The vasculature is composed of endothelial cells, vascular smooth muscle cells (VSMCs), fibroblasts, and immune cells with closely integrated functions. It is exposed to a variable environment of pulsatile flow and changing blood pressure, plus fluctuations in nutrient, oxidative, and cytokine stress. Adaptation to this changing environment is critical for sustained vascular health. VSMCs undergo a phenotype change in response to vascular injury, including migration, proliferation, and matrix production, also known as VSMC activation or phenotypic modulation. VSMC activation contributes to the progression of atherosclerosis and postangioplasty restenosis. Understanding the endogenous regulators of vascular plasticity and adaptation has revealed potential targets for pharmacological intervention to prevent vascular stenosis. For example, Ross established cAMP as a critical signaling pathway for the maintenance of VSMC quiescence. Since that time, agents that increase cAMP, such as phosphodiesterase inhibitors, have demonstrated usefulness for the vasodilators, with clinical implications for pulmonary vascular plasticity restenosis. For example, Ross established cAMP as a critical signaling pathway for the maintenance of VSMC quiescence. Since that time, agents that increase cAMP, such as phosphodiesterase inhibitors, have demonstrated usefulness for pulmonary hypertension.2,3 Intracellular accumulation of cAMP signals to protein kinase A and the cAMP-responsive Rap1 guanine nucleotide exchange factor, Epac; simultaneous activation of both of these pathways by cAMP is essential for the antiproliferative impact on VSMCs.3,4

The article by Chen et al5 in this issue demonstrates that the phosphodiesterase inhibitor cilostazol increases VSMC differentiation via cAMP signaling to the transcription factor cAMP response element binding protein (CREB). This result is consistent with reports that active CREB prevents mitogen-stimulated migration and proliferation in VSMCs and that dominant-negative CREB or CREB silencing has the converse effect.6,7 Contradictions to the VSMC differentiating effect of CREB were suggested by an earlier report that balloon angioplasty increases CREB phosphorylation transiently and that adenoviral delivery of dominant-negative CREB at the time of balloon angioplasty decreases neointimal plaque formation.8 Consistent with Tokunou et al,8 Chen et al8 demonstrate that balloon injury leads to CREB phosphorylation. The data of Chen et al offer some new insights into how to interpret these apparently conflicting data. Chen et al demonstrate that cilostazol leads to CREB phosphorylation and nuclear localization, whereas balloon injury leads to CREB phosphorylation with exclusion from the nucleus. In vivo proliferation with CREB nuclear export is consistent with our original report demonstrating loss of pulmonary artery CREB overlapping with increased proliferation detected by Ki67 in the hypoxic neonatal calf model.7 We have previously reported nuclear exclusion of phosphorylated CREB in response to platelet-derived growth factor, oxidized low-density lipoprotein, and cytokine mixtures.6,9,10 Cellular localization, nuclear environment (redox state, activity of other transcription factors, and corepressor or coactivator proteins), and DNA context (acetylation, methylation) all contribute to the nuclear interpretation of CREB phosphorylation.11 Acute nuclear exclusion of CREB in response to balloon injury would be expected to acutely decrease the cAMP-dependent CREB gene expression that maintains VSMC differentiation. It remains enigmatic that adenoviral dominant-negative CREB also decreases neointimal formation, suggesting a difference between the CREB regulation by cilostazol and the transcriptional response to the dominant-negative CREB adenovirus.

VSMC plasticity is critical for vascular health and is acutely regulated by nuclear localization of transcription factors and cofactors. In response to injury, changes in VSMC proliferation, migration, and matrix production are essential for adaptive remodeling, such as wound healing. In restenosis or the neointimal phase of atherosclerosis progression, this remodeling response is exaggerated. Nuclear export of CREB is a robust response to VSMC mitogen or oxidant challenge and now balloon injury.6,10 Reports indicate that neuronal CREB is excluded from the nucleus in response to stress and can be targeted to the mitochondria to enhance mitochondrial oxidative gene expression.12,13 The report by Chen et al5 suggests CREB nuclear export in a regulatory mechanism that occurs in vivo and correlates with VSMC phenotype. Dynamic CREB nuclear export in the vascular remodeling is similar to other transcriptional responses leading to phenotypic modulation. For example, leupaxin is a LIM domain protein family member and cofactor for serum response factor. In response to focal adhesion kinase signaling (such as can be stimulated by fibronectin), leupaxin is sequestered in the cytosol, leading to decreased expression of the serum response factor–dependent contractile proteins α-smooth muscle actin and smooth muscle-myosin heavy chain.14 Myocardin and myocardin family members are critical serum response factor cofactors and determinants of VSMC differentiation. Myocardin is constitutively located in the nucleus, but other family members are translocated to the
Figure. Nuclear export in vascular remodeling: Transcription factors such as myocardin and CREB maintain the quiescent vascular smooth muscle cells (VSMC) phenotype. In response to vascular injury they are exported from the nucleus. This provides an additional mechanism for acute and reversible VSMC phenotypic modulation.

nucleus in response to activation of Rho kinase on bone morphogenic protein 4 signaling, leading to increased VSMC contractile protein expression.15,16 Thus, control of VSMC phenotype is tightly and rapidly regulated by nuclear trafficking.

The new data presented by Chen et al5 add support to the following model (Figure): in response to vascular injury, VSMCs undergo a rapid and reversible phenotype switch to permit wound healing. Nuclear exclusion of CREB and other cofactors is likely a permissive transcriptional modulator of this phenotype switch. Agents or local factors that stimulate nuclear CREB or myocardin nuclear localization, such as nitric oxide or cilostazol, will attenuate the proliferative response at the completion of adaptive remodeling. In disease states with diminished VSMC CREB content, the remodeling response may go unabated, thereby contributing to the progression of vascular disease.

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References


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