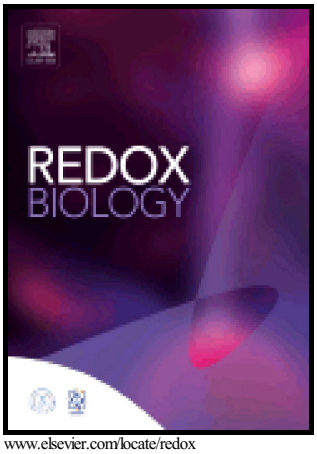

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Abstract

Glutaredoxin 2 (GRX2), a mitochondrial glutathione-dependent oxidoreductase, is central to glutathione homeostasis and mitochondrial redox, which is crucial in highly metabolic tissues like the heart. Previous research showed that absence of Grx2, leads to impaired mitochondrial complex I function, hypertension and cardiac hypertrophy in mice but the impact on mitochondrial structure and function in intact cardiomyocytes and in humans has not been explored. We hypothesized that Grx2 controls cardiac mitochondrial dynamics and function in cellular and mouse models, and that low expression is associated with human cardiac dysfunction. Here we show that Grx2 absence impairs mitochondrial fusion, ultrastructure and energetics in primary cardiomyocytes and cardiac tissue. Moreover, provision of the glutathione precursor, N-acetylcysteine (NAC) to *Grx2*-/- mice did not restore glutathione redox or prevent impairments. Analysis of genetic and histopathological data from the human Genotype-Tissue Expression consortium we demonstrate that low *GRX2* is associated with fibrosis, hypertrophy, and infarct in the left ventricle. Altogether, GRX2 is important in the control of cardiac mitochondrial structure and function, and protects against human cardiac pathologies.

Abbreviations

E/A, early filling wave peak (E) and atrial contraction wave peak (A) ; ECAR, extra cellular acidification rate; EF, ejection fraction; Grx, glutaredoxin; IVS, intraventricular septum; LV, left ventricle; LVID, left ventricular internal dimension; LVPW, left ventricular posterior wall; NAC, N-acetylcysteine; OCR,