CaMKII activation and necroptosis augment in diabetic cardiomyopathy via a RIPK3-dependent manner

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May 5, 2020

Abstract

Background and Purpose Activation of Ca2+/calmodulin-dependent protein kinase (CaMKII) has been proved to play a vital role in cardiovascular diseases. Receptor-interaction protein kinase 3 (RIPK3)-mediated necroptosis is crucially participated in cardiac dysfunction. The study aimed to investigate the effect as well as mechanism of CaMKII activation and necroptosis on diabetic cardiomyopathy (DCM). Experimental Approach Primary cardiomyocytes were treated with AGEs (200 μg/mL) for 24 h. Cell injury, CaMKII activity and necroptosis were detected. Wild type (WT) and the RIPK3 gene knockout (RIPK3-/-) mice were intraperitoneally injected with 60 mg/kg/d streptozotocin (STZ) for 5 consecutive days. After 12 w feeding, 100 μL recombinant adenovirus solution carrying I1PP1 gene were injected into the caudal vein of mice. Echocardiography, myocardial injury, CaMKII activity, necroptosis, RIPK1 expression, MLKL phosphorylation, mitochondrial ultrastructure were measured. Key Results Cardiac dysfunction, CaMKII activation and necroptosis were aggravated in streptozotocin (STZ) stimulated mice, as well as in (Lepr) KO/KO (db/db) mice. RIPK3 deficiency alleviated cardiac dysfunction, CaMKII activation and necroptosis in DCM. Cell injury, CaMKII activation and necroptosis were augmented in advanced glcation endproducts (AGEs)-stimulated cardiomyocytes, which was attenuated after RIPK3 down-regulation. Furthermore, inhibitor 1 of protein phosphatase 1 (I1PP1) over-expression reversed cardiac dysfunction, myocardial injury and necroptosis augment, and CaMKII activity enhancement in WT mice with DCM, but not in RIPK3 knockout mice with DCM. Conclusion and Implications CaMKII activation and necroptosis augment in DCM via a RIPK3-dependent manner, which may provide therapeutic strategies for DCM.

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