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At the Checkpoint: Lung CD8$^+$ T Cells, Respiratory Viruses, and Chronic Obstructive Pulmonary Disease

CD8$^+$ T cells possess frightening potential to harm us while protecting against viruses and other pathogens. Given how rapidly activated CD8$^+$ T cells divide, if they were not subject to tight physiological control, their metabolic needs alone could sap us as quickly as any malignancy. Fortunately, once viruses are defeated, most effector CD8$^+$ T cells are rapidly eliminated by Fas-induced apoptosis. Even earlier, the potentially destructive power of their proinflammatory cytokine production is regulated by complex feedback inhibition. But some viral infections cannot be defeated, and then these same inhibitory pathways become part of elaborate schemes of molecular détente with the pathogen. Because CD8$^+$ T cells respond not to intact organisms, but to small peptides presented in the context of class I major histocompatibility molecules, one result can be impaired ability to combat related, and even distinct, respiratory viruses. In extreme cases, notably chronic HIV infection, but also in some persistent nonviral infections and cancers, such counterinflammatory measures culminate in CD8$^+$ T-cell exhaustion (1).

These principles are relevant to a tantalizing clinical puzzle: Why are patients with chronic obstructive pulmonary disease (COPD) plagued by enhanced susceptibility to viral lower respiratory tract infections (VLRTI)? Evidence of such susceptibility includes the prominent role for rhinoviruses, a largely innocuous nuisance in healthy subjects, as triggers of acute exacerbations (2), as well as exaggerated lethality after influenza infection in COPD. In both cases, emerging evidence at least partially implicates bacterial superinfection (3, 4). Such opportunists exploit virally damaged epithelia and specific regulatory mechanisms that dampen inflammation after viral eradication. Nonetheless, could acquired (or perhaps minor genetic) defects in mucosal immunity also make patients with COPD simply less able to eliminate incipient VLRTIs? Smoking definitely decimates lung innate immune defenses (5), including antiviral recognition (6). Yet COPD can clearly progress, despite decades of smoking cessation. At the molecular level, how is prolonged susceptibility to VLRTI sustained?

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In this issue of the *Journal*, McKendry and colleagues (pp. 642–651) provide a novel answer, by showing that lung $CD8^+$ T cells from patients with COPD respond defectively to H3N2 influenza virus *in vitro* (7). They identify the culprit to be a specific inhibitory cell surface receptor, programmed cell death protein 1 (PD-1), also known as CD279. PD-1 is a member of the CD28 family, part of the immunoglobulin domain superfamily that figures so prominently in communication between immune cells. Unlike CD28, but similar to CTLA4, PD-1 possesses immunosuppressive signaling motifs. Hence, binding of its ligands PD-L1 and PD-L2, which are expressed by multiple cell types, arrests $CD8^+$ T cell activities. If PD-1 sounds familiar, it should, as it is the chief target of checkpoint inhibition, the recent transformative breakthrough in tumor immunotherapy (8). By blocking PD-1 (or related molecules), these agents potently unleash selective tumor cell killing.

This innovative study (7) has multiple strengths, including its application of cutting-edge immunological concepts and techniques. It employed a model devised by the authors (9), in which strips of tissue from human lungs removed for clinical indications are virally infected, permitting elegant *in vitro* dissection of the pulmonary immune response. Results show that, relative to smokers without COPD, H3N2 infection more greatly up-regulated PD-1 expression on lung $CD8^+$ T cells of COPD subjects. Conversely, CD107a expression in response to virus (a measure of degranulation, and thus a surrogate for killing of infected cells) was less robust in COPD. Evidence was also found for antiviral responses by lung $CD4^+$ T cells, an unexpected finding predicted from animal models but poorly documented in humans.

Several findings of McKendry and colleagues merit discussion regarding superficially disparate results from other investigative groups also using surgical specimens. The depressed antiviral capacity of lung $CD8^+$ T cells the researchers found in COPD might be seen to contradict evidence that this cell type has an exaggerated capacity to produce proinflammatory cytokines on polyclonal or antigenic stimulation (10–12). Importantly, however, McKendry and colleagues also found greater inducible IFN-γ release by lung $CD8^+$ T cells in COPD (7). Similarly, by demonstrating retained expression of mRNA transcripts for the T-cell immunoglobulin domain and mucin domain 3 molecule, they verified that lung $CD8^+$ T cells in COPD did not meet one classic definition of T-cell exhaustion. That result complements the finding that in some subjects with advanced COPD, lung $CD4^+$ T cells are highly resistant to polyclonal activation, although similarly negative for multiple molecules characteristic of anergy or exhaustion (13). These two examples suggest that immunodeficiency localized to the lungs may prove as common in advanced COPD as evidence of autoimmunity.

