The Missing Link between Smoking and COPD Autoreactivity?

It increasingly seems likely that autoimmunity plays a role in the pathogenesis of chronic obstructive pulmonary disease (COPD). A growing number of independent and generally congruent recent reports have shown that various IgG antibodies with avidities for lung autoantigens are present in many patients with COPD (1–6, and others). The concurrent presence of both disease-causing and clinically irrelevant autoantibodies is a common feature of autoimmune syndromes (7). Thus, it is almost certain that some of the autoantibody specificities in patients with COPD already described, or soon to be described, will ultimately be shown to have little clinical or pathological importance. Nonetheless, and within the interval of only the last few years, studies have already shown that characteristics of some COPD autoantibodies are associated with disease manifestations (1–3, and others), that patient-derived IgG immunoglobulins have cytotoxic potential (4), and that pathognomonic features of antibody-mediated injury mechanisms (i.e., antigen–antibody complex and complement depositions) are evident in diseased lungs (1, 4). In aggregate, these reports are as compelling as the evidence for many conventional (and less controversial) autoimmune syndromes (7, 8).

Skeptics can (and do) argue that autoimmunity in patients with COPD is more likely epiphenomenal than causal. Admittedly, unequivocal proof that autoimmune processes cause or contribute to COPD lung injuries of human patients has not yet been established. However, it seems only fair to bear in mind that unraveling the specific processes by which autoimmune responses exert their pathophysiological effects is typically a difficult and lengthy endeavor. For example, despite appreciation of antinuclear autoantibodies in systemic lupus erythematosus for more than 50 years, the immunologic mechanisms of tissue damage in this syndrome (and many other autoimmune disorders) are still not yet fully understood (8). Moreover, for obvious reasons we will never completely fulfill Koch's postulates by experimentally inducing COPD in normal subjects. The development of autoimmune animal models that recapitulate human disease phenotypes may the next best thing (9), and will provide valuable supportive evidence.

By analogy to other analogous syndromes (7), a plausible paradigm of autoimmune lung injury begins with CD4 T cell cognate recognition of a specific short peptide antigen presented in the context of a particular human leukocyte antigen (HLA) molecule. Under appropriate circumstances, this activated T cell undergoes repeated cell divisions, and the resultant, often prodigious numbers of clonal daughter progeny can produce numerous mediators that directly injure proximate (and sometimes distant) tissue (10). In addition, T cell elaborations activate, alter functions, and/or recruit successive waves of pulmonary somatic cells and other immune effectors (11), including providing the "help" to B cells that is necessary for the latter to efficiently produce IgG antibodies against protein antigens and autoantigens.

The adaptive immune system evolved to defend against microbes, noxious environmental agents, and malignancies, and is usually highly efficient, specific, and self-limited. For a variety of reasons, however, probably only some of which are known, an inflammatory cascade that is initially and appropriately targeted at a distinct foreign (e.g., microbial) or tumor-specific antigen can become misdirected by epitope spread or by cross-reactions with immunologically similar autologous peptides ("mimicry") to now also target self-antigens (7, 8). Normally inert self-proteins that have had conformational or other structural changes induced by chemical modifications also have the potential to be inappropriately recognized as foreign, "neo-antigens" and trigger immunologic responses, although the role of this particular process in lung autoimmunity has heretofore only been speculated (4).

Regardless of the mechanism(s) by which they are initially generated, self-reactive IgG autoantibodies with avidities for cell membrane–bound or extracellular matrix antigens can induce both cell-dependent and cell-independent cytotoxicities (Figure 1) (4, 12). Complement cascades triggered by antigen–antibody complexes also activate and recruit phagocytes to the inflammatory foci, which in turn add their potentially deleterious proteolytic and oxidative mediators (12). Autoantibodies are also capable of exerting adverse effects on target cell functions after binding to cell surface receptors (13) or by gaining access to intracellular ligands via endocytosis. In addition, autoimmune responses tend to be self-perpetuating since the immunogenic self-antigens are continually renewed, despite removal of the inciting injury (e.g., by smoking cessation). Furthermore, the deleterious autoimmune processes need not be particularly fulminate to cause or meaningfully contribute to the pathogenesis of chronic lung disease, given that these clinical disorders tend to develop slowly and are most frequently manifest in older individuals. Thus, the pathophysiology of COPD and other autoimmune lung diseases could reflect the cumulative effects of insidious immune injuries from low titer autoantibodies that occur over the course of many years.

The report by Kirkam and coworkers in this issue of the *Journal* (pp. 796) appears to fill an important missing piece of the COPD autoimmune paradigm by identifying biologically plausible autoantigen(s) that are capable of triggering inflammatory conflagrations (Figure 1) (1). Their study shows that carbonyl-modified self-proteins, comparable to those generated by oxidative reactions mediated by cigarette smoke (or ozone), are immunogenic in subjects with COPD. This report has some arguable limitations. Notably, the authors did not isolate carbonyl-modified proteins directly from diseased lungs and then demonstrate these are unique autoantigen(s) of patients with COPD. Hence, this study does not address the possibility that development or progression of COPD is associated with (and possibly conditional on) the generation of specific carbonyl-modified (or other) neo-antigens that somehow differ from those of smokers with minimal or no airflow obstruction. Nor did the authors here show concurrent

Supported in part by NIH grants: HL107172 and HL084948.

