ADAM9: A Damaging Player in Chronic Obstructive Pulmonary Disease

The inflammatory smoking-associated condition chronic obstructive pulmonary disease (COPD) can be broadly conceived as simple alveolar enlargement coupled with airway inflammation (1), which together culminate in airflow obstruction (2). However, underlying these qualitative changes in the lungs of COPD sufferers is a host of complex, interdependent processes combined in a sometimes paradoxical fashion, all of which conspire to increase airway resistance. The emphysema seen in COPD is a well-known example of excessive extracellular matrix degradation leading to proteolytic tissue loss (3). In part because of this loss of matrix anchoring (4), and in part because of reduced resiliency (and a tendency toward apoptosis) of the alveolar pneumocytes (5), the cellular units that overlie these septae also are lost in COPD, causing emphysema. However, it is now established that COPD is also associated with excesses of abnormal extracellular matrix deposition in the pulmonary parenchyma (6), which, probably along with other mechanisms (7, 8), culminates in dramatic pruning of the small airways. The third major pathophysiologic derangement of COPD pertains to the larger airways, which undergo hypertrophic and metaplastic remodeling, causing increased mucus production and large-airway inflammation, that is, chronic bronchitis. These complex and seemingly disparate disease characteristics, as well as a predisposition to local and systemic inflammation, generally carry forward in patients, albeit at a slower rate, even if smoking cessation is achieved once COPD has become established (9, 10).

In this issue of the *Journal*, Wang and colleagues (pp. 1500–1518) describe a mediator, ADAM9 (a disintegrin and metalloprotease domain-9), that was previously linked to acute lung injury (11) and appears to be upregulated in inflammatory cells in response to cigarette smoke (CS) injury (12). They relate the activity of this enzyme to a surprising number of the diverse pathologies seen in COPD . . . almost one for each of the seven functional domains on this pleiotropic enzyme. This suggests a potential proximity of ADAM9 to the pathogenetic epicenter of COPD, and thus implies that ADAM9 has considerable potential as a therapeutic target in these wide-ranging dysfunctions. The authors used a combination of ADAM9^{-/-} CS-exposed animals, enzymologic studies, and studies of tissue, cells, and clinical samples from subjects with and without various degrees of COPD and/or CS exposure to demonstrate these findings *in vivo* and *in vitro*. The findings include multiple distinct effects of ADAM9 on all three of the key pathophysiologic mechanisms of COPD mentioned above (Figure 1): 1) emphysema (direct elastolysis, excessive alveolar pneumocyte apoptosis, and increased accumulation of leukocytes, especially alveolar macrophages); 2) small-airways fibrosis (which may be due to both the

aforementioned inflammatory cell accumulation and effects on fibroblast/myofibroblast collagen deposition); and 3) chronic bronchitis (an increase in bronchial epithelial cell mucus metaplasia and bronchial inflammation).

Although some of these findings are preliminary and obscure with regard to mechanism, Wang and colleagues show that the metalloprotease domain is involved in several of these effects (most notably in causing apoptosis through shedding of the EGFR [epidermal growth factor receptor] and VEGFR [vascular endothelial growth factor receptor] of alveolar pneumocytes). Future studies using tissue-selective and/or ADAM9 domain-specific knockouts, along with more specific inhibitors of ADAM9 activity, will likely be necessary to dissect specific mechanisms underlying some of the other ADAM9-associated pathologies reported here.

It should also be noted that ADAM9 knockout was associated with a few findings that are somewhat discordant with the overall antiinflammatory quality of this model (e.g., increased TNF- α [tumor necrosis factor- α] levels and increased neutrophil accumulation with chronic CS exposure). Although these may be compensatory or indirect effects, future work to explain these complexities will be needed before the use of ADAM9 as a therapeutic target can be seriously pursued. Other important directions of research generated by this study include the specific mechanisms of ADAM9 upregulation by CS exposure and how its expression becomes perpetuated in the lungs of individuals with COPD, especially those who are ex-smokers. Similarly, the relative roles of intracellular, membrane-bound, and soluble ADAM9 in COPD deserve further investigation.

This research adds to mounting evidence that the ADAM family of proteases contributes to human lung disease and COPD in particular. Interestingly, ADAM8, a related protease that shares with ADAM9 a relative resistance to most tissue inhibitors of metalloprotease, was recently found by the same group to have an antiinflammatory role and to be downregulated in the COPD lung (13). Whether there is a molecular switch or interplay between these ADAMs, and how this might occur in disease, remains unknown. These findings point to the exciting possibility that modulation of proteases, such as these in the ADAM family, may someday provide a long-sought disease-modifying therapy for COPD. ■

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Figure 1. ADAM9 (a disintegrin and metalloprotease-9) contributes to a host of processes in chronic obstructive pulmonary disease (COPD). ADAM9 activity increases accumulation of alveolar macrophages with cigarette smoke exposure, likely through increased levels of macrophage cytokines such as CCL-3 (chemokine [C-C motif] ligand 3) and growth factors such as GM-CSF (granulocyte-macrophage colony-stimulating factor) and M-CSF (macrophage colony-stimulating factor). The mechanisms by which these are increased are unclear. Elastases and collagenases produced by macrophages contribute directly to emphysema, chronic bronchitis, and airway fibrosis. ADAM9 is capable of direct hydrolysis of alveolar interstitial elastin, contributing further to emphysema. Alveolar pneumocytes, damaged by loss of extracellular matrix anchoring from the aforementioned mechanisms, are further induced to undergo apoptosis by ADAM9 owing to shedding of cell-surface expression of EGFR (epidermal growth factor receptor)/VEGFR (vascular endothelial growth factor receptor). ADAM9 also appears to have some effect on pulmonary fibroblasts, leading to deposition of increased collagen; how this is mediated remains unknown. Bronchial epithelial cells also are affected by ADAM9 in the presence of cigarette smoke and undergo increased mucus cell metaplasia, which contributes to chronic bronchitis.

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