These three phenomenon (impaired host defense, exaggerated inflammation, and loss of self-tolerance) are quite possibly interrelated. COPD progression appears to be characterized by increasingly dysfunctional responses to multiple classes of microbes that are handled by healthy hosts with little or no inflammation. The quandary is, Why? Certain microbes, including influenza viruses and *Pseudomonas aeruginosa*, are unquestionably uniquely capable of devastating damage. Thus, one possibility is that COPD progression depends primarily on the acquisition of specific "bad bugs." Alternatively, lung destruction in COPD might be driven by loss of tolerance to the local microbial community itself, as in inflammatory bowel disease. These two processes, each potential outcomes of impaired immunity, might contribute to different COPD phenotypes or predominate at different times in individual patients with COPD. By exposing normally hidden self-antigens, either could lead to autoimmunity, especially in emphysema (14).

McKendry and colleagues have produced a significant contribution to the understanding of COPD immunopathogenesis, a topic of immense global importance. Checkpoint inhibition is revolutionizing cancer treatment. Could the same principles improve antiviral responses in COPD, ideally without inducing autoimmune mayhem (15)? The significant monetary cost of available checkpoint inhibitors, mostly humanized monoclonal antibodies, currently makes this approach impractical in COPD. However, development of small-molecule inhibitors might change that situation.

Finally, the molecular basis for the exaggerated PD-1 expression in COPD remains to be determined. Some possibilities include epigenetic changes intrinsic to lung $CD8^+$ T cells, lack of appropriate help from equally defective lung $CD4^+$ T cells, and inappropriate signals from monocytes that matured into dendritic cells in a toxic environment. The field is open for yet more imaginative suggestions. ■

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Chronic Mucus Hypersecretion and the Natural History of Chronic Obstructive Pulmonary Disease

Coughing up phlegm from the chest is one of the most common respiratory symptoms and can be observed in most lung diseases. Yet, although highly prevalent among patients with bronchiectasis, lung cancer, and asthma, the presence of chronic phlegm, often referred to as chronic mucus hypersecretion (CMH) or chronic bronchitis, has for many decades been strongly associated with chronic airflow limitation and in particular with the condition we today label chronic obstructive pulmonary disease (COPD) (1, 2).

The beliefs of the importance of CMH as the link connecting smoking and inhalation of other noxious inhaled particles with the development of airflow limitation have varied substantially over the years. Before the seminal study by Fletcher and Peto (3), most researchers believed mucus hypersecretion was the first step leading to the development of airflow limitation by promoting recurrent episodes of infections that could permanently damage the lungs and airways. However, on the basis of their longitudinal study, Fletcher and colleagues concluded there were two distinct but commonly associated disorders: the hypersecretory disorder, with mucus hypersecretion and recurrent airways infections, and the obstructive disorder, resulting from both airway disease and emphysema (3). The most important finding of their study was that both disorders were favorably affected by smoking cessation, resulting in normalization of the FEV_1 decline and remittance of CMH in most quitters. They also concluded that mucus hypersecretion should not be regarded as the factor defining susceptibility to future development of airflow limitation; in other words, smokers who do not report CMH are also at high risk of developing airflow limitation. After publication of these results, supplemented by a collaborative study of several cohorts indicating that airflow limitation but not CMH was strongly related to mortality (4), research interest in CMH and recurrent respiratory infections diminished for some years, and the main research focus was directed toward studies of airflow limitation. Yet, based on longitudinal observations of cohorts of working men from Paris, Kauffmann and Annesi suggested that presence of mucus hypersecretion was perhaps not as innocent as described by Fletcher and colleagues (5, 6). This notion was further supported by Copenhagen studies showing a nontrivial association between CMH and FEV_1 decline and death from obstructive lung disease (7–9).

In this issue of the *Journal*, Allinson and colleagues (pp. 662–672) contribute new knowledge on the role of CMH in the natural history of COPD (10). This interesting study uses data from a British cohort of more than 4,000 men and women born in 1946 observed between the ages of 20 and 64 years, with almost 1,300 individuals assessed on six occasions. In contrast to Fletcher and colleagues, who only observed their cohort of approximately 800 men for 8 years, the much longer observation period in the study of Allinson and colleagues more clearly enables a documentation of the dynamics of mucus hypersecretions trough life and its relation to the development of airflow limitation. The authors present a wealth of data in a very elegant way, particularly in their figures, both in the main article and in the supplementary material. As in previous studies, the presence of CMH in their cohort was strongly related to smoking. The study shows an increasing prevalence of mucus hypersecretion with age, but under the surface of the overall prevalence are hidden considerable fluctuations reflecting incidence and remission of cough and mucus hypersecretion, as shown in Figure 3 of their article. Their Figure 4 gives an important message: Smoking cessation in individuals older than 50 years in most cases results in reduction of CMH to the levels observed in never-smokers. Thus, the presence of respiratory symptoms is fluctuating and subject to modification, especially after cessation of the triggering exposure. With regard to the association between mucus hypersecretion and the course of lung function, this study shows that the longer the symptoms are present, the more rapid the subsequent FEV_1 decline. Another interesting observation is the fact that among those with airflow limitation at age 60 to 64 years, the prevalence of chronic symptoms was only approximately 30%. This is likely to be explained by the fact that many of these individuals have stopped smoking, and is in keeping with the notion that cough and sputum remit after smoking cessation, whereas airflow limitation does not (3, 11).