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TXNDC5 is a novel therapeutic target of atrial fibrosis and fibrillation

Authors:
PC Wu1, BC Lin2, YH Yeh3, WJ Chen3, KC Yang4, 1National Taiwan University, Department and Graduate Institute of Pharmacology - Taipei - Taiwan, 2National Taiwan University, Department of Pharmacy - Taipei - Taiwan, 3Linkou Chang Gung Memorial Hospital, Cardiovascular Division - Tao-Yuan - Taiwan, 4National Taiwan University Hospital, Division of Cardiology, Department of Internal Medicine - Taipei - Taiwan.

Topic(s):
Basic Science - Cardiac Diseases: Arrhythmias

Citation:
Background: Atrial fibrillation (AF), one of the most common cardiac arrhythmias, increases the risk of stroke, systemic embolization and cardiovascular mortality. Atrial fibrosis, a hallmark of chronic AF, provides substrates to initiate/propagate fibrillation waves in the atria. There, however, lacks effective and specific therapeutics targeting atrial fibrosis. We have recently identified an endoplasmic reticulum (ER) protein thioredoxin domain containing 5 (TXNDC5) as a critical mediator of cardiac ventricular fibrosis. We hypothesized that TXNDC5 could also play an important role in the pathogenesis of atrial fibrosis and fibrillation.

Purpose: To determine the role of TXNDC5 in atrial fibrosis and fibrillation.

Methods & Results: TXNDC5 transcript and protein levels were both significantly upregulated in the atrial tissue from patients with AF. In addition, TXNDC5 mRNA expression levels were positively correlated with those of transcripts encoding transforming growth factor β1 (TGFβ1) and extracellular matrix (ECM) proteins in human atrial tissue. Knockdown of TXNDC5 in human atrial fibroblasts (hAF) attenuated TGFβ1–induced hAF activation, proliferation and ECM protein upregulation, whereas overexpression of TXNDC5 was sufficient to trigger hAF activation, proliferation and ECM protein production. Further experiments revealed that the fibrogenic effects of TXNDC5 were dependent on c-Jun N-terminal kinase (JNK) signaling. Furthermore, using a-MHC-TGFβcys33ser mice, a transgenic mouse model with cardiac-specific overexpression of constitutively active TGFβ, which develop extensive atrial fibrosis and inducible AF, we showed that TXNDC5 was strongly upregulated in the fibrotic atria of a-MHC-TGFβcys33ser mice and specifically enriched in collagen-secreting atrial fibroblasts. Targeted deletion of TXNDC5 (Txndc5−/−) in a-MHC-TGFβcys33ser mice considerably mitigated the extent of atrial fibrosis. In addition, transesophageal atrial burst pacing induced AF in 75% (3 out of 4) a-MHC-TGFβcys33ser mice, whereas knockout of Txndc5 markedly reduced the inducibility of AF (25%, 3 out of 12) in a-MHC-TGFβcys33ser mice (Figure).

Conclusion: The present study revealed that ER protein TXNDC5 augments atrial fibrosis by promoting cardiac fibroblast proliferation and ECM protein production via JNK signaling activation. Targeted deletion of Txndc5 protects against TGFβ induced atrial fibrosis and AF. Targeting TXNDC5, therefore, could be a promising new therapeutic approach to treat or prevent atrial fibrosis and AF.
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