CHINESE-AMERICAN LUNG ASSOCIATION

CALA Happy Friday Seminar

December 16th, 2022

Time: EST 10:30 am; PST: 7:30 am; Beijing time: 11:30pm

Zoom: 849 9682 9273 (Password: 654321)

The RNA m^{6}A demethylase, FTO, Regulates Vascular Remodeling in the Pathogenesis of Pulmonary Arterial Hypertension

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Bio: Dr. Jingbo Dai obtained his B.E. from China Pharmaceutical University and completed Ph.D. training at the School of Life Sciences and Biotechnology, Shanghai Jiao Tong University. Then he joined Dr. Guofei Zhou' s laboratory at the University of Illinois at Chicago (UIC) as a postdoc fellow. During his two years in UIC, he studied the smooth muscle cell metabolic reprogramming in pulmonary arterial hypertension (PAH). Jingbo joined Dr. Youyang Zhao's lab in the Department of Pediatrics at Northwestern University Feinberg School of Medicine and the Ann & Robert H. Lurie Children's Hospital of Chicago in 2018. Currently, he is a research assistant professor and his study focused on the role of Fat mass and obesity-associated protein (FTO), as a major m^{6}A eraser, acts as a key regulator of endothelial cell dysfunction and pulmonary vascular remodeling in the pathogenesis of PAH. This part of work was supported by the American Heart Association (AHA) career development award and Jingbo presented this work at the AHA scientific session in 2022.

Abstract: PAH is a devastating disease characterized by obliterative pulmonary vascular remodeling and progressive elevation of pulmonary vascular resistance that leads to right heart failure and premature death. Post-transcriptional regulation of mRNAs such as N6-methyladenosine (m^{6}A) modifications that can affect expression of key PAH-related genes and pulmonary vascular function remain largely unexplored. We hypothesized that FTO, as a major m^{6}A eraser, acts as a key regulator of endothelial cell dysfunction and pulmonary vascular remodeling in the pathogenesis of PAH. Our study found that FTO expression level is markedly elevated in the endothelial cells of idiopathic PAH (IPAH) patients. The *Tie2Cre-Fto* (CKO) mice which *Fto* was disrupted in endothelial cells exhibited inhibited PH under hypoxia treatment as evident by reduced RVSP and lower RV/(LV+S) ratio, indicator of right ventricle hypertrophy. Histological and immunofluorescent staining showed that media layer of pulmonary arteries had less cell proliferation and reduced pulmonary vascular remodeling including wall thickness as well as distal pulmonary arterial muscularization in CKO mice compared with WT mice. Moreover, preclinical MCT-rat PAH model showed attenuated PAH phenotype as well as pulmonary vascular remodeling with pharmacological inhibition of FTO. These studies demonstrate that FTO expression markedly elevates in the EC of IPAH patients. Tie2-Cre mediated loss of FTO in EC protects mice from hypoxia-induced PAH. Thus, targeting FTO is a promising therapeutic strategy for effective treatment of PAH and thereby promoting survival.