The six-transmembrane protein Stamp2 protects from hypoxia-induced pulmonary vascular remodeling and pulmonary hypertension via actions in mononuclear cells and CXCL12

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Background: The six-transmembrane protein of prostate (Stamp2) is a potent anti-inflammatory player in adipocytes and also in macrophages. Stamp2’s actions in these cells protects from diet-induced diabetes and from atherosclerosis mice. As chronic inflammation is a hallmark of pulmonary arterial hypertension (PH), we sought to investigate the role of Stamp2 in PH.

Methods and Results: Morphometric analyses of small pulmonary arteries after 3 weeks of chronic hypoxia (10% O2) showed aggravated pulmonary vascular remodeling in Stamp2-/- mice as compared to WT, demonstrated by a significantly reduced number of non-muscularized vessels and higher extent of fully-muscularized vessels. Consequently, right ventricular systolic pressure (RVSP, Millar catheter via right jugular vein) was significantly higher in Stamp2-/- mice (33.4±0.7 mmHg vs. 30.3±1.4, p<0.05). As endothelial (EC) and smooth muscle cells (PASMC) are critical for remodeling processes in PH, the role of Stamp2 in these cells was explored. However, siRNA-mediated knock-down of Stamp2 in human microvascular EC had no effect on apoptotic susceptibility (CellDeath Detection ELISA), or release of IL-6 (qPCR). Furthermore, Stamp2-deficiency in isolated primary PASMC had no effect on proliferation (BrdU incorporation) and chemotaxis (modified Boyden chamber). As Stamp2 deficiency promotes higher expression of inflammatory cytokines (IL6, IL1b, MCP1, TNFa, CXCL12, qPCR) and increased numbers of CD68-positive cells in the lung, actions of Stamp2 in macrophages are potentially driving vascular remodeling in PH. To test this hypothesis, PASMC proliferation and chemotaxis were assessed in response to treatment with supernatants from primary thioglycolate-elicited peritoneal Stamp2-/- or WT-macrophages. These experiments revealed that supernatants from Stamp2-/-macrophages induced PASMC proliferation and chemotaxis significantly stronger, thus providing a link between inflammatory actions in Stamp2 deficiency and vascular remodeling. To gain further insights, a cytokine array was performed with supernatants from Stamp2-/- and WT-macrophages, revealing CXCL12 as the most relevant candidate. Experiments with neutralizing antibodies confirmed the role of CXCL12 in driving Stamp2’s actions on vascular remodelling processes in PASMC.

Importantly, Stamp2 expression (qPCR, western blot analyses) was significantly lower in the lung of humans with idiopathic PAH (IPAH), as well as in experimental PH in rats (monocrotalin, sugen/hypoxia) and in mice (hypoxia).

Conclusions: Stamp2 deficiency aggravates hypoxia-induced pulmonary vascular remodeling and pulmonary hypertension in mice. On the cellular level, actions of Stamp2 in macrophages drive vascular remodelling processes in smooth muscle cells via secreted factors such as CXCL12. The finding of decreased expression of Stamp2 in human and various experimental forms of PH points towards a general protective role of Stamp2.