

## **The role of the PI 3-Kinase isoform p110 $\alpha$ for vascular remodeling in experimental pulmonary hypertension**

Pulmonary arterial hypertension (PAH) is a devastating vascular disease characterized by chronically elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), which is mainly due to vascular remodeling processes occurring in pulmonary arterioles. Pulmonary arterial smooth muscle cells (PASMCs) are crucially involved in these processes as they display an increased proliferation and migration, mainly triggered by peptide growth factors. Previous work demonstrated that PI 3-kinase (PI3K) is a central mediator of SMC proliferation and migration.

The main aims of this thesis were (i) to systematically characterize the importance of the catalytic class IA PI3K isoforms (p110 $\alpha$ , p110 $\beta$ , p110 $\delta$ ) – which signal downstream of receptor tyrosine kinases – for cellular responses in human PASMCs, and (ii) to characterize the role of the identified isoform for the pathobiology of PH *in vivo* by utilizing a genetic and a pharmacological approach.

In lung samples from PAH patients and from hypoxia-exposed mice, phosphorylation of the PI3K target AKT was profoundly increased as compared to healthy subjects/control mice, suggesting enhanced signaling via PI3K in these disease conditions. Using isoform-specific PI3K inhibitors, the catalytic subunit p110 $\alpha$  was identified as the central downstream mediator of growth factor-induced proliferation and migration of human PASMCs. Based on these findings, a genetic mouse model was generated, harboring a targeted deletion of p110 $\alpha$  in SMCs. Using this genetic model, it was demonstrated that lack of p110 $\alpha$  in SMCs blunts PASMC proliferation and migration induced by numerous growth factors that all contribute to disease progression. SM-specific ablation of p110 $\alpha$  and pharmacological inhibition using the p110 $\alpha$  specific inhibitor PIK75 prevented vascular remodeling in the hypoxia-induced mouse model *in vivo*. The increase in the fraction of fully muscularized small pulmonary vessels by hypoxia and the decrease in the fraction of non-muscularized vessels were both normalized to nearly normoxia levels. Additionally, hypoxia-induced medial wall thickening of the small vessels, elevation of right ventricular systolic pressure (RV<sub>sys</sub> as a measure of PAP), determined by invasive hemodynamic measurement, and RV hypertrophy were prevented in both approaches. Furthermore, it was demonstrated that pharmacological inhibition of

p110 $\alpha$  activity was able to profoundly reduce medial wall thickness and the degree of muscularization in a second model, monocrotaline-induced PH in the rat, even when the disease was fully established before treatment was initiated. This was associated with a significant reduction of the elevated RVP<sub>sys</sub> and partial reversal of RV hypertrophy in this model.

These results reveal *τηατ βοτη, γενετιχ ανδ πηαρμαχολογιχαλ αβλατιον οφ π110α* signaling prevent and reverse vascular remodeling and experimental PH, indicating an important role of p110 $\alpha$  in the pathobiology of experimental PH. Therefore, inhibition of p110 $\alpha$  represents a promising strategy for the treatment of PAH.