Autoantibodies in Patients with Chronic Obstructive Pulmonary Disease

Carol A. Feghali-Bostwick^{1*}, Aneal S. Gadgil^{1*}, Leo E. Otterbein², Joseph M. Pilewski¹, Michael W. Stoner¹, Eva Csizmadia², Yingze Zhang¹, Frank C. Sciurba¹, and Steven R. Duncan¹

¹Division of Pulmonary, Allergy, and Critical Care, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; and ²Transplant Center, Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Rationale: Adaptive immune responses are present in patients with chronic obstructive pulmonary disease (COPD), and it has been postulated that these processes could be autoreactive.

Objectives: To ascertain if humoral autoimmunity could play a role in COPD pathogenesis.

Methods: Circulating IgG autoantibodies were detected by immunofluorescence and immunoprecipitation. Immunohistochemistry and immunofluorescence were used to evaluate intrapulmonary IgG and complement (C3) deposition in human lung explants. Autoantibody pathogenicity was also investigated with an antibody-dependent cell-mediated cytotoxicity assay.

Measurements and Main Results: The prevalence of anti-HEp-2 epithelial cell autoantibodies in 47 smokers/former smokers with COPD (GOLD stages 1–4) was greater than among 8 subjects with a smoking history but normal spirometry and 21 healthy control subjects who had never smoked (68 vs. 13 vs. 10%, respectively; $P < 0.0001$). Antibodies against primary pulmonary epithelial cells were found in 12 of 12 patients with COPD versus 3 of 12 never-smoked control subjects ($P < 0.001$). Self-antigens immunoprecipitated from 34 of 35 (97%) of COPD plasmas (vs. 0/12 never-smoked controls). Antibodies against a particular 130-kD autoantigen ($n = 7$) were associated with decreased body mass index (23.2 ± 2.1 vs. 29.5 ± 1.0 kg/m², $P = 0.007$). Intrapulmonary immune complexes were present in six of six and C3 was seen in five of six COPD lung explants, unlike zero of six and one of six normals, respectively. Cytotoxicity of pulmonary epithelial cells by allogeneic mononuclear cells also increased 46% after incubation with COPD plasmas ($n = 10$), compared with identical treatments with eight normal specimens ($P = 0.03$).

Conclusions: IgG autoantibodies with avidity for pulmonary epithelium, and the potential to mediate cytotoxicity, are prevalent in patients with COPD. Autoreactive adaptive immune responses may be important in the etiology of this disease.

Keywords: autoimmunity; humoral immunity; B cells; emphysema

Chronic obstructive pulmonary disease (COPD) is a major worldwide medical problem, resulting in millions of deaths annually, and inestimable health care expenditures and productivity losses (1, 2). Long-term exposure to tobacco smoke is the primary risk factor for COPD. However, smoking-associated lung injury is a complex heterogeneous syndrome with an incompletely un-

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The pathologic mechanisms involved in progression of chronic obstructive pulmonary disease (COPD) remain unknown, but immunologic processes have been implicated.

What This Study Adds to the Field

IgG autoantibodies with avidity for pulmonary epithelium, and the potential to mediate cytotoxicity, are prevalent in patients with COPD. Autoreactive adaptive immune responses may be important in the etiology of this disease.

derstood pathogenesis (3). Illness susceptibility appears to be highly variable, and severe disease occurs in only a minority of long-term tobacco smokers, suggesting that superimposed processes are the final determinants of COPD development (2, 4).

Recent evidence supports a likely role of adaptive immune responses in progression of COPD, including correlations of disease severity with characteristics of intrapulmonary and peripheral T cells (5–11). Antigen-specific “armed” effector T cells can cause various tissue injuries by direct cytopathic effects, production of diverse proinflammatory mediators, and/or recruitment and activation of other effector cells, including the provision of facultative help to antibody (and autoantibody)-producing B cells (12, 13). In particular, antibody isotype switch (e.g., from IgM to IgG), with increased antigen avidities and enhanced potential for pathogenesis, is typically dependent on activation (help) provided by CD4 T cells with unique specificity against the peptide epitopes presented by individual, antibody-producing B cells (14).

