Taming Peptides with Peptides: Neutralizing Proline-Glycine-Proline with L-Arginine-Threonine-Arginine to Treat Cigarette Smoke–induced Emphysema

Whether and how cigarette smokers develop chronic obstructive pulmonary disease (COPD) with or without emphysema remain among the most intriguing and unanswered questions that should concern the medical community and roughly 1 billion smokers worldwide (1). Progressive lung parenchymal destruction promotes severe hypoxemia that over time can be complicated with right-sided heart failure and disease exacerbation (2). A significant challenge in the field is to obtain a better understanding of the mechanism that is responsible for the pathophysiology of cigarette smoke–induced emphysema and associated heart failure in susceptible individuals. Several preclinical models of cigarette smoke–induced lung inflammation and emphysema have provided invaluable insights into the pathogenesis of emphysema (3). Specifically, upstream mediators such as IL-17A secreted by T-helper cell type 17 (Th17) cells provide one of the mechanisms that are responsible for cigarette smoke–mediated airway neutrophilia (4). Direct administration or overexpression of IL-17A selectively recruits neutrophils to the lungs through processes that require CXC chemokine and proinflammatory cytokine (e.g., IL-1β and TNF-α) expression (5). Interestingly, activated neutrophil-derived exosomes can also display surface-bound neutrophil elastase that binds and degrades extracellular matrix (ECM) via cell-surface integrins (6).

Despite advances in our fundamental understanding of emphysema pathogenesis, current treatments for smoke-induced lung diseases are quite limited because they are centered on alleviating symptoms and/or reducing COPD exacerbations. Therefore, there is an unmet need for novel therapies that could prevent emphysema development and progression in smokers.

The lung's ECM proteins and their degraded fragments play critical physiological roles in health and disease (7). For instance, a bioactive fragment of collagen, proline-glycine-proline (PGP), forms a prototypic matrikine that was first identified as a biomarker in smokers with COPD, and its concentration correlates with COPD exacerbation (8). Follow-up studies showed that the acetylated species of PGP (acPGP) is a more stable and potent chemoattractant that binds to chemokine receptors to promote emphysema in mice (9). However, whether neutralizing the same biomarker, acPGP/PGP, could tame inflammation or be used as a treatment strategy in emphysema remained unknown.

In this issue of the *Journal*, Abdul Roda and colleagues (pp. 560–566) examine the role of a complementary tripeptide, L-arginine-threonine-arginine (RTR), in neutralizing acPGP in acute and chronic models of smoke-induced lung inflammation and emphysema (10). They provide evidence that concurrent treatment with RTR during an acute model of cigarette smoke exposure mitigated airway inflammation, with a significant reduction in macrophage and neutrophil recruitment to the airway compared with mice receiving vehicle or a control tripeptide. To assess the translational relevance of their studies, the authors next exposed mice to cigarette smoke for 10 weeks, followed by RTR treatment over the final 13 weeks of smoke exposure. Consistent with their short smoke exposure model, RTR treatment significantly reduced inflammatory cell recruitment to the airway and inhibited smoke-induced emphysema (Figure 1). Notably, in this chronic model, they also found a significant reduction in right ventricular hypertrophy in mice treated with RTR, indicating a beneficial effect on cardiac remodeling. Although tobacco smoking is commonly associated with diseases related to the lung, its effects on multiple other organs, including the heart, have been well documented. Given the limited treatment options available to prevent smoke-induced inflammation and its long-term downstream effects on the lungs (e.g., emphysema) and heart (right ventricular remodeling), RTR holds promise as a new therapeutic option. Considering these promising findings, it would be of great clinical importance to determine whether RTR-mediated inhibition of PGP and collagen degradation may protect other organs (e.g., bone, skin, and joints).

To determine a potential mechanism for the antiinflammatory function of RTR, the authors investigated whether cigarette smoke induces the expression of CXCR2, a chemokine receptor that has been shown to signal via acPGP, in airway epithelial cells. They found that CXCR2 was stably expressed in airway epithelial cells, and in response to acPGP stimulation, it increased its secretion of the neutrophil chemotactic cytokine IL-8 and matrix metalloproteinase 9 (MMP9). Thus, this report emphasizes a novel, pathogenic role of the airway epithelium in a potentially vicious cycle in response to tobacco smoke (Figure 1). In response to tobacco smoke, proteinases derived from recruited immune cells and their associated exosomes cleave the lung's ECM to produce bioactive matrikines. The newly produced peptides not only recruit more proteinase-producing neutrophils to the lung, they also bind locally to epithelial cells, causing secretion of chemotactic factors and metalloproteinases. Furthermore, Abdul Roda and colleagues demonstrate that the cycle of ECM destruction and inflammation can be interrupted by neutralizing acPGP with its complementary tripeptide, RTR. This prevents CXCR2 signaling, which ultimately dampens further recruitment of inflammatory cells and reduces epithelial secretion of

