Cause or Effect? Stretching to Understand the Inflammatory Role of Elastin Fiber Breakdown in Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a major healthcare burden and is characterized by persistent airflow limitation associated with chronic inflammation that predominantly affects the peripheral airways and lung parenchyma (1). The airflow limitation is often irreversible owing to structural changes in the lung, including those caused in pulmonary emphysema where there is an enlargement of alveoli and disruption of the alveolar attachments by degradation of elastin fibers by the increase in proteases and enzymes following inflammation (2). These structural changes then reduce the amount of elastic recoil that the lungs can exert to expel air during expiration (3, 4), leading to loss of pulmonary function and characteristic symptoms such as dyspnea.

Elastase models using either an intratracheal or aerosolized administration of elastase enzymes have contributed to the current understanding that the fundamental pathological aberration in emphysema is driven by destruction of the elastin framework of the lung (5). In this issue of the *Journal*, Mehraban and colleagues (pp. 699–706) describe the use of a Syrian hamster model to induce structural alteration of elastic fibers in the lung by a single, low dose of elastase to initiate the breakdown of interstitial elastic fibers to mimic airspace enlargement seen in emphysema (6). One week following administration of elastase, the animals were given a further single intratracheal dose of LPS to augment the pulmonary emphysema induced by the elastase and to mimic exacerbations (5). Unlike previous models, the authors have used a lower dose of elastase and reduced the time in between elastase and LPS administration to a single week (7, 8), enhancing the relative effect of LPS administration and allowing the investigation of potential synergistic interactions. Inflammation and airspace enlargement were monitored 48 hours and 7 days after administration, respectively.

The authors demonstrate that following elastase and LPS administration, there was increased airspace enlargement; however, this was not seen in the controls. There were also increased levels of the crosslink peptides desmosine and isodesmosine (DID) in the BAL fluid (BALF) 48 hours after LPS administration in the elastase and LPS group, indicative of elastin breakdown (6). Desmosine and isodesmodine are crosslink proteins unique to elastin and are significantly increased in the blood, urine, and sputum of patients with COPD (9). In addition, the LPS/elastase group also showed a statistically significant increase in total leukocytes and neutrophils in the BALF (6). It has previously been shown that in a COPD lung, there are increased neutrophils, macrophages, and lymphocytes as the disease progresses (10). The airspace enlargement, DID levels, and inflammation exceeded the sum of the individual effects of the two agents (6), indicating a synergistic effect between the elastase and the LPS administration.

Mehraban and colleagues also suggest that the structural changes in elastin fibers that occur during emphysema could have proinflammatory activity and therefore contribute to the accelerated decline in pulmonary function seen following COPD exacerbations. Using a chemotaxis assay, where naive untreated BALF leukocytes were treated with elastin peptides and LPS, elastin peptides alone, LPS alone, or culture medium and placed in a Boyden chamber, it was shown that exposure to elastin peptides or LPS significantly increased chemotaxis compared with controls; however, a combination of LPS and elastin had a much greater effect (6). This is in agreement with previous data that have indicated that elastin breakdown products lead to increased leukocyte chemotaxis *in vitro* and that *in vivo* administration of elastin fibers leads to increased inflammatory mediators in the BALF (11–13).

The authors used a hamster model for a number of reasons: notably, their lungs are large enough to measure both free and plasma-bound DID, unlike mice, and also have been shown to have a more severe disease as they have lower levels of inhibitory peptides such as α1 antitrypsin (6, 14).

Their data would suggest that a possible treatment for increased airspace enlargement in COPD could be to target the elastin breakdown itself, possibly by removal from the lung, or to introduce agents that bind and inhibit their activity. The authors have previously demonstrated that the glycosaminoglycan hyaluron reduces airspace enlargement in elastase models as it preferentially binds to the elastin fibers to prevent their breakdown (15). A preliminary clinical trial has indicated that in eight patients treated with aerosolized hyaluron, there was a significant decrease in plasma DID over 3 weeks with no effect in the placebo group (16), suggesting that a treatment targeting elastin fibers could be efficacious in COPD, in particular during exacerbations.

Given these promising data, it would be interesting to see the authors move to a more translational model to investigate this further. Although the elastase model is only a single treatment and is therefore easier to monitor, elastase-induced emphysema does not model all of the complicated mechanistic changes seen with cigarette smoke (5), which is the most common cause of the development of COPD (16). Therefore, it would be interesting to see a cigarette smoke model used to investigate the same endpoints, and whether a synergistic effect could be seen with LPS. In addition, this model could then be used to investigate the mechanisms by which a breakdown in elastin fibers leads to a subsequent inflammatory cell recruitment.

To conclude, these data reported by Mehraban and colleagues outline a possibly proinflammatory role of elastin fibers and also suggest that this model could be used to investigate novel therapeutics that modify elastic fiber injury. Although further

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investigation is required—possibly following cigarette smoke exposure and also in human tissue—this provides a possible mechanism to explain the increased pulmonary decline seen following exacerbations. ■

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