**CRUCIAL ROLE OF PI3-KINASE GAMMA IN VASCULAR SMOOTH MUSCLE CELL PROLIFERATION AND NEOINTIMA FORMATION BY REGULATING Skp2 AND p27(kip1)**

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**Objective:** Phosphoinositide 3-kinase gamma (PI3Kγ) is a key regulator of inflammatory responses and cardiovascular homeostasis. We and others have recently shown that PI3Kγ expressed in blood platelets and leukocytes plays a significant role in neointima formation in the response to vascular injury by regulating vascular inflammation. Because PI3Kγ is expressed not only in blood cells but also in vascular cells, here we examined the role of PI3Kγ contributed by vascular wall cells in vascular smooth muscle cell (VSMC) proliferation and neointima formation in the response to vascular injury.

**Methods:** Vascular injury response was studied in mice using two different models: carotid artery ligation and femoral artery wire-denudation injury. PI3Kγ chimeric mice were created by bone marrow transplantation.

**Results:** Four weeks after injury, neointimal lesion size was reduced by 90% in PI3Kγ knockout (KO) compared with wild type (WT) mice in both injury models. Intriguingly, bone marrow chimeras revealed a marked reduction (>80%) in neointima formation in chimeric mice lacking either vascular wall- or bone marrow- associated PI3Kγ in both injury models. VSMC Proliferation was significantly reduced to similar levels in PI3Kγ KO mice and the chimeric mice lacking vascular wall-associated PI3Kγ. In vivo and in vitro data further showed that deletion of PI3Kγ in VSMC inhibited cell proliferation by regulating two key cell cycle regulators, i.e. reduced level of Skp2 (S-phase kinase-associated protein 2) and increased level of p27(Kip1), leading to cell cycle arrest at the G0/G1 phase. No differences in apoptosis between PI3Kγ KO and WT VSMCs were observed.

**Conclusions:** PI3Kγ signaling in VSMCs seems to be centrally involved in VSMC proliferation and neointima formation by regulating Skp2 and p27(kip1). Modulating PI3Kγ signaling on local vascular wall may become a new therapeutic target against proliferative vascular disease.