Fibroblast growth factor-21 ameliorates cardiac dysfunction in diabetic cardiomyopathy via AMPK-mediated NLRP3 inflammasome pathway

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Introduction: Diabetic cardiomyopathy (DCM) is one of the most severe macrovascular complications and a major cause of mortality in diabetes mellitus. To explore a new therapeutic strategy target the pathogenesis of DCM urgently needs to be resolved.

Methods: DCM model was induced to mice in the DCM groups by streptozotocin injection. Neonatal rat cardiomyocytes were exposed to normal and high-concentration glucose and palmitic acid, while FGF21/AMPK expression was inhibited by siRNA interference. Real-time PCR, immunoblot and immunohistochemistry were performed for the expression of targeted genes/proteins.

Result: The animal experiment showed that fenofibrate (FF) improved DCM by upregulation of FGF21. The above results suggest that FGF21 could improve DCM, but how FGF21 improved DCM and its mechanism are still unclear. In addition, exogenous administration of FGF21 DCM improvement by activating AMPK signaling pathway and inhibit the activation of NLRP3 inflammatory body in vivo. In high glucose treated primary myocardial cells, decreased FGF21 induced AMPK activation disorder and ultimately triggered NLRP3 inflammatory activation leading to pyroptosis. And, inhibition of AMPK activation by Compound C/SiRNA partially abolished FGF21-induced protection in cardiomyocytes.

Conclusion: Thus, the results indicate that FGF21 mediates NLRP3 inflammasome via AMPK inhibition, and further consolidate the evidence for the FGF21/analog being a pharmacotherapeutic target for T2DM and its related DCM.