SY11-5  TGF-β Mediates Pacing-Induced Cellular Remodeling in Cultured Atrial-Derived Myocytes

Chi-Tai Kuo, Yung-Hsin Yeh, Yi-Hsin Chan, Wei-Jan Chen
First Cardiovascular Division, Chang-Gung Memorial Hospital, Chang-Gung University College of Medicine, Taiwan

Structural remodeling in atrial fibrillation (AF) is mainly evidenced by interstitial fibrosis. Angiotensin II downstream induces TGF-β mRNA expression. Primarily, TGF-β acts through the Smad signaling pathway to stimulate collagen production. TGF-β can affect atrial myocytes via autocrine and/or paracrine mechanisms. Our experimental results indicate that rapid activation in atrial myocytes promotes myofibril degradation through an autocrine TGF-β signaling and increased oxidative stress. Inhibition of both atrial tachycardia-induced autocrine effect and oxidative stress represents a useful target for therapeutic intervention in AF. Several studies have indicated that AF is often accompanied by oxidative changes, which include up-regulation of NADPH oxidase (Nox), a major producer of ROS. The ROS can be also mediated by the RAAS. ROS activates ERKs, JNK and p38-MAPK in both atrial myocytes and fibroblasts. The pro-fibrotic effects of ROS involve an increase in fibroblast proliferation, the expression of pro-fibrotic genes and alterations in extracellular matrix metabolism. Recently, we have also shown atrial fibroblasts exhibiting greater fibrotic and oxidative responses to TGF-β than ventricular fibroblasts in adult male Wistar rats. Nox4-derived ROS production mediates the susceptibility of atrial fibroblasts to TGF-β via activating TGF-β/Smad signaling cascade, which represents a novel mechanism linking atrial fibrosis to the pathogenesis of AF. In Conclusion, understanding the molecular mechanisms that mediate atrial fibrosis may promote novel approaches for AF management in the future.

Keywords: atrial fibrillation, TGF-β, oxidative stress