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Letter to the Editor
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Thromboxane-Prostanoid Receptor Signaling as Potential Therapy for Pulmonary Fibrosis

Li-Chao Fan[1], Ke-Bin Cheng[1], Zheng-Yao Lei[2] and Xiang-Hua Yi[2]*

[1]*Department of Respiratory and Critical Care Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, China*

[2]*Department of Pathology, Shanghai Tongji Hospital, Tongji University School of Medicine, China*

Letter to the Editor

Idiopathic Pulmonary Fibrosis (IPF) is a fibrosing interstitial pneumonia, which characterized by radiological and histologic features of Usual Interstitial Pneumonia (UIP) [1]. The clinical manifestation of IPF patients is dry cough and dyspnea [2]. The causes remain unknown and the prognosis is poor. IPF occurs mainly in middle-aged and elderly adults, which is a progressive, lethal disease [3]. A meta-analysis reported that the overall 3 to 5-year Cumulative Survival Rates (CSRs) were between 45.6% and 61.8% [4]. IPF lacks of effective treatment, nintedanib and pirfenidone are the limited antifibrotic drugs slowing of disease progression [5]. Therefore, understanding the mechanism of IPF is urgent for clinicians to looking for new drugs.

The exact pathophysiological mechanisms underlying IPF remain unknown. The current paradigm is that dysregulated cell types interplayed together through complex signaling pathways to trigger fibroblasts and myofibroblast activation and differentiation. Myofibroblast exerts to excessive deposition of the Extracellular Matrix (ECM), which is leading to aberrant lung repair [6,7]. Recent single-cell RNA sequencing studies of IPF lungs support the epithelial injury model [8]. Nonetheless, mechanistic insight into how the activation of fibroblast in pulmonary fibrosis has not been fully elucidated.

Thromboxane (TXA2) is mainly produced by platelets and can induce platelet aggregation and smooth muscle contraction [9]. In the current study, Suzuki et al. outline a new mechanism by which thromboxane-Prostanoid receptor signaling modulates fibroblast activation, thereby initiating myofibroblast activation. In both patients of IPF lung tissue and Bleomycin (BLM) induced mice fibrosis model, TBXA2R expression increased detected by western blot and immunofluorescence staining, compared with controls. Moreover, using TBXA2R^{iKO} mice further demonstrated that TBXA2R signaling could be responsible for IPF development. It has been demonstrated that F2-Isoprostanes (F2-IsoPs) can be mediators of lung fibrosis, including cell proliferation, collagen synthesis and fibroblast activation to myofibroblasts [10]. By isolating Mouse Lung Fibroblasts (MLFs) from WT and tamoxifen-treated TBXA2R^{iKO} mice, the authors provide evidence that F2-IsoPs enhanced MLFs proliferation, α-Smooth Muscle Actin (α-SMA) expression as well as collagen accumulation in WT but not from TBXA2R^{iKO} mice. Classically, Transforming-Growth Factor beta (TGF-β) was demonstrated as important mediator for myofibroblast differentiation [11,12]. Mechanistically, the authors illustrate that TGF-β pathway was activation in WT MLFs but not TBXA2R^{iKO} MLFs. Together, these findings suggest that F2-IsoPs promote fibroblast activation through TBXA2R-mediated potentiation of TGF-β signaling. On other hand, the authors demonstrate that TBXA2R antagonist (Ifetroban) blocks fibroblast activation both *in vitro* and *in vivo*, which indicates that Ifetroban could be as a potential therapeutic target for pulmonary fibrosis. Together, these findings suggest that F2-isoprostanes activate TBXA2R signaling in fibrosis, which could be attenuated by Ifetroban.

