ADAM17: A Therapeutic Target for Patients with Emphysema?

Since Laurell and Eriksson first described the antiprotease α-1 antitrypsin in 1963, the exploration of the mechanisms of a protease imbalance in lung health and disease has been frequently investigated. The dysregulation of the protease–antiprotease balance significantly contributes to the pathobiology of several lung diseases, including chronic obstructive pulmonary disease (COPD). COPD with pulmonary emphysema is a leading cause of death in the United States and is primarily attributed to cigarette smoke inhalation. The dysfunction of proteases is associated with the pathogenesis of emphysema, including elevated activities of MMPs (matrix metalloproteases), cathepsins, and leukocyte-associated proteases (1). Indeed, proteases are primarily associated with extracellular matrix remodeling but they also have multifunctional roles, including immunity, inflammation, DNA replication and transcription, cell proliferation and differentiation, tissue morphogenesis and remodeling, heat shock and unfolded protein responses, angiogenesis, neurogenesis, wound repair, stem cell mobilization, hemostasis, blood coagulation, autophagy, senescence, necrosis, and apoptosis (2). Therefore, uncovering the dysregulated mechanisms of proteases can provide a unique perspective into the physiology, disease pathogenesis, and therapeutic targets of emphysema.

Also known as TACE (TNF-α converting enzyme), ADAM17 (a disintegrin and metalloprotease-17) is a membrane-anchored proteinase that is ubiquitously expressed in human lung tissue and its expression is upregulated in lung diseases including asthma, COPD, and endotoxin-induced acute lung injury (3). Aberrant activation of ADAM17 influences several features of emphysema pathology, including pulmonary inflammation, cell proliferation, and epithelial barrier function. ADAM17 plays a significant role in the activated shedding of EGFR ligands (TGF-α, amphiregulin, epiregulin, HB-EGF) and cleaves membrane-bound TNF-α, IL6R, TNF-R, NOTCH receptors, L-selectin, ICAM-1, and E-cadherin (Figure 1) (4). This is important in emphysema as elevated levels of IL6R are observed in peripheral blood leukocytes of patients with COPD (5), and its genetic variants are linked with COPD severity (6). In addition, ADAM17 is reported to further activate membrane responses depending on its phosphorylation status. Cigarette smoke–induced reactive oxygen species result in the activation of SRC kinases and PKCε leading to phosphorylation of ADAM17 at serine/threonine residues, with subsequent EGFR activation and hyperproliferation of lung cells (Figure 1) (7). Moreover, phosphorylation of ADAM17 is linked to MAPK (mitogen-activated protein kinase) responses, with both ERK and p38 responses implicated in elevated ADAM17 phosphorylation at the Thr^{735} (735-threonine) site and the subsequent ADAM17 shedding activity (Figure 1) (8). Together, ADAM17 responses are altered by cigarette smoke, and elevated ADAM17 phosphorylation could result in elevated levels of IL6R, inflammation, cell proliferation, and epithelial barrier function in emphysematous lungs.

In this issue of the *Journal*, Saad and colleagues (pp. 183–195) show the possible role of ADAM17 in emphysema pathogenesis by using human samples and mouse models of emphysema (9). They report that ADAM17 undergoes Thr^{735} phosphorylation in emphysema samples. They used the $gp130^{F/F}$ mouse, which possesses a subtle knock-in mutation in *gp130* that deregulates intracellular signaling by the IL-6 cytokine family, resulting in the spontaneous development of emphysema by 6-months of age (10). Smoke exposure and the $gp130^{F/F}$ mouse phenotype resulted in elevated phosphorylation of ADAM17, PKCε, and SRC kinases within the lungs of mice (Figure 1). Crossbreeding the $gp130^{F/F}$ mice with $Adam17^{ex/ex}$ mice, a mouse model with reduced *Adam17* expression, protected the animals from developing emphysema. Equally, $ADAM17^{ex/ex}$ mice were protected from cigarette smoke–induced emphysema. Moreover, loss of ADAM17 signaling was observed to decrease serum levels of sIL-6R, apoptosis, type II pneumocyte survival, and CD45 + cell frequency as well as the expression of IL-17, TNFα, IL-1β, CXCL1, CXCL2, and CCL3 (Figure 1). The $gp130^{F/F}$ mouse exhibits elevated expression of other proteases, MMP2 and MMP9 (10). Therefore, ADAM17 could also be contributing to an additional protease burden in the lungs of the $gp130^{F/F}$ mouse.

