PDE1C Negatively Regulates Growth Factor Receptor Degradation and Promotes VSMC Proliferation

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The endothelium regulates the contractile status of vascular smooth muscle cells (VSMCs).[1] The interaction between endothelial cells (ECs) and VSMCs plays an important role in regulating vascular homeostasis. ECs release vasoactive factors, such as prostacyclin, (nitric oxide [NO]), and endothelium-derived hyperpolarizing factor, which participate in the regulation of vascular tone.[1] Endothelial dysfunction induces the increased expression of adhesion molecules for inflammatory cells. Accumulated inflammatory cells generate an oxidizing environment, which involves abundant reactive oxygen species, inflammatory cytokines/chemokines, and growth factors that contribute to VSMC phenotypic modulation.[2] Thus, EC damage is a trigger underlying VSMC phenotypic change and pathological vascular remodeling.

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Under normal physiological conditions, VSMCs in the media of vessels are quiescent with a low turnover rate and insignificant secretory activity. They are highly differentiated cells, which show a contractile phenotype and regulate vascular tone. However, VSMCs are among the most plastic of all cells in their ability to respond to different stimuli and retain a degree of plasticity to allow phenotypic modulation. It is thought that VSMCs change from a quiescent/contractile to an active/synthetic phenotype in several vascular diseases.[3] Synthetic VSMCs downregulate contractile proteins and upregulate growth factors, receptors, extracellular matrix proteases, and inflammatory proteins. Besides VSMC phenotypic change, the transdifferentiation of adventitial fibroblasts,[4] the differentiation of progenitor cells/stem cells,[5,6] and endothelial-to-mesenchymal transition may also contribute as the sources of synthetic VSMCs.[7] Regardless of the sources, synthetic VSMCs proliferate, migrate, and secrete proteins, including extracellular matrix proteases, proinflammatory cytokines/chemokines, and growth factors. Therefore, it is of great interest to develop novel strategies targeting the VSMC phenotypic change from the contractile to synthetic state.

Vascular ECs themselves produce abundant molecules, which play a crucial role in EC protection.[8] EC-dependent relaxation is mediated by prostacyclin, NO, and endothelium-derived hyperpolarizing factors.[9] Prostacyclin and NO stimulate the production of cAMP and cGMP, respectively, in adjacent VSMCs.[8] cAMP and cGMP promote VSMC relaxation and inhibit VSMC proliferation, migration, and extracellular matrix production. Cyclic nucleotide phosphodiesterases regulate the intracellular cyclic nucleotide signaling by catalyzing the hydrolysis of cAMP and cGMP to 5′AMP and 5′GMP.[7] Among the various phosphodiesterase isozymes expressed in different types of VSMCs, 1C (PDE1C), which hydrolyzes both cAMP and cGMP, is induced in synthetic VSMCs[10] and promotes VSMC proliferation.[11] In this issue of *Circulation Research*, Cai et al[12] designed experiments to understand the regulation and function of phosphodiesterases in the modulation of VSMC phenotype, and the mechanism whereby PDE1C promotes VSMC proliferation. The authors demonstrate that PDE1C is an important regulator not only of VSMC proliferation but also of VSMC migration and neointimal hyperplasia, and that the mechanism involves, at least in part, endosome/lysosome-dependent platelet-derived growth factor receptor β (PDGFRβ) degradation and degradation of other growth factor receptors (Figure). First, to understand the specific cyclic nucleotide signaling pathway responsible for the synthetic VSMC phenotype, the authors performed screening for phosphodiesterase isozymes that are specifically expressed in synthetic VSMCs when compared with those in contractile VSMCs. The authors found that the PDE1C isozyme is significantly upregulated in synthetic VSMCs, consistent with previous studies.[10] Next, the authors used in vitro and in vivo approaches and demonstrated that PDE1C plays a causative role in synthetic VSMC proliferation/migration and intimal hyperplasia.[12] Finally, the authors elucidated the molecular mechanism by which PDE1C promotes the protein stability of PDGFRβ and other growth factor receptors via negatively regulating endosome/lysosome-mediated degradation in an low-density lipoprotein receptor–related protein 1 (LRP1)–dependent manner (Figure).

