Cereblon in Pulmonary Disease

Chul-Gyu Yoo

Organization Chung-Ang University Hospital, Department of Internal Medicine
Current Position Professor

Educational background

1989-1991	Ph.D., Seoul National University
1987-1989	Ph.D., Seoul National University
1977-1983	Seoul National University College of Medicine

Professional experience

2024-Present	Professor Emeritus, Seoul National University College of Medicine
	Professor, Department of Internal Medicine, Chung-Ang University Hospital
2023-Present	President of the Asian Pacific Society of Respirology (APSR)
2016-2019	Chairman of the Board in the Korean Association of Internal Medicine
2014-2018	Chairman of Department of Internal Medicine, Seoul National University College of Medicine & Seoul National University Hospital
2005-2024	Professor in Seoul National University College of Medicine

Cereblon (CRBN) has been shown to play a crucial role in regulating the inflammatory response and endoplasmic reticulum stress, thereby contributing to the development of various diseases. However, little is known about the role of CRBN in pulmonary diseases.

We first investigated the role of CRBN in the pathogenesis of **chronic obstructive pulmonary disease (COPD)**. We found that CRBN protein levels in lung homogenates from patients with COPD were lower than those from never-smokers and smokers without COPD. Elastase-induced emphysematous changes were significantly exacerbated in CRBN **knockout** (KO) mice compared to wild-type (WT) mice. Neutrophil infiltration, lung cell injury, and protein leakage into the bronchoalveolar space were also more severe in CRBN KO mice. Furthermore, CRBN KO resulted in increased release of neutrophilic chemokines and inflammatory cytokines from lung epithelial cells and macrophages. The transcriptional activity of **nuclear factor-κB (NF-κB)** was significantly elevated in CRBN knockdown cells. These findings indicate that CRBN deficiency may contribute to the development of emphysema by enhancing NF-κB activation.

We next explored whether CRBN is involved in the development of pulmonary fibrosis. BLM-induced fibrosis and the expression of collagen and fibronectin mRNA were increased in the lung tissues of WT mice but were significantly reduced in CRBN KO mice. CRBN knockdown suppressed TGF-β1-induced activation of **small mothers against decapentaplegic 3 (SMAD3)**, whereas CRBN overexpression enhanced it. TGF-β1-induced SMAD3 activation led to increased expression of **α-smooth muscle actin (α-SMA)** and collagen. CRBN was also found to colocalize with adenosine monophosphate-activated protein kinase α1 **(AMPKα1)** in lung fibroblasts. CRBN overexpression inactivated AMPKα1. Treatment with metformin, an AMPK activator, significantly suppressed CRBN-induced SMAD3 activation and the upregulation of α-SMA and collagen expression. These findings suggest that CRBN contributes to the development of pulmonary fibrosis via inactivation of AMPKα1.

Together, our findings indicate that CRBN is a common regulator of COPD and lung fibrosis and may be a promising therapeutic target for both.