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The Phosphodiesterase 4D interacting protein averts volume overload - but not pressure overload-induced pathological myocardial remodeling

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Background: Although volume- and pressure-overload (VO and PO, respectively) are hemodynamic stress, each results in distinct phenotypes. The Phosphodiesterase 4D interacting protein (PDE4DIP) is a protein involved in cardiac muscle contraction and suggested to play a role in cardiomyopathy. We previously identified Pde4dip transcript as being downregulated in VO but upregulated in PO.

Objective: We wanted to address whether Pde4dip deletion would alter the progression of pathological myocardial remodeling and heart failure (HF) following hemodynamic stress.

Methods: Pde4dip knockout (Pde4dip-KO) and age- and sex-matched wild-type (WT) mice were exposed to aortocaval shunt-triggered VO or transthoracic aortic constriction (TAC)-induced PO. Mortality rates were assessed and the cardiac structure and function were determined by serial echocardiography.

Results: The PDE4DIP protein levels decreased significantly in volume-overloaded hearts. However, pressure-overloaded hearts did not alter PDE4DIP protein levels, suggesting different posttranscriptional modifications that might affect the PDE4DIP protein expression in VO versus PO. The Pde4dip-KO Hearts were structurally and functionally normal in echocardiographic and morphometric analyses. However, Pde4dip deletion mildly attenuated the mortality rates in shunt-, but not in TAC-operated mice. A significant deterioration of left ventricle geometry and function was observed in volume-overloaded WT hearts at 12 weeks after shunt, but preserved cardiac function were noticed in shunt-operated Pde4dip-KO mice. On the other hand, TAC-operated WT and Pde4dip-KO mice exhibited a significant, but comparable deterioration of cardiac structure and function compared to sham mice.

Conclusion: Here we identified the PDE4DIP as an essential regulator of pathological myocardial remodeling following VO, but irrelevant to the development of cardiac dysfunction after TAC. Further investigations are warranted to dissect the possible mechanisms underlying the protective role of PDE4DIP deletion in the setting of VO.