A novel function of PI3Kγ on cAMP regulation, role in arterial wall hyperplasia through modulation of smooth muscle cells proliferation

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Arterial fibrosis and stiffness are characterized by vascular smooth muscle cells (vSMC) proliferation. These hyperplastic processes involved inflammation as well as disrupted flow contributing to vascular remodeling in hypertension and intimal hyperplasia after percutaneous angioplasty. Our previous results have identified phosphoinositide 3-kinase gamma (PI3Kγ), a GPCR activated PI3K, as an essential actor of inflammatory processes in arterial wall. In this work, we identified for the first time a key role of PI3Kγ in vSMC proliferation through a kinase independent mechanism. Indeed, comparison of post angioplasty intimal hyperplasia (IH) in mice deleted for PI3Kγ (PI3Kγ-KO) or mice expressing an inactive form of PI3Kγ (PI3Kγ-KD) specifically in extra medullar compartment revealed that a catalytic independent function of PI3Kγ in non-immune cells promotes IH development. In addition a flow induced arterial remodeling model shown that PI3Kγ-KO mice present a lower medial hyperplasia compared to PI3Kγ-KD mice or WT mice, demonstrating a catalytic independent function of PI3Kγ.

We then investigate in aortic smooth muscle cells molecular mechanism involved. We showed that forskolin induced higher elevation of cAMP in PI3Kγ-KO genotype compared to PI3Kγ-KD and WT cells indicating that PI3Kγ could modulate degradation of this nucleotide through a catalytic independent function. Analysis of phosphodiesterase activity in PI3Kγ-KO, PI3Kγ-KD and WT smooth muscle cells showed that absence of PI3Kγ was responsible for a decrease in phosphodiesterase (PDE) 4B and 4D isoforms activity. Moreover, we showed that loss of PI3Kγ expression in smooth muscle potentiates the regulation effect of forskolin on smooth muscle cell proliferation. Finally, we develop a novel therapeutic strategy using a permeant peptide able to interact with PDE complex blocking docking function of PI3Kγ. In vitro, this peptide prevented vSMC proliferation in presence of forskolin as observed in absence of PI3Kγ. Finally, local delivery of this peptide decreased flow induced medial vSMC hyperplasia in WT mice. These data provide evidence for a novel function of PI3Kγ in regulation of SMC in arterial remodeling through activation of PDE 4B and 4D. These results indicate that novel strategies targeting docking function of PI3Kγ could be considered in the treatment of cardiovascular diseases.