Editorials

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Pathways of Proliferation
New Targets to Inhibit the Growth of Vascular Smooth Muscle Cells

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Excessive proliferation of vascular smooth muscle cells (VSMCs) contributes to the pathogenesis of many cardiovascular diseases, including atherosclerosis and pulmonary arterial hypertension (PAH). VSMC proliferation also underlies the failure of many therapies, notable examples being restenosis following coronary angioplasty, vein graft failure in patients with coronary artery bypass grafts, and transplant vasculopathy. Few therapies directly target excess VSMC proliferation, in part, because the underlying pathways have been unknown. Recently, several pathways of VSMC proliferation have been defined, and new therapeutic targets have emerged.

An example of the power of preventing VSMC proliferation in reducing human cardiovascular disease is the rapamycin (sirolimus)-coated coronary stent. After dozens of agents failed to prevent the 30% restenosis rate postangioplasty, this VSMC proliferation inhibitor reduced the number to ~6%. However, rapamycin has toxicities, limiting its systemic use.

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Regulation of VSMC Proliferation
Although it is not possible to discuss all molecules involved in controlling VSMC proliferation, some are noteworthy because...
they are recently recognized or are targeted by drugs that are either in clinical use or preclinical development. These are the low-hanging fruit that may be harvested in the attempts to selectively decrease VSMC proliferation in vascular disease.

**Mammalian Target of Rapamycin**

Mammalian target of rapamycin (mTOR) (Figure) is an ubiquitously expressed kinase that integrates cellular energy and nutrient status with external mitotic signals. When sufficient nutrients and appropriate mitogens are present, mTOR will lead to proliferation by the expression of several proteins including cyclin D1. Mitochondrial dysfunction, energy depletion, and amino acid deprivation all lead to mTOR inactivation, effectively blocking proliferation. The interaction of mTOR with mitochondria raises the possibility that changes in mitochondrial function would alter VSMC proliferation. Impaired mitochondrial function, and fusion has been proposed to be responsible for the development of certain forms of pulmonary arterial hypertension. In a potential link between this pathway and the present study, rapamycin upregulates CDK inhibitors p21WAF1 and p27KIP1 in VSMCs.

**PPARα Agonists**

Thiazolidinediones, such as rosiglitazone, are PPARα agonists (Figure) developed for the therapy of type 2 diabetes mellitus. They decrease VSMC proliferation by inhibiting mitogen-induced degradation of the CDK inhibitors p21WAF1 and p27KIP1. PPARα agonists might have a role in preventing transplant vasculopathy and neointima formation in PAH. For example, rosiglitazone reduces both pulmonary hypertension and vascular remodeling in pulmonary hypertensive apolipoprotein E–knockout mice fed a high-fat diet.

**Survivin**

Survivin (Figure), a known apoptosis inhibitor, was traditionally thought to be exclusively expressed in cancers but more recently has been found in vascular injury and PAH. However, survivin not only impairs apoptosis but also increases proliferation by initiating cell cycle entry. When survivin is translocated to the nucleus, it competes with CDK4 for interaction with p16INK4a, a potential link to the pathway described by Gizard et al. Inhibition of survivin can be therapeutically exploited to prevent neointima formation and reverses pulmonary hypertension and vascular obstruction in experimental models.

**Pre–B-cell Colony-Enhancing Factor and Histone Deacetylase**

The pre–B-cell colony-enhancing factor (PBEF) is a regulator of SMC proliferation that increases nicotinamide phosphoribosyltransferase activity, upregulating supplies of nicotinamide adenine dinucleotide (NAD+) for the SIRT transcription regulators. PBEF family members regulate transcription and apoptosis through their ability to deacetylate histones and nonhistone proteins (eg, p53 and TERT). PBEF is able to shift VSMC from a proliferative to a contractile phenotype. PBEF overexpression enhances cell survival whereas PBEF knockdown increases SMC apoptosis. Through regulation of histone deacetylase (HDAC) activity, PBEF modulates VSMC proliferation and survival. There is a potential interaction between the cyclin-CDK-telomerase pathway and HDAC. The HDAC inhibitor trichostatin A results in histone hypermethylation of the p21WAF1 promoter, leading to increased p21WAF1 expression and cell cycle arrest in a variety of cells, including VSMCs.

**Bone Morphogenetic Protein Receptor Type 2**

Loss of function mutations in bone morphogenetic protein receptor type 2 (BMPR2) (Figure) are common in familial PAH, a disease characterized by excessive VSMC proliferation, particularly in response to transforming growth factor (TGF)β. Signaling from the BMPR2 receptor involves the
SMAD signaling cascade. The connection of BMPR2 signaling to the cyclin–CDK–telomerase pathway is unknown; however, BMPR2 inactivation, which decreases VSMC differentiation, does lowers p27KIP1 expression.\textsuperscript{21}

**Future Studies**

There are several areas which were not addressed by Gizard et al\textsuperscript{2} that merit further study.

First, TERT activity can also be regulated at the posttranslational level by phosphorylation. For example, hypoxia (a well-established cause of pulmonary hypertension and excessive PASMC proliferation) increases TERT phosphorylation, which increases SMC proliferation.\textsuperscript{22} Thus, both activity and expression of TERT modulate telomerase activity and the role of “activity” deserves further study.

Second, there are many parallels between proliferation of VSMC and cancer cells.\textsuperscript{23} A recent publication demonstrated reduced TERT expression in cancer cells exposed to TGFβ, which was dependent on the −252 to +3 region of the TERT promoter.\textsuperscript{24} Comparative studies of this pathway in cancer and vascular disease may be profitable.

Third, as with most pathways, there is tissue heterogeneity in this pathway. Depending on cell type, E2F transcription factors can promote or inhibit TERT expression\textsuperscript{7} and different E2F transcription family members can have opposing effects on TERT promoter activity. The complexity of TERT expression needs further study to allow this mechanism to be therapeutically exploited.

**Conclusion**

Several signaling pathways exist in VSMCs to control proliferation (Figure). Although there are many upstream initiators of proliferation, there are fewer crucial downstream decision steps for determining whether VSMCs will proliferate. First, mTOR activation occurs only when the cellular environment is conducive for proliferation (sufficient nutrients/energy and absence of prohibitive signals). Second, many signaling pathways, including PPARα, converge in having effects of the CK inhibitors, including p16\textsuperscript{INK4a}, p21\textsuperscript{WAF1}, and p27\textsuperscript{KIP1}. Third, we now have another potential common point at which to attack proliferation-TERT.

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None.

**References**


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