IP3R1/GRP75/VDAC1 complex mediated endoplasmic reticulum stress-mitochondrial oxidative stress in diabetic atrial remodeling

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Background: Mitochondrial oxidative stress is an important mechanism of atrial remodeling and atrial fibrillation (AF) in the setting of diabetes. Currently, endoplasmic reticulum (ER) stress is regarded as the key link from homeostasis to dysfunction, and is a central feature of metabolic diseases such as type 2 diabetes. However, the molecular mechanisms underlying these processes have not been fully elucidated.

Objective: To explore the potential role of ER stress-mitochondrial oxidative stress in atrial remodeling and AF induction in diabetes.

Methods: Mouse atrial cardiomyocytes (HL-1 cells) , type 2 diabetic rats and GRP75 conditional knockout mice were used as models systems. These findings were correlated with biomarker findings in human diabetic patients with confirmed atrial fibrillation.

Results: In the diabetic rat atria, significant ER stress was observed. Treatment with tunicamycin (TM), an ER stress agonist, mass spectrometry (MS) demonstrated many known ER stress and calmodulin proteins, including Heat shock protein family A (Hsp70) member (Hspa) 5 (GRP78) and Hspa9 (GRP75) and in situ proximity ligation assay (PLA) indicated that TM led to increased protein expression of the IP3R1 (inositol 1,4,5-trisphosphate receptors 1)/GRP75 (glucose-regulated protein 75)/VDAC1 (voltage-dependent anion channel 1) complex in HL-1 cells. Silencing of GRP75 using siRNA in HL-1 cells and GRP75 conditional knockout in our mouse model led to impaired calcium transport from the ER to mitochondria, and alleviated mitochondrial oxidative stress and calcium overload. Moreover, GRP75 deficiency attenuates atrial remodeling and AF progression in Myh6-Cre+/Hspa9flox/flox + TM mice.

Conclusions: The IP3R1/GRP75/VDAC1 complex mediates endoplasmic reticulum stress-mitochondrial oxidative stress plays an important role in diabetic atrial remodeling.

Abstract Figure