Basigin Promotes Vascular Smooth Muscle Proliferation and Pulmonary Hypertension

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Background: Cyclophilin A (CyPA) is secreted from vascular smooth muscle cells (VSMC) by oxidative stress and promotes VSMC proliferation. However, the role of CyPA and its extracellular receptor Basigin (Bsg) in the pathogenesis of pulmonary hypertension (PH) remains to be elucidated. In this study, we tested our hypothesis that CyPA/Bsg signaling promotes the development of PH.

Methods and Results: In the pulmonary arteries of PH patients, immunostaining revealed strong expression of CyPA and Bsg (n=5). In cultured human pulmonary arterial VSMC, hypoxia (O2 2%) significantly increased CyPA secretion and Bsg expression compared with normoxic condition (O2 21%) (n=4 per group). To determine the role of CyPA/Bsg signaling in PH development, CyPA+/− and Bsg+/− mice were exposed to hypoxia (O2 10%) for 4 weeks. The pulmonary arteries (PA) of CyPA+/− and Bsg+/− mice exposed to normoxia did not differ in morphology compared with their littermate controls. In contrast, CyPA+/− (n=12) and Bsg+/− mice (n=15) exposed to hypoxia revealed significantly reduced right ventricular systolic pressure (RVSP), PA remodeling and RV hypertrophy compared with their littermate controls (all P<0.01). Importantly, after transplantation of bone marrow, the severity of PH was still exacerbated in Bsg+/+ recipient mice compared with Bsg+/− recipient mice regardless of the source of bone marrow (Bsg+/+ or Bsg+/−), suggesting the crucial role of Bsg in PA. To further evaluate the role of Bsg, we harvested VSMC from Bsg+/− and Bsg+/− mice. VSMC proliferation was significantly reduced in Bsg+/− compared with Bsg+/+ in response to 2% FBS, suggesting the crucial role of Bsg in VSMC proliferation. Mechanistic studies demonstrated that Bsg+/− VSMC revealed reduced expression of oxidative stress genes, less secretion of cytokines/chemokines and growth factors. Finally, in the clinical study, plasma CyPA levels in PH patients were increased in accordance with the severity of pulmonary vascular resistance (P<0.001). Furthermore, event-free curve revealed that high plasma CyPA levels predicted poor outcome in PH patients (death or lung transplantation, P<0.001).

Conclusions: These results indicate the crucial role of extracellular CyPA and vascular Bsg in the pathogenesis of PH.