**Involvement of the cardiomyokine FGF21 in protection against oxidative stress damage in the heart**

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**Introduction:** Oxidative stress mediated by reactive oxygen species (ROS) plays a striking role in the pathogenesis of heart failure and it has been shown that antioxidants attenuate cardiac remodeling in experimental models of cardiac damage. We have recently shown that FGF21, an endocrine member of the FGF family, is produced by the heart and exerts protective effects preventing cardiac hypertrophy development. The aim of the study was to determine the effects of FGF21 on oxidative stress processes in the heart.

**Methods:** Studies in vivo were performed in hearts from wild-type (wt) and Fgf21-null mice. To assess the effects of the inflammatory process, mice were subjected to intraperitoneal (i.p.) injection of lipopolysaccharide (LPS) for 4 hr. To induce cardiac hypertrophy mice were subjected to isoproterenol (ISO) infusion for 7 days. Cell culture of neonatal cardiomyocytes from rats and mice were used for the in vitro studies. Cardiomyocytes in culture were treated with LPS for 24 hr in the presence or absence of FGF21.

**Results:** We found that treatment of FGF21 in cardiomyocytes in culture induces the expression of genes involved in anti-oxidative pathways such as mitochondrial uncoupling proteins (UCP2 and UCP3) and superoxide dismutase-2 (SOD2). Moreover, FGF21 reduces reactive oxygen species production in cardiac cells. In keeping with this, Fgf21-null mice presented reduced expression of antioxidant genes in response to stimulation with LPS-induced pro-inflammatory pathways or ISO-induced cardiac hypertrophy in the heart. Moreover, we showed that FGF21 is expressed in and released by cardiomyocytes in response to LPS, and its expression is under the control of the Sirt1 (sirtuin-1) pathway. Using neonatal cardiomyocytes in culture from wt and Fgf21-null mice we found that the FGF21 released by cardiomyocytes acts in an autocrine manner to protect the cells against oxidative stress. Finally, the analysis of samples from infarcted human hearts confirmed the association between FGF21 induction and the control of cardiac oxidative stress pathways (i.e. SOD2 induction).

**Conclusions:** Our data indicate that FGF21 regulates in an autocrine manner genes involved in anti-oxidant pathways such as UCP2, UCP3 and SOD2 thus preventing reactive oxygen species production in cardiac cells. Therefore FGF21 acts in the heart as an antioxidant factor preventing pro-oxidative pathways induced by inflammatory/hypertrophic conditions.