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The adult heart requires baseline expression of the transcription factor Hand2 to withstand right ventricular pressure overload

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Introduction: Heart and neural crest derivatives expressed-2 (Hand2) has been identified as an important embryonic basic helix-loop-helix-transcription factor, with different functions in the development of the first and second heart field, from which the left and right ventricle originate, respectively. Our previous work revealed that Hand2, under conditions of left ventricular (LV) pressure overload, is re-expressed in the adult heart and activates a "fetal gene" program contributing to pathological cardiac remodeling. Ablation of cardiac expression of Hand2 resulted in protection to cardiac stress and attenuated maladaptive remodeling.

Purpose: In this study, we aimed at unraveling the role of Hand2 during cardiac remodeling in response to right ventricular (RV) pressure overload induced by pulmonary artery banding (PAB).

Methods: Hand2F/F and MCM– Hand2F/F mice were treated with tamoxifen (control and knockout, respectively) and subjected to six weeks of RV pressure overload induced by PAB. Echocardiographic and MRI derived hemodynamic parameters, and molecular remodelling were assessed for experimental groups and compared to sham-operated controls (Fig. 1a). RNA sequencing and gene ontology enrichment analysis were performed to compare the dysregulated genes between the pressure overloaded RV of the control and Hand2 knockout mice.

Results: After six weeks of increased pressure load (Fig. 1b), levels of Hand2 increased in the control banded animals but, as expected, remained absent in the knockout hearts (Fig. 1c). In contrast to the what was previously observed for the pressure overloaded LV, in the pressure loaded RV, Hand2 depletion resulted in more severe remodelling and dysfunction as reflected by increased hypertrophic growth, increased RV end-diastolic and end-systolic volumes as well as decreased RV ejection fraction (Fig. 1d–g). In addition, RNA sequencing revealed a distinct set of genes that are dysregulated in the pressure-overloaded RV, compared to the previously described pressure-overloaded LV. These include components of the extracellular matrix structure, collagen assembly and organization and several types of collagens. Genes associated with inflammation response, adhesion and muscle organization were also affected in the RV of the Hand2 KO mice (Fig. 1h).

Conclusion: Cardiac-specific depletion of Hand2 is associated with severe cardiac dysfunction in conditions of RV pressure overload. While inhibiting Hand2 expression can prevent cardiac dysfunction in conditions of LV pressure overload, the same does not hold true for conditions of RV pressure overload. This study highlights the need to better understand the molecular mechanisms driving pathological remodelling of the RV, in contrast to the LV, in order to better diagnose and treat patients with RV or LV failure.

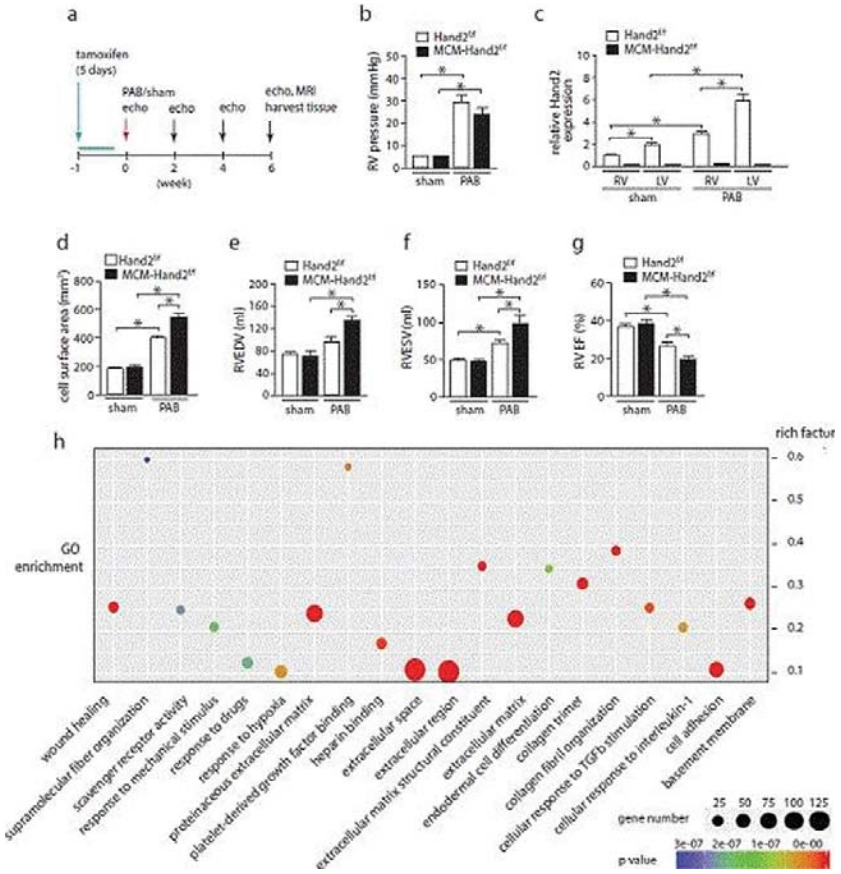

Figure 1