Given the presence of active adaptive T-cell responses in COPD (5–11), we undertook a series of investigations to look for the presence of autoantibody production in these patients. The present studies show that IgG antibodies with avidity against pulmonary airway epithelial and endothelial cells, and the potential to mediate pathogenic effects, are prevalent in patients with COPD. Appreciation of these autoimmune processes may ultimately enable the development of novel diagnostic, prognostic, and/or treatment approaches for this otherwise medically refractory disease.

Some of the results of these studies have been previously reported in the form of an abstract (15).

METHODS

See the online supplement for additional methodologic details.

Subjects

Subjects with COPD with tobacco-smoking histories of 10 pack-years or more were recruited through the Emphysema–COPD Research Center

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*These authors contributed equally to this article.

Correspondence and requests for reprints should be addressed to Steven R. Duncan, M.D., Pulmonary, Allergy, and Critical Care Medicine, 628 NW MUH, 3459 Fifth Avenue, University of Pittsburgh, PA 15213. E-mail: duncsr@upmc.edu

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(ECRC) at the University of Pittsburgh. All subjects were stable at the time of the examination, and had no known comorbidities. GOLD (Global Initiative for Chronic Obstructive Lung Disease) scores were assigned on the basis of pulmonary function criteria (16). Subjects with a smoking history of 10 pack-years or more (either past or current), but normal spirometry (smoking control subjects), were also recruited through the ECRC. Healthy control subjects with no history of smoking (never-smoked control subjects) were recruited by solicitation.

Blood was obtained from subjects by venipuncture and heparinized, and plasma was isolated by centrifugation.

COPD lung tissues were dissected from surgical explants from pulmonary transplantations. Normal lung specimens were similarly obtained from cadaveric harvests.

Written, informed consent was given by all subjects, in accordance with the University of Pittsburgh Institutional Review Board.

Cell Lines

Primary human pulmonary airway epithelial cells were isolated from cadaveric donor lungs and cultured as described (17). Primary human pulmonary artery endothelial cells were obtained from Cambrex (Walkersville, MD) and cultured in media (ECM) from this manufacturer. Cells for indirect immunofluorescence studies were cultured on chamber slides and fixed in 2% paraformaldehyde before staining. K562 cells for immunoprecipitations were cultured as previously described (18).

Autoantibody Detection by Indirect Immunofluorescence

Plasma samples were diluted 1:40 in phosphate-buffered saline, and incubated with either HEp-2 cells (Fluorescent HEp-2000 ANA; ImmunoConcepts, Sacramento, CA) or human pulmonary cells (*see above*) for 30 minutes. IgG antibodies were detected using fluorescein isothiocyanate-conjugated anti-human IgG antibody. Fluorescent microscope images were characterized by blinded investigators.

Autoantibody Immunoprecipitation

Autoantibodies were also detected in plasma by immunoprecipitation (IP), as detailed previously (18) (*see also* the online supplement). Standard autoantibody reference samples from patients with known connective tissue diseases were used as positive controls.

Immunohistochemistry for Detection of Immune Complexes

Explanted human lung tissues were fixed in paraformaldehyde, sectioned, and successively incubated with mouse (IgM) anti-human IgG (Serotec, Oxford, UK) followed by biotinylated goat anti-mouse IgM secondary antibody (Vector Laboratories, Burlingame, CA). AB Complex HRP (Dako Cytomation, Glostrup, Denmark) was added and color developed with DAB substrate. Microscopic images of six to nine randomly selected fields per specimen were scored by an investigator blinded to subject characteristics.

Immunofluorescence for Detection of Complement (C3)

Frozen human lung tissues were cut, paraaldehyde fixed, successively incubated with chicken anti-human C3 antibody (Genesis Biotech, Inc., Boca Raton, FL) and Alexa Fluor-conjugated goat anti-chicken IgG antibody (Invitrogen, Carlsbad, CA), and then counterstained with Hoechst 33258 (Invitrogen). Microscopic images were scored as described above.