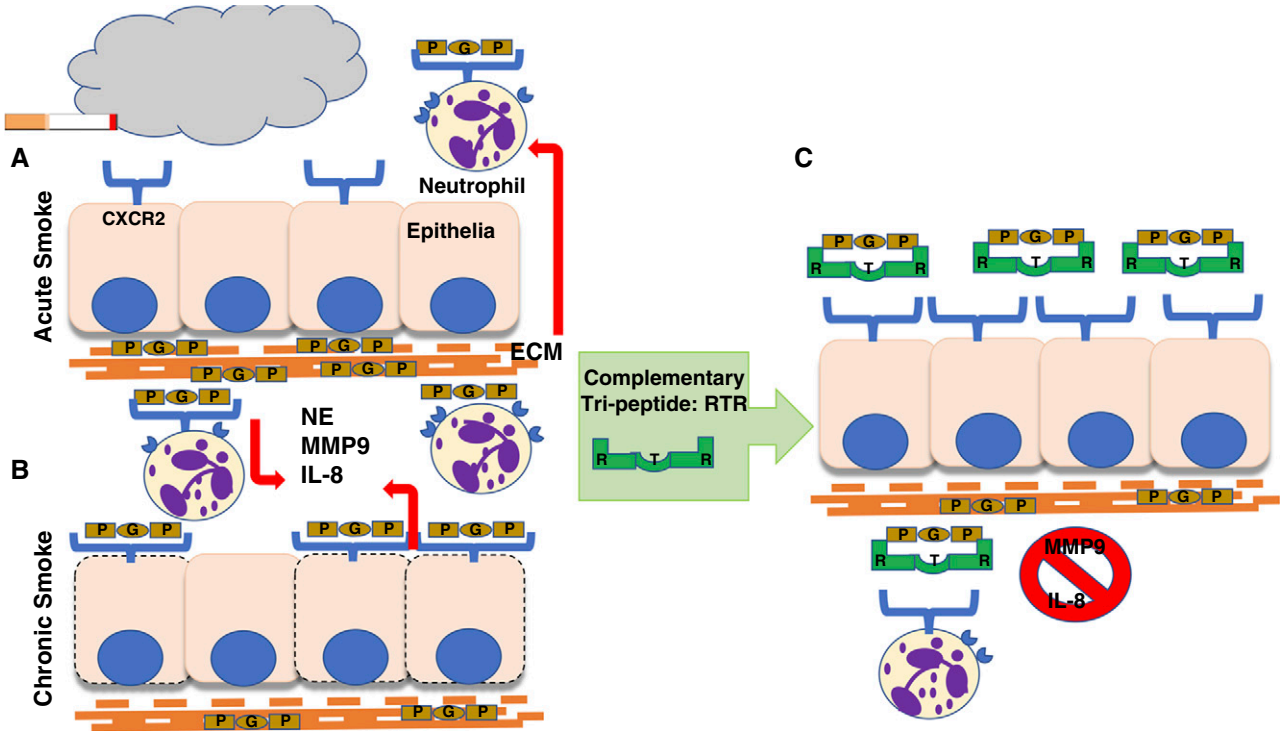

Figure 1. Complementary tripeptide RTRs neutralize the proline-glycine-proline (PGP)-associated inflammation in response to tobacco smoke. (*A*) Acute tobacco smoke promotes the induction of proteinases (e.g., matrix metalloproteinase 9 [MMP9] and neutrophil elastase [NE]) from immune cells, which degrade collagen and elastin in the lung's extracellular matrix (ECM) to release bioactive fragments (PGPs). (*B*) Chronic inflammation increases the concentration of acetylated PGP (acPGP), which binds to airway epithelial cells via CXCR2 and increases the expression of epithelial-derived chemokines and proteinases. This further promotes the expression of chemokines and matrix-degrading enzymes from the immune and airway epithelial cells. (*C*) PGP and acPGP bind to the complementary tripeptide, RTR, which neutralizes acPGP and prevents its binding to CXCR2, and reduces neutrophil recruitment and IL-8 and MMP expression in the lungs. The antiinflammatory effect of RTR can restore lung tissue despite smoke exposure. CXCR2 = motif chemokine receptor 2; RTR = L-arginine-threonine-arginine.

proinflammatory mediators in the lung. Altogether, this work demonstrates a potential new therapeutic option that can locally target chemokine receptors in airway epithelia using inhibitory RTR peptides to tame proinflammatory PGP peptides in smoke-induced lung inflammation.

Collectively, these findings reveal a novel mechanism whereby acPGP could initiate production of proinflammatory mediators through a chemokine receptor expressed in airway epithelia, thus supporting the concept that delivering RTR to the airway could provide an attractive therapeutic option. Also in support of this concept, other ECM-derived matrikines (e.g., MMP-cleaved laminin-5) can bind to epithelial cells and signal through EGFR (epidermal growth factor receptor) to activate downstream MAPK (mitogen-activated protein kinase) pathways (11). Here, however, Abdul Roda and colleagues emphasize a critical new immunological role for epithelial cells in the pathogenesis of COPD, highlighting the possibility that the immune cells are not uniquely responsible for the MMP-mediated tissue destruction observed in emphysema. The extent to which acPGPs can alter airway epithelial cells remains less clear; however, in a mouse model of asthma, acPGP has been shown to increase mucus expression in airway epithelia (12). ■

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