The role of cardiac p22phox in the development of pulmonary hypertension due to chronic adult hypoxia and transient gestational hypoxia

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Background: Hypoxia and reactive oxygen species (ROS) have been shown to play an important role in the pathophysiology of many cardiovascular and -pulmonary diseases such as pulmonary hypertension (PH). Current pathogenetic concepts indicate that pulmonary vascular remodeling and subsequently elevated pulmonary arterial pressure increase right ventricular afterload, leading to right ventricular hypertrophy and eventually right heart failure upon exposure to chronic hypoxia in adulthood. However, more recently this concept has been challenged suggesting that the right ventricle might also react to hypoxia independently of pulmonary obstruction. In addition, preclinical animal models suggested that exposure to hypoxia during pregnancy might be sufficient to promote the development of PH later on in life. Based on our previous observations that general loss of ROS-generating NADPH oxidases protects against the development of hypoxia-induced PH we hypothetized that loss of NADPH oxidases solely in the heart might be sufficient to promote right ventricular hypertrophy upon exposure to hypoxia in adulthood or pregnancy.
Aim: To clarify the impact of a loss of p22phox, an essential subunit of NADPH oxidases, on the development of right ventricular hypertrophy and pulmonary hypertension in response to fetal and adult hypoxia.
Methods: Wildtype (WT) mice and mice lacking p22phox in cardiomyocytes (αMHCCre p22phox-floxed) were either exposed to 3 weeks of chronic hypoxia during adulthood or to transient gestational hypoxia from gestational day E10.5 to E11.5 followd by normoxia until adulthood. Right ventricular pressure was determined hemodynamically, and lungs and the right heart were analyzed by immunohistochemistry, Western blot and qPCR.
Results: Exposure to chronic hypoxia promoted the development of PH in adult WT mice as expected. Exposure to transient gestational hypoxia was sufficient to result in pulmonary vascular remodeling, increased right ventricular pressure and right ventricular hypertrophy in adult WT mice. In contrast, loss of p22phox in cardiomyocytes protected not only from the development of right ventricular hypertrophy, but also from pulmonary vascular remodeling and elevated right ventricular pressure in response to chronic hypoxia in adulthood or transient gestational hypoxia. In line, oxidative DNA damage as evaluated by 8OHdG staining was diminished in the absence of cardiomyocyte p22phox. Fate mapping studies using mice expressing a tdTomato transgene that converts to green fluorescent protein (GFP) in solely in cardiomyocytes indicated that hypoxia promotes hyperplasia of cardiomyocytes lining pulmonary veins.
Conclusion: These data show that loss of p22phox-dependent NADPH oxidases in cardiomyocytes is sufficient to protect from PH induced by chronic adult or transient gestational hypoxia and suggest a possible role of pulmonary vein cardiomyocytes in this response.