Am J Respir Crit Care Med Vol 184. pp 747–755, 2011
Internet address: www.atsjournals.org

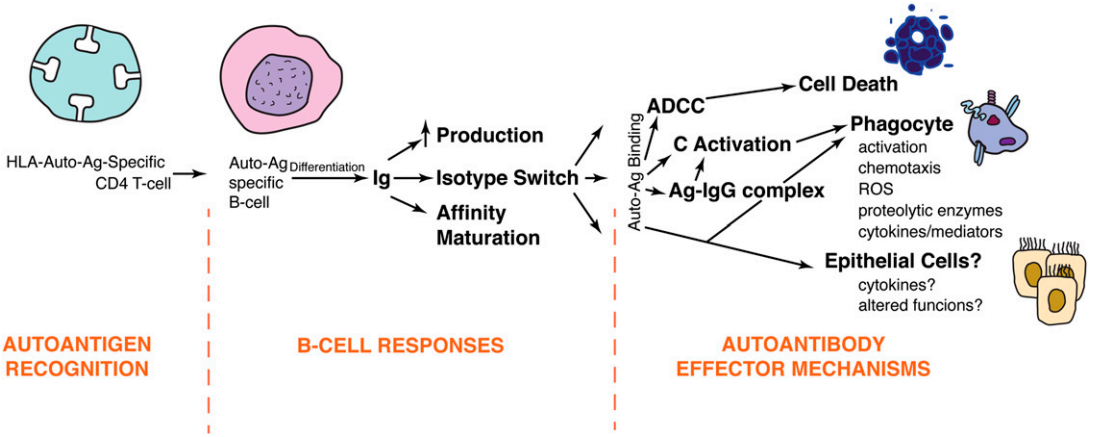

Figure 1. Schematic representation of autoantibody response and effector cascade. HLA = human leukocyte antigen; Auto-Ag = autoantigen; Ig = immunoglobulin; ADCC = antibody dependent cell cytotoxicity (4); C activation = complement activation (11); Ag-IgG = antigen-antibody (immune) complex (11); ROS = reactive oxygen species (11).

T cell autoreactivity to these neo-antigens or HLA allele-biased responses in the patients with COPD, which are hallmarks, if not *sine qua nons,* of autoimmune syndromes (7). Furthermore, the present findings do not address the potential role that antigens of airway microbes might also play in COPD immunopathogenesis. These limitations do not detract much from the likely importance of this investigation, however, and it seems destined to be recognized as the seminal evidence that neo-antigen generation by chemical modification of self-proteins can potentially evoke autoimmune responses in smoke-exposed humans.

There are many tangible reasons why better understanding of the role(s) autoimmunity plays in chronic lung disease will shape subsequent research and eventually benefit patients. Foremost among these, it seems possible that directing potential therapies at the upstream elements of the autoimmune cascade (Figure 1) could ultimately be an efficacious counter for these diseases, whereas targeting of individual, far-downstream injury processes may more likely be confounded by overlap and redundancy. It may also be important to bear in mind that autoantibody-mediated injuries are often refractory to treatment with simple immunosuppressive regimens, whereas therapies specifically targeted at immunoglobulins or B cells *per se* can be far more effective (14).

However appealing and potentially fruitful this approach may be, many questions need to be answered before treatments designed to obviate autoimmune lung injuries can be widely utilized. Among other considerations, the clinical efficacy of autoimmune-directed treatment could require early intervention, prior to the development of irreversible lung injury or inexorable autoimmunity. If so, we will need to identify and develop biomarker assays (e.g., tests for antigen-specific immunologic responses) that antedate COPD and have sufficient specificity to avoid burdensome and probably expensive treatments in the majority of smokers (and preferably ex-smokers) who are not actually fated to develop clinically significant lung disease (11). Particularly since these interventions may also require prolonged therapy, the possibility that the treatments could eventually cause more problems than the disease *per se* will need careful reflection and evaluation. Nonetheless, some focused autoantibody treatments recently approved and/or under development do not appear to predispose for opportunistic infections, and have (so far) favorable long-term safety profiles (15). Moreover, there is reason to hope too that shorter-than-anticipated treatment courses, perhaps in conjunction with other modalities (obviously including smoking cessation), could possibly break the cycle of pulmonary autoimmunity.

We have gotten a late start in the study of autoimmune lung diseases, relative to investigations of analogous disorders by our rheumatologist colleagues, but have lately been making considerable progress. The recent profusion of reports in this field indicates that we are entering an exciting period of discovery, with the potential for eventual development of novel, more efficacious treatments. But several other key questions remain unanswered, not the least of which is establishing the mechanisms by which autoimmune responses cause these pulmonary injuries, and how we will best be able to beneficially modulate these processes. With respect to the study of lung autoimmunity, the investigations to date (1–6, and others), are certainly not the end, nor even the beginning of the end, put perhaps they reflect the end of the beginning for research in this area.