PDGF receptor signaling has a variety of actions in VSMCs, including proliferation, migration, protein production/secretion, and phenotypic modulation. Therefore, this study provides novel information about the role of PDE1C in PDGF signaling, which serves as an important multifunctional regulator in synthetic VSMCs. Elevation of cAMP generated by transmembrane adenylyl cyclase activates cAMP-dependent protein kinase A, then phosphorylates LRP1, and promotes endocytosis of PDGFRβ, which proceeds to lysosome-mediated

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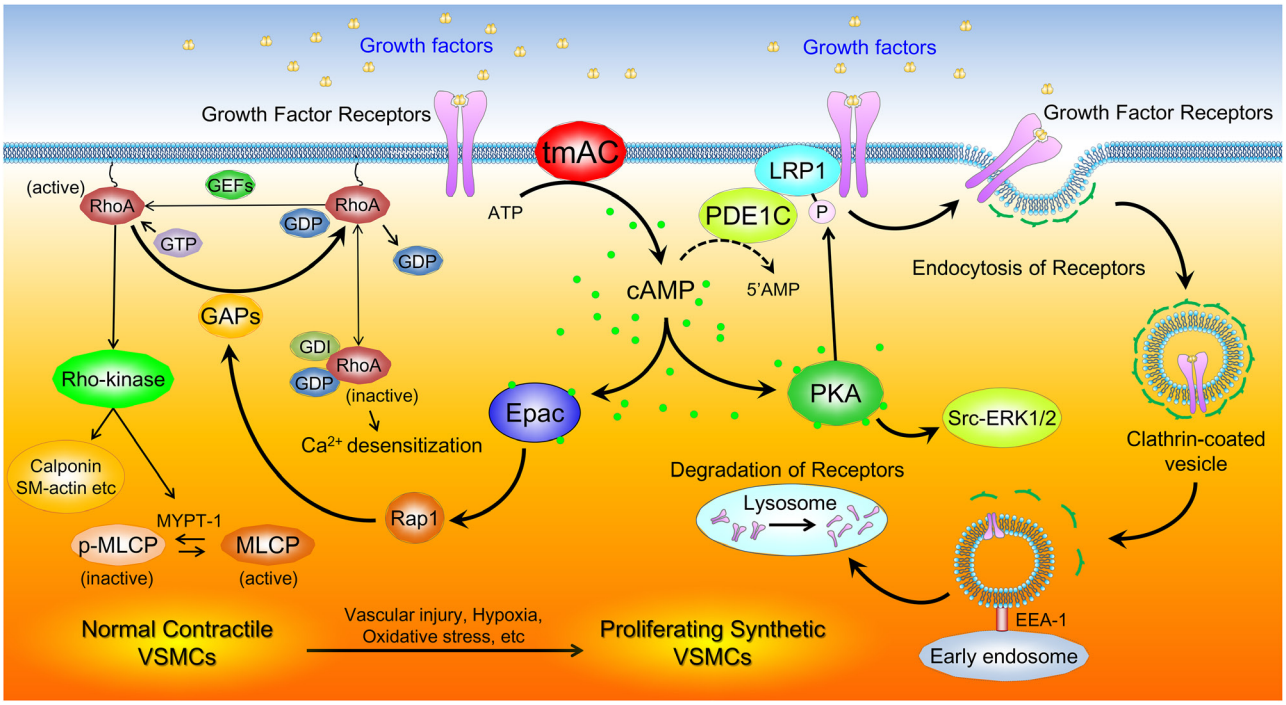

