HDAC6: A Neglected Player in Chronic Obstructive Pulmonary Disease?

Although chronic obstructive pulmonary disease (COPD) is a major public health problem, the molecular mechanisms have not been fully elucidated, and consequently, effective therapies to modify this disease are limited. In 2005, we published the HDAC profiles in COPD in the *New England Journal of Medicine* (1); the selective reduction of HDAC2 in the lung and alveolar macrophages was demonstrated to be involved in airway inflammation in COPD and corticosteroid insensitivity via acetylation of glucocorticoid receptor (1, 2). The HDAC family in mammals contains 18 HDAC members that are grouped into four classes according to their homology to yeast deacetylases. Class I includes four HDAC isoforms, HDAC1, HDAC2, HDAC3, and HDAC8; class II HDAC contains HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10; and class IV HDAC contains HDAC11 and the sirtuin family (3). Although HDAC2 levels were found to be selectively reduced in the lung and alveolar macrophages from subjects with COPD, HDAC6 was shown, unexpectedly, to be upregulated in alveolar macrophages from patients with COPD (1). That observation has remained unexplained until now, when—in this issue of the *Journal* (pp. 603–614)—Su and colleagues shed light on the role of HDAC6 in the pathogenesis of COPD (4).

HDAC6 is a unique member of the type II HDACs and, at 1,215 amino acids, is the largest protein of the HDAC family. Unlike other HDACs that are mostly localized in the nucleus, HDAC6 is mainly localized to the cytoplasm, where it regulates the acetylation status of several nonhistone cytosolic proteins, which play crucial roles in inflammation and the proliferation of fibroblasts, endothelial cells, and smooth muscle cells (5–7). For example, α-tubulin was the first identified nonhistone substrate of HDAC6, and the deacetylation of α-tubulin by HDAC6 can affect microtube stabilization and function, which is a key regulator of cell movement. Heat shock protein 90 (HSP90) is another nonhistone substrate of HDAC6, and its main function is to promote the maturation and maintenance of protein structures. HDAC6 is also known to promote autophagy by recruiting and deacetylating cortactin, which is necessary for autophagosome and lysosomes (8). Because HDAC6 is involved in cancer cell proliferation, it has been considered as a novel target for cancer therapy. The protein expression of HDAC6 has also been shown to be upregulated in cardiac fibrosis tissues (6) and in human and experimental models of pulmonary arterial hypertension (7). The overexpression of HDAC6 increased the proliferation and migration of vascular smooth muscle cells (9). Furthermore, inhibition of HDAC6 prevented cigarette smoke–induced exacerbation of acute lung injury *in vivo* (10) and decreased vascular remodeling in a rodent pulmonary arterial hypertension model (7). Treatment with an HDAC6 inhibitor was found to reduce airway inflammation and was associated with decreased IL-4, IL-5, and total inflammatory cell count as well as goblet cell metaplasia and subepithelial fibrosis in mice sensitized and challenged with ovalbumin (11). Thus, HDAC6 inhibition has been shown to exhibit antiinflammatory and anti–tissue-remodeling properties, suggesting that it is a potential therapeutic target of respiratory diseases.

The current study by Su and colleagues focused on HDAC6-dependent progressive airway and pulmonary vascular remodeling due to the increased proliferation of bronchial and pulmonary arterial smooth muscle cells as well as the production of extracellular matrix. They selected cigarette smoke extract, IL-6, and PDGF as stimulants, which were found to induce overexpression and activation of HDAC6, leading to increased collagen synthesis and proliferation via deacetylation and subsequent activation (via phosphorylation) of ERK1/2. The authors then extended their previous finding that ERK1/2 signaling contributes to the elevation in collagen production and proliferation of bronchial smooth muscle cells and pulmonary arterial smooth muscle cells (12) by linking this to the HDAC6 observation. The initial observation was also impressively confirmed by an HDAC6 inhibitor (tubastatin A) or siRNA *in vitro* and/or *in vivo*. This is a well-organized target validation study, but some important questions remain to be answered when considering the implications of the results. First, the study is somewhat limited by its sole reliance on analysis of samples obtained from only late-stage patients with COPD, and it is difficult to understand whether or not HDAC6 overexpression is a key driver of disease progression. Commendably, the cigarette smoke–exposed rat model was used as a model for early-stage COPD. This is particularly important for understanding the potential target population of patients with COPD and the clinical treatment regimen of HDAC6 inhibitors. We also need to see HDAC6 expression in samples from other respiratory diseases, such as severe asthma, idiopathic pulmonary fibrosis, cystic fibrosis, etc., in order to understand the specificity of this finding in COPD. Second, although the consequence of HDAC6 upregulation is well documented here, there is still mystery regarding how HDAC6 is upregulated after PDGF/IL-6/cigarette smoke extract stimulation. Potentially, it could result from HDAC6 promoter activation by a particular transcription factor, alterations in epigenetic control, or increased protein stability. In addition, as the authors are aware, there are no data showing how ERK acetylation is linked to phosphorylation. If the authors believe that ERK deacetylation is related to disease status, ERK should be

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consistently acetylated in healthy cells. If so, this could potentially be used as a marker of disease status. Thus, further translational and molecular analyses are required to complete the target validation study.

In conclusion, upregulated HDAC6 appears to be involved in airway and vascular remodeling in COPD, which could have important implications for pathogenesis and disease progress. Fundamentally, this study provides important groundwork for target validation of HDAC6 in COPD, providing encouraging data to explore the effects of an HDAC6 inhibitor in COPD. Luckily, several selective HDAC6 inhibitors are currently in clinical trials (phases 1–2) for cancer treatment and seem to be well tolerated (13–15). In particular, ricolinostat (ACY-1215) has attracted wide attention and an increase in the acetylation of tubule proteins after treatment has been confirmed (14). Key questions include identification of a target population (disease stage) of patients with COPD, duration of treatment, and a sensitive biomarker/endpoint. If clinical studies are appropriately designed, their results might bring new hope for patients with COPD. ■

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Kazuhiro Ito, Ph.D.
National Heart and Lung Institute
Imperial College
London, United Kingdom

ORCID ID: 0000-0001-9320-2717 (K.I.).

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