Reactive oxygen species (ROS) and insulin resistant hypertrophic cardiomyopathy

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Reactive oxygen species (ROS) such as superoxide are known to be implicated in the induction of cardiac hypertrophy in various pathologic states. The role of ROS in the etiology and/or exacerbation of insulin resistant hypertrophic cardiomyopathy is not well understood. Our recent studies have utilized Cre-lox mice with cardiac GLUT4 deletion (GLUT4-knockout), superimposed on global GLUT4 suppression (GLUT4-knockdown) to explore the relationship between insulin resistance and ROS-mediated myocardial pathology. In the GLUT4-knockout mice (compared with the knockdown mice) a marked cardiac hypertrophy is observed, characterized by an increase in cardiac weight index, elevated expression of the hypertrophy marker gene B-type natriuretic peptide (BNP). These hearts also exhibit moderate fibrosis associated with elevated expression of the pro-fibrotic gene, pro-collagen III. Of particular interest is the upregulated expression of the gp91(phox) and Nox1 subunits of NADPH oxidase.

In one series of experiments the influence of *in vivo* anti-oxidant treatment on myocardial measures of hypertrophy and oxidative stress was examined (Ritchie *et al.*, 2007). Anti-oxidant treatment using tempol significantly attenuated all of these abnormalities in GLUT4-knockout mice. Surprisingly the antioxidant treatment did not significantly reduce the NADPH-driven superoxide generation in this experimental setting of relatively short term treatment (4 week). These findings suggest that while suppression of oxidative stress in the insulin-resistant myocardium exerts an antihypertrophic effect, NADPH generated ROS may not be the only cellular target of the antioxidant therapy.

Additional studies using DNA microarray analyses to profile mRNA expression differences between GLUT4-knockout GLUT4-knockdown hearts have been informative in relation to global metabolic remodeling which occurs in these insulin-resistant hypertrophic hearts (Huggins *et al.*, 2008). In GLUT4-knockout hearts DNA microarray analysis detected downregulation of a number of genes centrally involved in mitochondrial oxidation and upregulation of other genes indicative of a shift to cytosolic beta-oxidation of long chain fatty acids. In particular gene expression evidence suggests that peroxisomal production of ROS in these hearts may be increased. Thus the benefit of antioxidant therapy in the GLUT4-knockout hearts may offset the deleterious effects of both NADPH- and peroxisomal-generated ROS.

These structural and molecular findings have important implications for understanding the role of ROS in the etiology of cardiac hypertrophy in the setting of insulin resistance, and highlight a potential role for antioxidant therapy in the treatment of diabetic cardiomyopathy.

Ritchie RH, Quinn JM, Cao AH, Drummond GR, Kaye DM, Favaloro JM, Proietto J, Delbridge LMD. (2007) *Journal of Molecular Cellular Cardiology* **42**, 1119-1128.

Huggins CE, Domenighetti AA, Khalil N, Favaloro J, Richie ME, Smyth GK, Proietto J, Pepe S, Delbridge LMD. (2008) *Journal of Molecular Cellular Cardiology* **44**, 270-80.