Neutrophil-Mediated Lung Damage: A New COPD Phenotype?

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Chronic obstructive pulmonary disease (COPD) is a menace affecting 300 million people worldwide and is responsible for 3 million deaths annually [1]. Despite this, its pathophysiology is not well understood. It is now well accepted that lung inflammation exists in COPD and that the inflammatory process intensifies with disease progression [2]. The most important environmental risk factor in COPD is cigarette smoking; it is responsible for more than 50% of the cases worldwide. Interestingly, although all smokers eventually develop lung inflammation, only about 15–20% of smokers incur COPD [3]. On the other hand, nearly 100% of smokers with rare genetic mutations in the SERPINA1 gene located in the long arm of chromosome 14 develop lung inflammation and COPD in their 40s and 50s [4]. Nearly 100% of all individuals with the null-null allele in this gene, which encodes for alpha-1-antitrypsin (A1AT) (resulting in undetectable serum A1AT concentrations), develop COPD and 80–100% of those with the S-Z allele (resulting in serum A1AT concentrations of 2.5–7 mmol/l) develop COPD [4]. Why are individuals with A1AT deficiency so susceptible to COPD? It is postulated that with cigarette smoking neutrophils and other inflammatory cells are recruited to the lungs. When activated, neutrophils release proteolytic enzymes such as elastase and other proteolytic enzymes, inducing a proteolytic burden in the lung microenvironment. Under normal circumstances, A1AT and other antiproteases neutralize this threat posed by neutrophils. However, in A1AT deficiency, defenses are perturbed, leading to elastic degradation on lung tissue resulting in emphysema. While most COPD patients do not have A1AT, this genetic syndrome serves as a useful human model of how disturbances in the protease-antiprotease system can lead to emphysema. Since most patients with COPD have adequate circulating levels of A1AT, according to this theory, aberrant neutrophil activity is at the heart of COPD pathogenesis and by turning off excess neutrophil recruitment and activation (e.g. through smoking cessation) COPD progression can be halted. However, even with smoking cessation, the inflammatory process in the lungs persists once COPD becomes firmly established and in many patients the disease continues to progress [5]. The reason for these observations is obscure.

In this issue of Respiration, Milara et al. [6] offer new insights into the role of neutrophils in COPD that may in part explain the conundrum of disease progression in COPD in ex-smokers. The authors studied subjects with severe COPD developed at an early age (<56 years) and showed that, despite years of smoking cessation, the neu-
The overall inflammatory response in COPD subjects is characterized by persistent neutrophil activation. These neutrophils have enhanced chemotaxis, increased production of reactive oxygen species, and enhanced elastase release when stimulated compared to controls. Furthermore, these neutrophils are more resistant to apoptosis, indicating an activated state. Pretreatment with a nonspecific antioxidant, N-acetylcysteine, can reverse this phenotype and restore the neutrophils to near-normal behavior.

The study by Milara et al. [6] suggests that circulating neutrophils remain activated for years after smoking cessation. These activated neutrophils could provide a major source of ongoing elastolytic burden in the lungs, especially during acute exacerbations. The data from Milara et al. [6] also offer hope, as pretreating these neutrophils with an antioxidant can reverse their activated state.
COPD is a very heterogeneous disorder and not all patients with severe COPD demonstrate circulating neutrophil activation, which may explain the largely disappointing therapeutic trials of antioxidants in COPD. However, this group of COPD subjects that develop severe disease at an early age may represent a unique COPD phenotype where activated circulating neutrophils significantly contribute to alveolar wall damage. The data by Milara et al. [6] also suggest that targeting these activated neutrophils with antioxidants may ameliorate the course of COPD in these patients, providing new hope for millions of patients with COPD around the world.

References


