PI 3-kinase isoform PI3Kalpha controls smooth muscle cell functionality and protects against aortic aneurysm formation

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Background: Class I PI 3-kinase isoform PI3Kα is a lipid kinase and signals downstream of receptor tyrosine kinases. Smooth muscle cells (SMCs) lacking PI3Kα are characterized by impaired proliferation, migration and survival. Mice, harbouring a smooth muscle specific PI3Kα deficiency (SM-PI3Kα–/–), display reduced vascular wall thickness and impaired vascular remodeling in response to vessel injury. We hypothesize that SM-PI3Kα–/– mice are prone to aortic aneurysm (AA) formation due to impaired SMC functions. Herein, we investigated, how PI3Kα-dependent signaling in SMCs affect aortic aneurysm (AA) formation, aortic wall structure, and expression of extracellular matrix (ECM) components.

Methods and results: AA formation in SM-PI3Kα–/– mice and wild-type littermates was examined by means of the "porcine pancreatic elastase" (PPE) AA model. PPE was infused into the infrarenal aorta to induce AA formation. Ultrasound examination revealed a significantly increased aortic diameter in SM-PI3Kα–/– mice (1.22±0.12 mm) compared to wild-type animals (0.96±0.02 mm, p=0.014). These data indicate a protective function of SM-PI3Kα in AA formation. In addition, the media thickness in the abdominal aorta was significantly reduced in SM-PI3Kα–/– mice (29.0±3.1 vs. 42.5±4.1 µm). Ultrastructural analysis of aortic wall morphology in SM-PI3Kα–/–mice using transmission electron microscopy (TEM) showed a deranged tunica media with detached SMCs and increased apoptotic cell death. Consequently, SM-PI3Kα deficiency significantly diminished responsiveness of aortic rings to vasodilator acetylcholine and NO-donor nitroglycerin, further indicating impaired aortic wall structure. Western blots demonstrated a reduced elastin and fibrillin expression in SMCs from SM-PI3Kα–/– mice. Furthermore, immunofluorescence stainings of PI3Kα–/– and wild-type SMCs, cultured for seven days under 10% fetal calf serum containing DMEM medium, showed significantly disturbed structures of elastin-, fibrillin-1- and collagen-1-fibers. These data indicate that PI3Kα signaling contributes to elastic fiber homeostasis thus affecting SMC phenotypic modulation. Immunoblots demonstrated that PDGF and insulin induced phosphorylation and inactivation of key regulators of SMC differentiation and dedifferentiation including FoxO1, FoxO3a, Foxo4, and GSK3b, respectively, were reduced or even abrogated in PI3Kα–/– SMCs.

Conclusion: These data show that deficiency of PI3Kα in SMCs promotes the formation and progression of AA. Causative is a deranged aortic structure of SM-PI3Kα–/– aortae which can likely be attributed to an impaired production of elastic fiber components by PI3Kα–/– SMCs.