Antibody-dependent Cell-mediated Cytotoxicity

Subconfluent single-donor human pulmonary epithelial cells were pulsed with ³H-thymidine (1 μ Ci) for 24 hours and then incubated with either tissue culture media (media control) or plasma specimens, in turn from either normal subjects or patients with COPD. Single-donor allogeneic peripheral blood mononuclear cells (PBMC) (9×10^5 cells/well) were added (19), and residual ³H-thymidine incorporation measured 20 hours later. Relative cytotoxicity was calculated using a JAM test to detect DNA fragmentation, described elsewhere (20). Specific antibody cytotoxicity in COPD and normal plasma-pulsed wells, re-

spectively, was calculated by subtracting the relative cytotoxicity of media controls.

RESULTS

Subjects

Characteristics of the 47 subjects with COPD are detailed in Table 1. Because cigarette smoking has been reported to affect immunoglobulin and autoantibody production (21), separate analyses of the subjects with COPD who no longer smoke were also subsequently denoted. There were no systematic differences of demographic or physiologic parameters between the aggregate group of subjects with COPD versus the subpopulation of those with airflow obstruction who were former smokers (cessation >3 mo) (Table 1). The eight smoking control subjects (with normal spirometry) had a male predominance (nonsignificantly different, χ^2) and lesser tobacco smoking exposures than the subjects with COPD, but were otherwise well matched with respect to demographic characteristics (Table 1). The ages (60 ± 2 yr) and sex distributions (48% male) of the 21 healthy, never-smoked control subjects were similar to those of the patients with COPD. All of the subjects studied here were white except for one African American with COPD (GOLD stage 2).

Presence of Antiepithelial Antibodies

Plasma samples from all subjects were screened for the presence of antiepithelial (HEp-2) IgG antibodies by indirect immunofluorescence. The proportion of subjects with autoantibodies was markedly increased among those with COPD compared with former or current smokers with normal spirometry (smoking control subjects) and the never-smoked control subjects (68, 13, and 10%, respectively) (Figure 1A). There were no significant differences in antibody prevalence within the various GOLD

TABLE 1. CHARACTERISTICS OF SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	COPD (All)	COPD (Former Smokers Only)	Smoking Controls
Number	47	38	8
Age, yr	63 ± 1	64 ± 1	63 ± 3
Sex, % male	53	47	75
GOLD stage, n			
1	8	5	
2	14	10	
3	11	10	
4	14	13	
FEV ₁ %predicted	50 ± 4	47 ± 4	$95 \pm 4^*$
FEV ₁ /FVC	0.44 ± 0.02	0.42 ± 0.02	$0.78 \pm 0.2^*$
D _{LCO} %predicted	48 ± 4	43 ± 4	$67 \pm 3^†$
Smoking, pack-years	55 ± 4	50 ± 4	$28 \pm 3^*$
BMI, kg/m ²	28.4 ± 0.9	29.1 ± 1.0	27.7 ± 1.5

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; D_{LCO} = diffusing capacity for carbon monoxide, as a percentage of predicted values; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

"Former Smokers Only" denotes the subpopulation from within the total COPD group who no longer smoke (cessation >3 mo previously). "Smoking Controls" denotes subjects with a history of tobacco smoking (>10 pack-years) but normal spirometry. Two of these subjects were smoking at the time of testing, whereas the others had quit more than 3 months previously. None of these parameters were significantly different in intergroup comparisons between the two COPD groups. GOLD scores are established on the basis of pulmonary function tests (16).

* $P < 0.001$ in comparisons of all subjects with COPD versus smoking control subjects.

† $P < 0.03$ in comparisons of all subjects with COPD versus smoking control subjects.