Figure. Phosphodiesterase 1C (PDE1C) is an important regulator of vascular smooth muscle cell (VSMC) phenotypic change in part through modulating endosome/lysosome-dependent growth factor receptor internalization and endocytosis. Cyclic nucleotide PDE1C upregulation antagonizes the transmembrane adenylyl cyclase (tmAC)-cAMP-cAMP-dependent protein kinase A (PKA) signaling and thus suppresses growth factor receptor (GFR) degradation, which facilitates VSMC phenotype modulation. Low-density lipoprotein receptor–related protein 1 (LRP1) is an important mediator in PDE1C–cAMP regulation of GFR protein degradation. Internalized GFRs have many different fates: sustained signaling within early endosomes, recycling to the plasma membrane, or trafficking to lysosomes for degradation. GFR endocytosis and lysosome degradation prevent sustained growth factor activation on the plasma membrane. Ras homolog gene family member A (RhoA) acts as a molecular switch that cycles between an inactive GDP-bound and an active GTP-bound conformation interacting with downstream targets to elicit a variety of cellular responses. The activity of RhoA is controlled by the guanine nucleotide exchange factors (GEFs) that catalyze exchange of GDP for GTP. In contrast, GTPase activating proteins (GAPs) stimulate the intrinsic GTPase activity and inactivate RhoA. Here, cAMP-exchange protein activated by cAMP (Epac)-Rap1 activation regulates GAPs, which contribute to RhoA inactivation and potentially contribute to the VSMC phenotypic switch. Rho-kinase was identified as the effector of Rho. Phosphorylation of myosin light chain (MLC) is a key event in the regulation of VSMC contraction. MLC is phosphorylated by Ca^{2+}-calmodulin–activated MLC kinase and dephosphorylated by MLC phosphatase (MLCP). The substrates of Rho-kinase have been identified, including MLC, myosin-binding subunit or myosin phosphatase target subunit (MYPT-1), ERM family, calponin, and smooth muscle (SM) actin. Rho-kinase mediates agonist-induced VSMC contraction. EEA-1 indicates early endosome antigen 1; ERK1/2, extracellular signal–regulated kinase 1/2; GDIs, guanine nucleotide dissociation inhibitors; p-MLCP, phosphorylated MLCP; and Rap1, Rho GTPase activating protein 1.

PDGFRβ degradation and subsequently reduces the PDGFRβ protein level (Figure). Consistently, previous studies have shown that LRP1 depletion in VSMCs resulted in elevated PDGFRβ level and activation, increased VSMC proliferation and migration, and accelerated atherosclerosis and aortic aneurysm in VSMC-specific LRP1 knockout mice.[13] LRP1 plays diverse roles in a variety of biological processes, including lipoprotein metabolism, clearance of plasma proteins, protease degradation, as well as receptor trafficking and signaling. This study clearly demonstrates that LRP1 is important in PDE1C/cAMP-mediated regulation of PDGFRβ stability and availability. Based on this study and the previous reports, cAMP/PKA directly modulates LRP1 function, likely through PKA phosphorylation of LRP1. cAMP might also regulate VSMC phenotypic change by modulating RhoA activity and downstream Rho-kinase (Figure). Taken together, these data implicate the induction of PDE1C as an important component of VSMC phenotypic change from the contractile to synthetic state.

Clinical Perspectives

The authors have shown that PDE1C regulates soluble adenylyl cyclase/cAMP signaling and lysosome-mediated collagen I protein degradation.[14] Besides in VSMCs, PDE1C is also expressed in human cardiac myocytes with an intracellular distribution distinct from that of phosphodiesterase 3A.[15] These findings may have great therapeutic impact as it may lead to the development of novel therapeutic strategies using PDE1C-selective inhibitors for cardiovascular diseases.[16] Here, blockade of PDGFR signaling by oral administration of Imatinib (a tyrosine kinase inhibitor) has been shown to inhibit pulmonary VSMC proliferation and ameliorate the development of pulmonary arterial hypertension (PAH).[17,18] The pathobiology of PAH includes EC dysfunction, VSMC proliferation/migration, and inflammation.[19–23] PDGF has been implicated in these processes[24] and altered PDGF signaling is involved in the vascular remodeling observed in PAH.[22] Thus, PDE1C may represent a novel therapeutic target for VSMC phenotypic modulation in systemic hypertension, aneurysms, and PAH.[25] The present findings in VSMCs may also be applicable to pulmonary artery

VSMCs, and PDE1C inhibition may represent a novel strategy to target PDGFR degradation in PAH. Because PDE1C is markedly induced in synthetic VSMCs, PDE1C inhibitors may show less adverse effects compared with Imatinib. Highly selective PDE1C inhibitors that can target synthetic VSMCs are likely to be developed in the near future. Additionally, clinical trials will be required to investigate whether inhibition of PDE1C prevents the development of PAH, in which the phenotypic change of VSMCs from a quiescent state to a proliferating state significantly contributes to the underlying pathology.

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Disclosures

None.

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