Because ADAM17 is ubiquitously expressed in human lung tissue, the role of ADAM17 in specific cell types in emphysema remains to be determined. Saad and colleagues (9) demonstrate staining for ADAM17 in alveolar macrophages and type II pneumocytes. The use of ADAM17 tissue–specific or inducible models would further enhance our knowledge of ADAM17's role in emphysema pathogenesis. Equally, it would be of interest to profile ADAM17 activity and its phosphorylation status in varying degrees of emphysema severity, including during an exacerbation. Mishra and colleagues demonstrated that inhibiting ADAM17 activity can regulate neutrophil recruitment and enhance bacterial clearance in animal models of sepsis (11). However, further research is needed to elucidate the biological mechanisms in the setting of disease exacerbations in emphysema.

Inactivation of ADAM17 early in development results in severely hypoplastic lungs at birth, reduced branching morphogenesis and alveolar development, impaired epithelial cell proliferation, differentiation, and a delay in vasculogenesis (12). However, targeting ADAM17 in adults may not result in such drastic changes. The TIMP3 (tissue inhibitor of metalloproteinases-3) blocks ADAM17 activity via interacting with its ectodomain (13). Yet, the inner domain that becomes phosphorylated at Thr^{735} could remain active in the presence of TIMP3. Several membrane

Originally Published in Press as DOI: 10.1165/rcmb.2020-0467ED on December 1, 2020

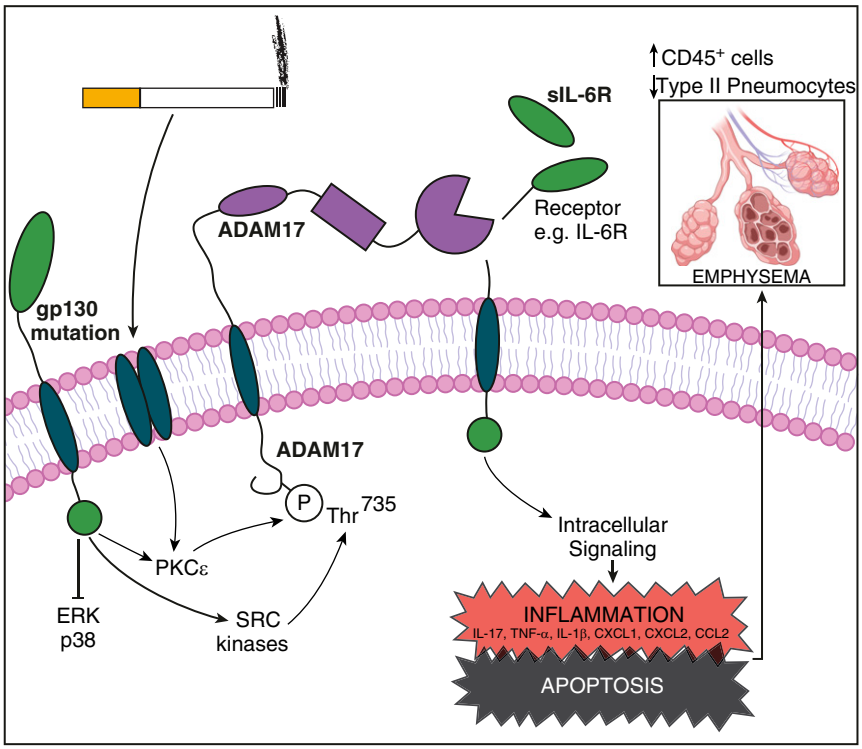

Figure 1. Schematic diagram illustrating the role of ADAM17 signaling in emphysema. The image of the emphysematous lungs was made in BioRender. ADAM17 = a disintegrin and metalloprotease-17; ERK = extracellular signal-regulated kinase; sIL-6 = soluble form of the IL-6; SRC = sarcoma; Thr^{735} = 735-threonine.

proteins, including the actin-binding protein, filamin, or lipid rafts, can regulate ADAM17 partially because of their proximity on the cell membrane and the sequestering of ADAM17 from the Golgi to the membrane by lipid rafts (14). Many research groups have examined the kinases that activate ADAM17. However, the phosphatases that inactivate ADAM17 through dephosphorylation remain to be uncovered. This represents a novel area in emphysema as the activity status of several phosphatases are altered because of cigarette smoke exposure or disease initiation. Recently, the regulatory subunit of PP2A, PP2A-B56, was observed to bind to the phosphorylation sites of ADAM17 and decrease growth factor signaling and tumor development in mice (15). Additional studies in emphysema may yield similar findings. Two other ADAM17 phosphorylation sites can also regulate its activity, Ser791 and Ser819, and their phosphorylation state in emphysema remains unknown. Of interest, there are several potential ADAM17 therapeutic inhibitory candidates proposed in the oncology field, such as small molecule inhibitors (INCB3619, INCB7839, and KP-457), peptides (Prodomain), and antibodies (D1 [A12], and A9 [B8]). These candidates may provide future therapeutic strategies in the setting of emphysema treatment by regulating the host immune response, thereby restoring the lung to a homeostatic state. In conclusion, the study by Saad and colleagues (9) adds to the growing evidence highlighting the importance of ADAM17 signaling in emphysema. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Bakr Jundi, M.D., M.M.Sc.
Patrick Geraghty, Ph.D.
Department of Medicine
State University of New York Downstate Health Sciences University
Brooklyn, New York

ORCID IDs: 0000-0003-3835-195X (B.J.); 0000-0003-1647-5505 (P.G.).

