Local and systemic RAGE axis changes in pulmonary hypertension: CTEPH and iPAH

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Abstract

Objective: The cellular and molecular determinants of chronic thromboembolic pulmonary hypertension (CTEPH) and idiopathic pulmonary arterial hypertension (iPAH) remain poorly understood. The receptor for advanced glycation endproducts (RAGE), its splice variant endogenous secretory (es) RAGE and its ligands: high-mobility group box1 (HMGB1) and members of the S100 family of proteins (S100A9) are involved in various inflammatory and immune disorders. We sought to investigate the role of the RAGE axis in patients with CTEPH undergoing pulmonary endarterectomy (PEA), idiopathic pulmonary hypertension (iPAH) undergoing lung transplantation (LuTX). The high pulmonary vascular resistance in these patients results in pressure overload of the right ventricle. We compared sRAGE measurements to that of patients with aortic valve stenosis (AVS) – pressure overload of the left ventricle – undergoing aortic valve replacement (AVR).

Methods: We enrolled 26 patients with CTEPH, 15 patients with iPAH, 15 patients with AVS and 33 volunteers. Immunohistochemistry was performed on paraffin-embedded PEA specimens and lung tissues from patients with iPAH. Sections were stained with antibodies to RAGE and HMGB1. We employed enzyme-linked immunosorbent assays to determine the

concentrations of soluble RAGE (sRAGE), esRAGE, HMGB1 and S100A9 in serum of volunteers and patients with CTEPH, iPAH, AVS before and after PEA, LuTX and AVR.

Results: In endarterectomised tissues from patients with CTEPH RAGE and HMGB1 were identified in myofibroblasts (α-SMA^{+}, vimentin^{+}, CD34^{-}), recanalizing vessel-like structures of distal myofibrotic tissues and endothelium of neointima. RAGE was differentially expressed in prototypical Heath Edwards lesions in patients with iPAH and in endothelial and smooth muscle cells in regular main PAs. We found significantly increased serum concentrations of sRAGE, esRAGE and HMGB1 in patients with CTEPH. In patients with iPAH serum sRAGE and esRAGE were significantly higher than in controls. Serum concentrations of sRAGE were significantly elevated in patients with iPAH ($p<0.001$) and CTEPH ($p=0.001$) compared to AVS. Serum sRAGE was significantly higher in iPAH compared to CTEPH ($p=0.042$) and significantly reduced in patients with AVS compared to controls ($p=0.001$). There were no significant differences in sRAGE serum concentrations before and after surgical therapy for CTEPH, iPAH or AVS.

Conclusions: Our data suggest a role for the RAGE pathway in the pathophysiology of CTEPH and iPAH. PEA improves the local control of disease with resultant decrease in pulmonary artery pressure but may not influence the systemic inflammatory mechanisms in CTEPH patients through the RAGE pathway.