of rapamycin (0.5 mg/kg×3 days before injury and 0.25 mg/kg for 14 days) was...
shown to significantly inhibit intimal proliferation in a porcine model of coronary artery balloon injury. Coronary arteries were analyzed at 4 weeks after injury revealing that rapamycin inhibited coronary intimal proliferation (control, 63±3.4% versus rapamycin, 36±4.5%, P<0.001). Rapamycin-coated stents were shown to inhibit restenosis in a porcine model of balloon injury/stent implantation. These preclinical data led to studies in humans demonstrating marked reduction of restenosis after rapamycin-coated stent implantation. Stents eluting analogs of rapamycin, including zotarolimus and everolimus, have also been shown to be efficacious in reducing restenosis after stent implantation.

Diabetic patients may remain at increased risk of developing in-stent restenosis, despite the use of rapamycin-coated stents. Hyperleptinemia, which is seen in diabetes and metabolic syndrome, is a risk factor for stroke and progression of coronary artery disease. Leptin can promote platelet aggregation, inflammation, endothelial dysfunction, and vascular smooth muscle proliferation and migration, which are involved in atherogenesis. Leptin activates the mTOR-signaling pathway in primary murine vascular smooth muscle cells, stimulating proliferation in vitro. Exogenous leptin, administered at levels comparable to those found in obese humans, promoted neointimal hyperplasia and significantly increased the dose of rapamycin required for effective inhibition of neointimal formation (Figure 3). Combination therapy with a PI3K inhibitor, LY294002, and rapamycin effectively inhibited the leptin-enhanced neointimal hyperplasia. These data suggest that in the setting of hyperleptinemia, higher doses of an mTOR inhibitor or combination therapy with mTOR and PI3K inhibitors may be more efficacious in limiting neointimal formation.

As discussed above, reendothelialization is an important component of the healing process after vascular injury. Rapamycin has been shown to prevent vascular endothelial growth factor–mediated and serum-stimulated proliferation of endothelial cells in vitro. Additionally, rapamycin inhibits endothelial cell migration in a p27Kip1-dependent manner. The first-generation drug-eluting stents are highly effective at blocking neointimal hyperplasia but also exhibit reduced stent endothelialization. These observations may be due to rapamycin’s direct effects on endothelial proliferation and migration.

Paclitaxel
Paclitaxel was isolated from the bark of the Western yew tree in 1971. Paclitaxel induces cell cycle arrest in vascular smooth muscle and inhibits neointimal formation in animal models. Paclitaxel is extremely lipophilic, which promotes the rapid cellular uptake of the drug. Paclitaxel triggers the assembly of microtubules into extraordinarily stable yet disorganized and dysfunctional polymers. Unlike colchicine, which inhibits microtubule assembly, paclitaxel shifts the microtubule equilibrium toward assembly and polymerization. Several important biological processes are inhibited by paclitaxel, including mitotic spindle formation during cell division, intracellular transport, maintenance of cellular shape, and motility. Paclitaxel inhibits smooth muscle cell proliferation and migration in vitro and in vivo. Stents eluting paclitaxel reduced neointimal formation in a porcine coronary artery injury model. The arteries demonstrated incomplete healing with the late persistence of macrophages and fibrin deposition. These findings indicated the need for tightly controlled drug release and a narrow toxic-therapeutic window. Clinical trials with the paclitaxel-eluting stent have shown efficacy in preventing in-stent restenosis.

Concluding Remarks
Smooth muscle proliferation and migration after percutaneous intervention represent the end result of natural healing processes triggered by vascular injury. Vascular smooth muscle cell proliferation, especially after stent implantation, plays a critical role in neointimal hyperplasia through cellular expansion and extracellular matrix deposition. Elucidating the molecular mechanisms responsible for smooth muscle cell proliferation has led to the development of novel therapeutic approaches, including rapamycin- and paclitaxel-eluting stents that have significantly improved the care of patients with coronary artery disease. To address the concerns about the potentially increased incidence of stent thrombosis in patients treated with drug-eluting stents, newer stents and coronary devices have been developed such as drug-eluting stents with biodegradable polymers, drug-eluting stents that are polymer-free, stents with novel coatings, completely biodegradable stents, bifurcation stents, and drug-eluting balloons. Many of these are currently undergoing preclinical and clinical trials. Newer, potentially more efficacious, more specific, and safer approaches may be on the horizon.
Although targeting miRNAs represents a potential therapeutic strategy to specifically inhibit vascular smooth muscle proliferation and migration, to inhibit vascular inflammation, or to enhance vascular reendothelialization, additional work is required to identify precise targets and improve delivery.

Disclosures

None.

References


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