Role of Heat Shock Factor 1 (HSF1) in Cardioprotection and Pathology

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Heat shock factor 1 (HSF1) is a highly conserved transcriptional regulator that binds to heat shock elements of genes encoding heat shock proteins (Hsps) under stress conditions and upregulates Hsp synthesis. Multiple functions of the evolutionary conserved Hsps include chaperone-like activities, solubilization of protein aggregates, cytoskeletal remodeling, and general maintenance of cellular homeostasis and protection from proteotoxic damage. In order to study HSF1 function in the heart, we generated a transgenic mouse model expressing cardiac specific, inducible but constitutively active HSF1 whose transcriptional competency does not require stressors. Both low and high expressor transgenic mouse lines were created, producing about 5-10 fold mutant HSF1 without effects on endogenous levels of HSF1, respectively. We hypothesized that a chronic exercise-swimming regimen could rescue the pathological hypertrophic program unexpectedly induced in the high HSF1 expressor animals. The low HSF1 expressor mice were examined similarly to elucidate whether the physiological hypertrophic gene program and concomitant Hsp expression would provide additional cardioprotection previously observed in this model. Following the chronic exercise regimen, hearts were harvested and cardiac hypertrophy was calculated. Tissues were analyzed for hypertrophic markers, HSF1 and Hsp expression levels and activation of known signaling pathways characteristic of hypertrophic gene programs. Our results indicate that exercise-induced physiological hypertrophy in the HSF1 high expressor mice was unable to rescue the pathological phenotype. Furthermore, the generally beneficial exercise regimen induced stress resulted in an increased mortality rate and sudden death of the HSF1 high expressor animals. In contrast, exercising the low expressor HSF1 mice generated elevated levels of HSF1, Hsp25, and Hsp70 expression, but did not affect mortality. The dichotomy between the low and high HSF1 expressor models presents an interesting insight into how activated HSF1 may generate both protective and pathological cardiac gene expression programs. Such studies may prove useful for understanding the mechanisms of sudden death in elite athletes during strenuous exercise.