However, several considerations should be taken attention. Firstly, Reactive Oxygen Species (ROS) was demonstrated contributes to fibrosis development [13,14]. The author's document strong evidence of TBXA2R is upregulated in fibroblasts during lung fibrosis. However, they did not explore the upstream molecular that induce TBXA2R expression. The study just mentioned that F2-IsoPs can mediate the effects of ROS on fibroblasts. It is worth to explore that how ROS regulate TBXA2R expression or the level of TBXA2R affect ROS production. Secondly, epithelial cell dysfunction has documented as an important pathophysiology of pulmonary fibrosis [15], especially Alveolar Type 2 (AT2) cells [16]. The authors found that apoptosis of lung epithelial

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Correspondence:
Xiang-Hua Yi, Department of Pathology, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai, China, Tel: 00862156051080; E-mail: yixhxf@163.com

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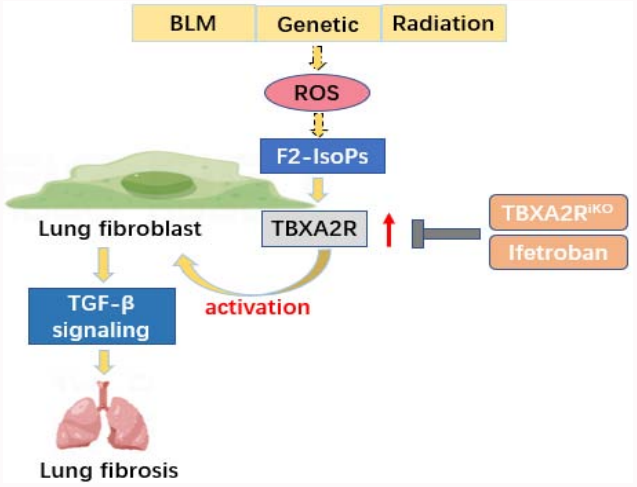

Figure 1: F2-isoprostanes activate TBXA2R signaling in fibrosis, which could be attenuated by Ifetroban. F2-isoprostanes (F2-IsoPs) induces thromboxane-prostanoidreceptor (TBXA2R) expression in lung fibrosis, which triggers TGF-β signaling activation during lung fibrosis. In contrast, ifetroban (TBXA2R antagonist) or TBXA2R gene deletion (TBXA2R^{iKO}) attenuate lung fibrosis *in vitro* and *in vivo* in three animals' model (BLM, Genetic and radiation-induced fibrosis).
BLM: Bleomycin; F2-IsoPs: F2-Isoprostanes; TBXA2R: Thromboxane-Prostanoid Receptor

cells was not affected by TBXA2R antagonism. It is better to understand the survival of AT2 cells by TBXA2R antagonism during lung fibrosis. Thirdly, it is reported that metabolism dysfunction drives pulmonary fibrosis [17,18]. Mechanically, it is important to illustrate how TBXA2R antagonism reduces proliferation, migration, and activation of fibroblasts. For example, whether metabolism was changes during those process. Fourthly, the authors demonstrate that TBXA2R expression is upregulated in fibroblasts during lung fibrosis both in the lungs of IPF patients and bleomycin challenge mouse fibrosis model. It is better to determine the level of TBXA2R expression in plasma or bronchoalveolar lavage fluid during lung fibrosis. MaybeTBXA2R can be a potential biomarker in clinical for pulmonary fibrosis. Fifthly, the authors document strong evidence that inhibition of TBXA2R with Ifetroban attenuates pulmonary fibrosis with three animal model (bleomycin, Hermansky-Pudlak mice and radiation-induced fibrosis). Fibroblast-myofibroblast differentiation is a critical cellular phenotype during the occurrence and development of pulmonary fibrosis. It remains to be determined how Ifetroban regulate certain cell signaling or key molecular to inhibit myofibroblast differentiation. The therapeutic potential of targeting this pathway for treating pulmonary fibrosis may be found.

In conclusion, Suzuki et al. have expanded our new understanding of thromboxane-prostanoid receptor signaling drives fibroblast activation in pulmonary fibrosis, which could be attenuated by inhibit TBXA2R (Figure 1). These new findings provide new direction for drug exploration. However, more studies are warranted to further explore the mechanical signaling which regulate the TBXA2R during lung fibrosis.

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