EZH2 as a Novel Therapeutic Target for Atrial Fibrosis and Atrial Fibrillation

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Introduction: Atrial fibrillation (AF) is characterized by abnormal differentiation of atrial fibroblasts and excessive deposition of extracellular matrix (ECM). Several studies suggesting that EZH2 inhibitor GSK126 represent clinical candidate compounds to treat advanced solid tumors. However, the effect of the GSK126 on AF is unclear.

Methods: The expression of EZH2 was examined in the left atria of AF patients, rapid pacing-induced AF dogs and Ang-II-induced atrial fibrosis mice. Primary atrial fibroblasts were subjected to Ang-II stimulation in the presence or absence of EZH2 inhibitior or silencing. EZH2 overexpression is used to support the loss-of-function conclusions. Fibroblasts differentiation, ECM secretion, migration and signaling pathway were assessed. Thirty-two mice were divided into saline, GSK126 alone (30mg/Kg/Day), Ang-II and Ang-II+GSK126 (cotreatment with Ang-II and GSK126). Atrial fibrosis, atrial enlargement and vulnerability to AF were assessed.

Result: The expression of EZH2 was increased in atrial muscle of AF patients, AF dogs and atrial fibrosis mice and in the cells models, resulting in fibroblasts activation and migration; this effect was significantly restored by GSK126 and prompted by EZH2 overexpression. EZH2 regulates fibroblast differentiation mainly through the TGF-β-Smads signaling pathway. In vivo, treatment with GSK126 significantly inhibits Ang-II-induced atrial enlargement and fibrosis, reduced AF vulnerability.

Conclusion: GSK126 inhibited atrial remodeling and reduced vulnerability to AF by regulating the fibroblasts differentiation through Ang-II-TGF-β-Smads pathway. The present study may provide a novel therapeutic strategy for AF.