Cardiac Fgf21 synthesis and release: an autocrine loop for boosting up antioxidant defenses in failing hearts

Fabio Di Lisa1* and Nobuyuki Itoh2*

1Department of Biomedical Sciences, University of Padova, Viale G. Colombo, 3, Padova 35131, Italy; and 2Department of Genetic Biochemistry, Kyoto University Graduate School of Pharmaceutical Sciences, Sakyo, Kyoto 606-8501, Japan

Online publish-ahead-of-print 24 February 2015

Fibroblast growth factors (Fgfs) are signalling proteins of ~150–300 amino acids with diverse functions, mainly in development and metabolism. The human/mouse Fgf family comprises 22 members. Fgfs can be classified as intracellular, paracrine, and endocrine Fgfs by their action mechanisms. Among Fgfs, Fgf2, Fgf16, Fgf21, and Fgf23 have been shown to be cardiomyokines playing pathophysiological roles in the heart.1 Fgf2 and Fgf16 are paracrine Fgfs, which usually function in an autocrine/paracrine manner. In contrast, so far Fgf21 and Fgf23 have been reported to function in an endocrine manner. Cardiac Fgf2 promotes cardiac hypertrophy and fibrosis by activating MAPK signalling through the activation of Fgf receptor (Fgfr). In contrast, cardiac Fgf16 may prevent them by competing with Fgf2 for the binding site of Fgfr. Although Fgf23 is an endocrine Fgf, cardiac Fgf23 induces cardiac hypertrophy by activating calcineurin/NFAT signalling in an autocrine/paracrine manner.1

Fgf21 is usually known to be a hepatic hormone involved in the control of glucose, lipid, and energy metabolism. These actions of Fgf21 are mediated by activating MAPK signalling through the activation of Fgfr in an endocrine manner.2 Fgf21 is also produced in the heart and prevents cardiac hypertrophy by activating MAPK signalling through the activation of Fgfr.3 Cardiac Fgf21 expression is induced by the protein deacetylase Sirt1,3 which protects against hypertrophy, ischaemia—reperfusion injury, and oxidative stress in the heart.4 However, the molecular basis of the cardioprotection action of Fgf21 remains to be elucidated.

Oxidative stress due to an imbalance between formation and removal of reactive oxygen species (ROS) plays a relevant role in the pathogenesis of heart failure. In this issue of Cardiovascular Research, Planavila et al.5 report that cardiac Fgf21 regulates genes involved in antioxidative pathways in an autocrine/paracrine manner, thus preventing ROS production in cardiac cells. Fgf21 induced the expression of genes encoding proteins involved in antioxidant pathways in cultured cardiomyocytes, especially SOD2 and UCP3. The expression of antioxidant genes in response to lipopolysaccharide (LPS)-induced stimulation of pro-inflammatory pathways or isoproterenol-induced cardiac hypertrophy in the heart was reduced in Fgf21 knockout mice. In addition, Fgf21 was produced in and released by cardiomyocytes in response to LPS. Furthermore, the expression of Fgf21 and antioxidant genes in the heart was significantly decreased in Sirt1 knockout mice, indicating that Fgf21 expression is under the control of the Sirt1 pathway. On the other hand, in neonatal cardiomyocytes, treatment with an Fgf21 antibody prevented Sirt1-induced expression of antioxidant genes. Thus, Fgf21 released by cardiomyocytes acts as an antioxidant factor in the heart preventing ROS accumulation caused by inflammatory or hypertrophic conditions. Although hepatic Fgf21 exerts its function in an endocrine manner, cardiac Fgf21 acts through an autocrine/paracrine mechanism. In this autocrine loop, Fgf21 expression is downstream of Sirt1 that is activated by upstream signals triggered by Fgf21 released into the extracellular space (Figure 1). Interestingly, an increased expression of Fgf21, but not of other Fgfs, was observed in samples from failing human hearts. Therefore, Fgf21 expression and release appear to represent both a cardiac response to oxidative stress and an efficacious dam preventing ROS overflow.

The novel findings in the report by Planavila et al.5 have revealed new roles and action mechanism of Fgf21 in the heart while confirming the role of SOD2 and UCP3 in cardiac pathophysiology.6,7 However, as usual novel findings raise novel questions. For instance, the mechanisms by which Fgf21 promotes Sirt1 activity and Fgf21 synthesis is stimulated by Sirt1 were not elucidated conclusively. In addition, futures studies should clarify how Fgf21 decreases ROS levels and define the link between Sirt1 and other pathways related to Fgf21 in increasing antioxidant defenses.

While clear evidence is provided that the Fgf21-Sirt1 axis promotes the expression of key enzymes involved in ROS removal, it would be worth investigating whether also ROS formation is affected. This is likely the case, since besides the cardioprotective Sirt1,8 Fgf21 stimulates the activity of kinases, such as Akt, ERK, and PI3K, that are involved in cell survival. Those kinases grouped under the acronym of RISK (reperfusion injury salvage kinase pathway) have been suggested to play a pivotal role in the cardioprotective efficacy of ischaemic preconditioning (IPC)9 and are likely to underlie also Fgf21-induced protection against ischaemia/
reperfusion injury. Cardioprotection includes almost invariably maintenance of mitochondrial function. Since in cardiomyocytes, mitochondria, especially when they become dysfunctional, are the main source of ROS, stimulation of pathways preventing mitochondrial dysfunction results in a decreased ROS formation.

Regarding the increased expression of SOD2 and UCP3, other factors related to Fgf21 stimulation might synergize with or act downstream of Sirt1. In response to oxidative stress, Sirt1 is known to bind and deacetylate FOXO3 that eventually promotes the transcriptional up-regulation of SOD2. This process might be strengthened by Sirt1-catalyzed deacetylation of PGC-1α that enhancing the expression of Nrf2 stimulates the up-regulation of antioxidant genes. On the other hand, the increased expression of UCP3 might be related to Fgf21 interaction with PPARRs. Therefore, Sirt1 might increase Fgf21 levels by stimulating the PGC-1α—PPARα axis.

The process initiating the Fgf21 autocrine loop was not investigated. Since Sirt1 activity depends on Fgf21 stimulation, other factors should trigger the initial rise in Fgf21 expression. In this respect, ROS-induced mitochondrial stress has been shown to activate the integrated stress response that increases Fgf21 expression in an ATF4-dependent mechanism. Of note, a ROS scavenger targeted to mitochondria prevented the increase in Fgf21 expression induced by the complex I inhibitor metformin. Therefore, mitochondrial dysfunction and ROS formation associated with cardiac disease appear to trigger a compensatory response that decreases ROS accumulation by stimulating the Fgf21 autocrine loop.

Future studies will fill the gap in our current understanding of the relationship between oxidative stress and Fgf21 expression. Nevertheless, the intracellular responses evoked by Fgf21 represent an appealing rationale for developing a novel modality of antioxidant treatment that would potentiate endogenous defenses only in diseased hearts.

Conflict of interest: none declared.

Funding
This work was supported by grants from the University of Padova and Fondazione Cariparo to F.D.L. and from a Grant-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan (25460065) to N.I.

References
reprogramming induced by CaMKIIdelta mediates hypertrophy decompensation. Circ Res 2015; doi: 10.1161/CIRCRESAHA.116.304682.


