The study by Lai et al., investigate the role of p300/p53/PAI-1 signaling pathway in aging-related atrial fibrosis. The authors deploy *in vitro* fibroblast culture and *in vivo* aged mouse model to dissect the regulation of p300/p53/PAI-1 signaling pathway in aged atrial fibrosis. Overall, the study is well designed, and the manuscript is written in a good shape. However, additional evidence needs to be provided to make the study accurately and integrally.

Major Concerns:

(1) As demonstrated in both *in vitro* cultured human and mouse atrial fibroblast, knockdown p300 or p300 inhibitor treatment reduces PAI-1 protein expression. Does p300 knockdown or p300 inhibitors also inhibit PAI-1 mRNA expression? As p300 regulates gene expression through epigenetic-based histone H3K27ac modification, the authors need to check whether p300 knockdown or p300 inhibitors decrease the H3K27ac deposition in the promoter and enhancer region of the PAI-1 gene locus. This will provide molecular basis how p300/PAI-1 signaling pathway regulates aged atrial fibrosis.

(2) In Figure 5, the authors use *in vivo* mouse model to study the activation of p300/p53/PAI-1 pathway contributes to the increased AF susceptibility. However, senescence of atrial fibroblast in mouse atrial specimens is not checked. SA-β-gal staining needs to be performed in mouse atrial specimens.

(3) In Figure 5D-F, immunoblotting of p21 is missing. Also, detection of mRNA expression of PAI-1 is also needed here.

Minor Concerns:

(1) In line 28, please “AF” should be “Atrial fibrillation (AF)”.