**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 suggest that EZH2 inhibitor GSK126 represents a clinical candidate compound to treat advanced solid tumors. However, the effect of 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 inhibitor 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-Smad signaling pathway. In vivo, treatment with GSK126 significantly inhibits Ang-II-induced atrial enlargement and fibrosis, reducing AF vulnerability.

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