Evidence for ANTXR2 as a therapeutic target on systemic-to-pulmonary shunt induced pulmonary arterial hypertension

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Introduction Pulmonary arterial hypertension secondary to congenital heart disease (CHD-PAH) with systemic-to-pulmonary shunt is characterized by proliferative vascular remodeling. Excessive proliferation and resistance to apoptosis of pulmonary artery smooth muscle cells (PASMCs) are the primary cellular bases of vascular remodeling. Anthrax toxin receptor 2 (ANTXR2) exhibits anti-proliferative properties. The effects of ANTXR2 on vascular remodeling and systemic-to-pulmonary shunt induced PAH remain unexplored.

Purpose The purpose of this study was to determine the possible roles of ANTXR2 in the pathogenesis of systemic-to-pulmonary shunt induced PAH and explore its possible mechanisms.

Methods Lung tissue sections from CHD-PAH patients, systemic-to-pulmonary shunt induced PAH rat model, ANTXR2-/- rats, and PASMCs were used. Immunohistochemistry, real time polymerase chain reaction, Western blot, proliferation, apoptosis, and next generation sequencing (NGS) were performed in this study.

Results ANTXR2 expression was reduced in severe CHD-PAH patient lung tissue and pulmonary arterioles, as well as in lung tissues from rats with systemic-to-pulmonary shunt induced PAH. Over-expression of ANTXR2 in cultured PASMCs inhibited cell proliferation and promoted apoptosis, while knockdown of ANTXR2 promoted cell proliferation and inhibited apoptosis. Male ANTXR2-/- rats showed more severe percent medial thickness and muscularization of pulmonary arterioles than wild type (WT) rats in basal conditions, and exhibited heavier PAH following exposure to systemic-to-pulmonary shunt. To further determine the underlying mechanism, NGS was performed in ANTXR2-/- rat lungs and that of WT littermates. A total of 1319 genes were found to be dysregulated, and biological processes influenced by these differentially expressed genes include negative regulation of blood vessel diameter, vasoconstriction, regulation of blood vessel diameter, regulation of blood vessel size, vascular process in circulatory system, etc.

Conclusion Our work identifies a novel role for ANTXR2 in systemic-to-pulmonary shunt induced PAH based on the findings that ANTXR2 deficiency could exacerbate systemic-to-pulmonary shunt induced vascular remodeling in the development of PAH. ANTXR2 may be a potential target for CHD-PAH treatment.