References

1. Kulkarni T, O'Reilly P, Antony VB, Gaggar A, Thannickal VJ. Matrix remodeling in pulmonary fibrosis and emphysema. *Am J Respir Cell Mol Biol* 2016;54:751–760.
2. López-Otín C, Bond JS. Proteases: multifunctional enzymes in life and disease. *J Biol Chem* 2008;283:30433–30437.
3. Stolarczyk M, Amatngalim GD, Yu X, Veltman M, Hiemstra PS, Scholte BJ. ADAM17 and EGFR regulate IL-6 receptor and amphiregulin mRNA expression and release in cigarette smoke-exposed primary bronchial epithelial cells from patients with chronic obstructive pulmonary disease (COPD). *Physiol Rep* 2016;4:e12878.
4. Gómez MI, Sokol SH, Muir AB, Soong G, Bastien J, Prince AS. Bacterial induction of TNF-alpha converting enzyme expression and IL-6 receptor alpha shedding regulates airway inflammatory signaling. *J Immunol* 2005;175:1930–1936.
5. Edmiston JS, Archer KJ, Scian MJ, Joyce AR, Zedler BK, Murrelle EL. Gene expression profiling of peripheral blood leukocytes identifies potential novel biomarkers of chronic obstructive pulmonary disease in current and former smokers. *Biomarkers* 2010;15:715–730.
6. Pérez-Rubio G, Silva-Zolezzi I, Fernández-López JC, Camarena Á, Velázquez-Uncal M, Morales-Mandujano F, *et al*. Genetic variants in IL6R and ADAM19 are associated with COPD severity in a Mexican Mestizo population. *COPD* 2016;13:610–615.
7. Lemjabbar-Alaoui H, Sidhu SS, Mengistab A, Gallup M, Basbaum C. TACE/ADAM-17 phosphorylation by PKC-epsilon mediates

premalignant changes in tobacco smoke-exposed lung cells. *PLoS One* 2011;6:e17489.
8. Díaz-Rodríguez E, Montero JC, Esparís-Ogando A, Yuste L, Pandiella A. Extracellular signal-regulated kinase phosphorylates tumor necrosis factor alpha-converting enzyme at threonine 735: a potential role in regulated shedding. *Mol Biol Cell* 2002;13:2031–2044.
9. Saad MI, McLeod L, Hodges C, Vlahos R, Rose-John S, Ruwanpura S, *et al*. ADAM17 deficiency protects against pulmonary emphysema. *Am J Respir Cell Mol Biol* 2021;64:183–195.
10. Ruwanpura SM, McLeod L, Miller A, Jones J, Bozinovski S, Vlahos R, *et al*. Interleukin-6 promotes pulmonary emphysema associated with apoptosis in mice. *Am J Respir Cell Mol Biol* 2011;45:720–730.
11. Mishra HK, Johnson TJ, Seelig DM, Walcheck B. Targeting ADAM17 in leukocytes increases neutrophil recruitment and reduces bacterial spread during polymicrobial sepsis. *J Leukoc Biol* 2016;100:999–1004.
12. Zhao J, Chen H, Peschon JJ, Shi W, Zhang Y, Frank SJ, *et al*. Pulmonary hypoplasia in mice lacking tumor necrosis factor-alpha converting enzyme indicates an indispensable role for cell surface protein shedding during embryonic lung branching morphogenesis. *Dev Biol* 2001;232:204–218.
13. Amour A, Slocombe PM, Webster A, Butler M, Knight CG, Smith BJ, *et al*. TNF-alpha converting enzyme (TACE) is inhibited by TIMP-3. *FEBS Lett* 1998;435:39–44.
14. Tellier E, Canault M, Rebsomen L, Bonardo B, Juhan-Vague I, Nalbone G, *et al*. The shedding activity of ADAM17 is sequestered in lipid rafts. *Exp Cell Res* 2006;312:3969–3980.
15. Kruse T, Gnosa SP, Nasa I, Garvanska DH, Hein JB, Nguyen H, *et al*. Mechanisms of site-specific dephosphorylation and kinase opposition imposed by PP2A regulatory subunits. *EMBO J* 2020;39: e103695.