[gw22-e1033]

HEAT SHOCK TRANSCRIPTION FACTOR 1 PROTECTS HEART AFTER PRESSURE OVERLOAD THROUGH PROMOTING MYOCARDIAL ANGIOGENESIS

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10.1136/heartjnl-2011-300867.258

Background Heat shock transcription factor 1 (HSF1) plays an important role in exercise-induced cardiac hypertrophy. However, its role in pressure overload-induced cardiac hypertrophy is not completely clear. We here elucidate whether and how HSF1 protects heart against chronic pressure overload.

Methods and Results A sustained constriction of transverse aorta (TAC) was imposed to HSF1 transgenic (TG), knockout (KO) and their littermate wild type (WT) mice to induce a pressure overload. Four weeks later, adaptive responses to TAC, such as cardiac hypertrophy, contractility and angiogenesis evaluated by echocardiography, catheterisation and immunohistochemistry, were well preserved in the TG but less in the KO compared to those in the WT mice. An angiogenesis inhibitor TNP-470 abrogated all these adaptive responses in the TG mice, while cardiac transfection of VEGF with angiopoietin-1 repaired the maladaptive heart in the KO mice. In response to TAC, p53 was downregulated and hypoxia-inducing transcription factor-1 (HIF-1) was upregulated not only in heart tissues but also in cultured cardiac endothelial cells (EC) of the TG mice compared to WT mice whereas these changes became opposite in the KO mice. A small interfere RNA (siRNA) of HIF-1 but not a p53 gene impaired the adaptive responses of the heart and EC in TG mice, and a siRNA of p53 but not a HIF-1 gene significantly reversed the heart and EC disorders in the KO mice after pressure overload.

Conclusions We conclude that HSF1 promotes cardiac angiogenesis through suppression of p53 and subsequent upregulation of HIF-1 in endothelial cells during chronic pressure overload, leading to the maintenance of cardiac adaptation.