Smooth muscle cell (SMC) accumulation in the arterial intima is a key event in restenosis after angioplasty and bypass surgery and in the development of atherosclerotic lesions. Restenosis, which is defined as “the arterial healing response after injury incurred during transluminal coronary revascularization,” has been the principal drawback of percutaneous coronary interventions (PCI) since their introduction. The accumulation of arterial SMCs is caused by a combination of proliferation and directed migration of arterial SMCs from the media into the intima. Both these activities can be induced by cytokines and growth factors produced within the arterial wall and circulating cells in response to the vascular injury. A commonly accepted model of the response to arterial injury suggests that growth factors are released after injury, thereby changing the composition of the extracellular matrix and triggering a proliferation and migration program. SMCs undergo a phenotypic modulation from a contractile to a synthetic phenotype (dedifferentiation), proliferate into the media, migrate from the media into the intima, and subsequently form the neointima.

SMC transition from G1 to Gs cell phase induces neointima formation and modulates the atherosclerotic growth. The cell cycle is regulated by the interaction of multiple proteins, including cyclins, cyclin-dependent kinases, and phosphatases. Molecular complexes containing CDKs, cyclins, proliferating cell nuclear antigen (PCNA), and several other proteins regulate the major cell cycle transition points at the G1/S and G2/M boundaries. In addition to p21 and PCNA, the CDK2/cyclin A kinase complex includes a 19-kDa protein (p19, or SKP1) and a 45-kDa protein (p45, or SKP2).2,3

SKP2 contains a binding motif of ≈40 residues, termed the F box associated with leucine-rich regions (LRRs). Essential for S-phase entry, Skp2, component of the SCFskp2 ubiquitin ligase, is responsible for polyubiquitylation of cell-cycle regulators.4–9 Its major physiological target is cdk inhibitor p27kip1.5,10 SKP2 specifically recognizes phosphorylated p27 predominantly in S phase rather than in G1 phase, decreasing its levels and forcing cells into S phase (see Figure).

Several in vitro and in vivo studies demonstrated that the activation of cAMP-PKA signaling leads to inhibition of SMC proliferation.11–13 Furthermore, it has been shown that the antiproliferative effects mediated by increase in cAMP and cGMP levels are mediated by the upregulation of p27kip1 levels and inhibition of CDK2.14–16 In addition, recent data show that phosphodiesterase 1A inhibition attenuates SMC proliferation through elevation of cGMP levels, p27kip1 upregulation, and cyclin D1 downregulation.16 To date it is poorly understood how cyclic nucleotides regulate intracellular cyclins trafficking and particularly p27kip1 levels.

Cyclic Nucleotides Modulates Skp2 Levels and SMC Proliferation

In this issue of Circulation Research, Wu et al show that S-phase kinase-associated protein-2 (Skp2) levels are upregulated in proliferating vascular smooth muscle cells (VSMCs) in vitro and after balloon injury of the rat carotid artery in vivo. Skp2 siRNA results in increased levels of p27kip1 and reduced proliferation. cAMP is shown to suppress Skp2 levels by inhibiting transcription and by decreasing protein stability. The authors show that Skp2 overexpression overcame cAMP-induced cell cycle arrest and upregulation of p27Kip1 showing that Skp2 is an important factor in VSMC proliferation and its inhibition of cyclic nucleotides in vitro and in vivo.17

A novel aspect of this work is that for the first time it has been shown that activating signaling downstream to cyclic nucleotides regulates Skp2 expression via inhibition of FAK. Interestingly, exogenous expression of a constitutively active mutant of FAK was able to rescue Skp2 expression and markers of G1-S phase progression after forskolin treatment, showing the role of FAK as mediator of cyclic nucleotides of SMCs proliferation (see Figure).

FAK activation is required to integrate integrin signals with those from receptor tyrosine kinases and G protein–coupled receptors through downstream activation of Rac1.18 FAK activation by the mechanical stress of the arterial wall triggers a molecular cascade involving the mitogen activated protein kinases (MAPKs)19,20 leading to cell proliferation. Several biological processes occurring in the arterial wall from angiogenesis to inflammation involve the focal adhesion molecules.21,22 FAK is also involved in controlling cell motility, an important step in neointima formation.23 Alternative signal pathways can modulate the molecular complexes of the adhesion system regulating a variety of cellular processes. Further investigation of the mechanisms that underlie Skp2 controlling from the PKA–FAK axis is needed. A crucial step that also needs to be investigated is p27kip1 breakdown control. Indeed, recent studies suggest that alter-
native molecular pathways can be involved in p27kip1 degradation.

Perspectives

The ability to modulate SMC proliferation in vivo has given the possibility to generate new therapeutic tools for cardiovascular disorders. Drug eluting stents are changing the outcome of patients undergoing percutaneous coronary interventions for the treatment of atherosclerotic lesions. The present study improves in a significant manner our understanding of cAMP signaling, a key pathway in the regulation of cardiovascular homeostasis. This work suggests new critical steps in the regulation of SMC proliferation. Further studies are needed to address the therapeutic potential of manipulating these pathways for vasculoproliferative disorders.

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References

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