Author Disclosure: The author does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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DOI: 10.1164/rccm.201107-1228ED

Thank God It's Friday!

Achieving Balance between Continuity of Care and Intensivist Burnout

The global demand of ICU care delivered by an intensivist continues to grow. The shortfall of intensivists is expected to worsen over the next two decades as the aging population increases (1). At a time in which debates regarding 24/7 coverage continue (2–5), fewer additional physicians may choose to enter the field due to the implications regarding physician lifestyle. Meanwhile, the current pool of available intensivists is decreasing for reasons including job burnout (6–8) and early retirement (9). Burnout syndrome (BOS) is an inability to cope with the emotional stress at work (10) or an excessive use of energy and resources, which can lead to feelings of failure and exhaustion (11). BOS has been associated with job withdrawal/absenteeism, retraining to another specialty, and high turnover. Moreover, burnout leads to lower effectiveness at work and is associated with decreased job commitment and satisfaction (12). People who experience burnout can negatively impact their colleagues with greater personal conflict and disruptive behavior (12). Clinical symptoms of BOS are nonspecific and include tiredness, headaches, eating disorders, insomnia, irritability, emotional instability, and rigidity in personal relationships. Although depression affects nearly every aspect of life, symptoms of burnout occur mostly at work. Wide variations in the prevalence of BOS in health care professionals have been reported (13), including half of French intensivists surveyed on a single day (8). Factors independently associated with BOS include impaired relationships with colleagues, physicians, and nurses. However, the leading factor is organizational staffing structure, including night shifts and the duration of time from the last nonworking week. Additional determinants of BOS include workplace climate and workload (14). Efforts to alter the work schedules of the intensivist may positively impact the current workforce and its future professional sustainability. Many observational studies have focused on the prevalence of burnout and its associated factors. As such, there is a great need for interventional studies.

In this issue of the *Journal*, Ali and colleagues (pp. 803) report the results of a prospective, cluster-randomized, alternating trial of two intensivist staffing schedules (15). Daily coverage by a single intensivist for half-month rotations (continuous schedule) was compared with weekday coverage by a single intensivist with weekend cross-coverage by intensivist colleagues (interrupted schedule). The study was performed in five medical ICUs at four academic centers in the United States. Intensivists rounded during the day with multidisciplinary teams including fellows and residents, who also performed overnight in house call, and intensivists took home call overnight. This study aimed to compare ICU length of stay (LOS) and physician burnout as primary outcomes between the two staffing models. Secondary outcomes were hospital LOS, ICU mortality, and hospital mortality. Intensivists completed surveys throughout the study period related to job burnout, work–home life imbalance, and job distress.

There were significant covariates on the measured outcomes including age, pre-ICU location, type and severity of illness, and ICU workload. After adjustment, ICU LOS, ICU, and hospital mortality did not differ between patients cared by intensivists on either schedule. However, burnout, work–home life imbalance, and job distress were significant with respect to the intensivists working in the continuous schedule.

This multi-center study has a number of strengths. First, the adherence rates to the assigned schedules are high. Second, 87% of participating intensivists completed surveys across 76% of the duration of the study. Third, the investigators were very careful to adjust for a number of confounders and performed additional methods of statistical analysis to determine differences in the primary and secondary outcomes, and found no difference between the two staffing schedules for LOS or mortality. Finally, this is the first interventional study aimed to reduce burnout in the ICU with observed findings that an interrupted schedule does not create worse patient-centered ICU outcomes.

There are several limitations. Two of the seven study sites dropped out after randomization had occurred. These two sites were likely assigned the continuous staffing schedule as the proportion of patients in each group was highly unbalanced. As a result, bias may have been introduced in measuring physician burnout. Also, the study is underpowered to determine the effect on ICU LOS and mortality. At 44% of the target, lack of effect on ICU LOS and mortality may be due to underenrollment. Cross-covering weekend intensivists, nurses, and families were also not surveyed to determine burnout, perceptions, and satisfaction of care, respectively. All of these limitations were noted and addressed by the authors. Furthermore, these findings may not be applicable outside academic centers in the United States. ICU staffing models that do not incorporate in-house physicians or in-training physicians may have different outcomes of LOS or mortality regardless of continuous or interrupted schedule.

Finally, we recognize the efforts of the investigators to identify and compare staffing models with the potential for less burnout. While more studies are needed to address strategies to reduce intensivist burnout, including those that measure long-term follow-up of quality of care, the efforts of Ali and colleagues are worthy of recognition. These targeted efforts to improve job satisfaction can help lessen the impact of shortages of trained intensivists for the growing aging population. Therefore, these staffing strategies should be strongly, though individually, considered for integration in clinical practice.