Crucial role of extra-domain A containing fibronectin for the development of pulmonary hypertension and associated right heart failure

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Background: Pulmonary vascular and right ventricular myocardial remodelling are unique phenomena in PH progression. Both processes are accompanied by an abundant re-expression of the extra-domain A of fibronectin (ED-A+ Fn) therefore qualifying as promising biomarker or even therapeutic target. Nevertheless, its functional role in PH pathogenesis remains unclear until now. Objective: The purpose of our study was to analyse the development of PH and RHF in a mouse model of monocrotaline (MCT)-induced PH comparing C57BL/6 ED-A+ Fn knockout (KO) and wild-type (WT) mice.

Methods: PH was induced by subcutaneous injection of a single dose of MCT (60 mg/kg body weight). Subgroups were additionally treated with the dual endothelin receptor antagonist Macitentan (MAC, 15mg/kg body weight per day from day 14 to 28). There were 6 experimental groups: sham-treated control WT mice (WTco, n=4); MCT induced PH WT mice (WTPH, n=6); MCT induced PH WT mice treated with MAC (WTPH_MAC, n=6); sham-treated control KO mice (KOco, n=4); MCT induced PH KO mice (KOPH, n=6); MCT induced PH KO mice treated with MAC (KOPH_MAC, n=6). Between day 26 and 28, transthoracic echocardiography and right heart catheterization were performed. Both, lung and cardiac tissue samples were subjected to histological analyses.

Results: Right heart catheterization revealed significantly increased RVPsys values in WTPH (87.0±16.4mmHg) compared to WTco (36.1±9.4mmHg; p=0.034) animals, which showed, at least in trend, a diminution in the WTPH_MAC group (67.1±20.9mmHg; p=n.s.). There was a non-significant increase in RVPsys in the KOPH (55.6±14.9mmHg) compared to KOco mice (37.2±5.6mmHg; p=n.s.) without any differences compared to the KOPH_MAC group (60.9±14.0mmHg; p=n.s.). When comparing the WTPH and the KOPH group, RVPsys was significantly lower in the KO animals (p=0.014), while there were no differences between the WTPH_MAC and the KOPH_MAC group (p=n.s.). Echocardiographic evaluation including surrogate parameters of right ventricular (RV) overload and failure were significantly altered in WTPH compared to WTco animals ($p<0.05$) and could not be shown to be relevantly improved in the WTPH_MAC group (p=n.s.). The majority of echocardiographic parameters did not significantly differ between the KOPH and the KOco group (p=n.s.). Lung tissue analysis revealed significant alterations in both, the WTPH and the KOPH group, each compared to the corresponding control ($p<0.05$). The level of lung tissue damage was significantly decreased in KOPH compared to WTPH mice ($p<0.05$). In RV, the amount of interstitial fibrosis was increased in the WTPH (p=0.009) but not in the KOPH group (p=n.s.), each compared to the corresponding controls.

Conclusions: The findings of the current study underline the hypothesis that ED-A+ Fn is a key player in the pathogenesis of PH and associated RHF. Thus, it might represent a promising therapeutic target, e.g., by the administration of neutralizing antibodies.