Figure 1. Antiepithelial autoantibodies in patients with chronic obstructive pulmonary disease (COPD). (A) The prevalence of autoantibodies detected by indirect immunofluorescence is much greater among subjects with COPD and abnormal expiratory airflow obstruction (GOLD stages 1–4) than in either healthy normal control subjects with no smoking history (NS Controls) or current or ex-smokers with normal spirometry (S Controls). Numbers of subjects in each population are denoted within columns. (B) Prevalences of antiepithelial autoantibodies among subjects with COPD and abnormal spirometry. Numbers of subjects in each population are denoted within columns. These respective prevalences (GOLD 1–4) are 62, 71, 73, and 64%. (C) Distributions of autoantibody fluorescence patterns among those subjects with COPD who had IgG autoantibodies detected by indirect immunofluorescence. (D) Predominant fluorescence patterns, clockwise from bottom left: speckled, nucleolar, mixed (both speckled and nucleolar), and negative specimens.

stages 1 through 4 (Figure 1B). Two GOLD stage 4 subjects and one GOLD stage 3 subject had been maintained on stable doses of 10 mg or less of oral prednisone at the time of testing, and both the former subjects were positive for antiepithelial antibodies, whereas the latter was negative. Similarly, the proportion of subjects with COPD who were positive for antibodies and who were taking inhaled corticosteroids (69%) was nearly identical to that of diseased subjects not prescribed these agents (67%) (*see also* Table E1 in the online supplement). Current smoking status also did not seem to overtly affect these measures, because the prevalences of antiepithelial antibodies among the COPD cohort of former smokers (Table 1) were nearly identical to the aggregate population (Figure 1) (i.e., 60, 64, 70, and 62% among GOLD stages 1 through 4, respectively).

No correlation was evident between fluorescence intensity of the COPD specimens and GOLD stage ($\tau = -0.07$, $P = 0.5$, data not shown) or autoantibody titers (*see* Figure E1). Fluorescence distribution patterns among the subjects with COPD are denoted in Figure 1C, and representative examples are illustrated in Figure 1D. A series of post hoc analyses were performed to evaluate whether specific fluorescent patterns were associated with particular disease manifestations. Given the often small numbers of subjects within some of these fluorescence classifications (Figure 1C), however, the power of these analyses is limited, and no significant associations were evident (*see* Table E2).

The presence of anticellular autoantibodies is a defining criterion of autoimmunity (22, 23). To minimize the possibility

that the anti-hepatoma (HEp-2) antibodies are merely irrelevant epiphenomena of COPD, however, we also examined whether these immunoglobulins have activity against primary human pulmonary cells. Randomly selected plasma samples from 12 subjects with COPD (including 2 who did not have anti-HEp-2 antibodies), with varied disease severities (*see* Table E3), were tested at 1:40 dilutions for the presence of anti-IgG autoantibodies against primary human pulmonary cells by indirect immunofluorescence. All 12 (100%) of these specimens had antipulmonary airway epithelial cell autoantibodies (*see* Figures E2A and E2B). In contrast, only 3 of 12 (25%) randomly selected never-smoked control plasma samples had autoantibodies against human primary pulmonary airway epithelial cells ($P < 0.001$) (Figures E2C and E2D). Six (50%) of these COPD plasmas also had IgG with activity against pulmonary artery endothelial cells (Figures E3A and E3B).

Autoantibody IP

To further characterize the nature of the COPD-associated autoantibodies, and identify the sizes of the protein autoantigens, we used an IP assay to evaluate 35 remaining plasma samples with adequate volumes. Thirty-four (97%) of these specimens immunoprecipitated autoantigens of various sizes (Figure 2A). Antigens of 62, 75, 115, and 130 kD predominated, and were detected in nine (26%), nine (26%), seven (20%), and seven (20%) of the COPD samples, respectively.

Figure 2. Detection of autoantibodies in patients with chronic obstructive pulmonary disease (COPD) by immunoprecipitation. (A) Multiple bands depicting cellular antigens precipitated by autoantibodies are evident in the representative COPD specimens (composite figure). Molecular weight marker is denoted by kD. Specimens from representative never-smoked control subjects are denoted by Control. Each lane depicts an individual subject specimen. The locations of the most prevalent autoantigens (62, 75, 115, 130) are denoted by arrows. (B) Body mass indexes (BMI) were significantly decreased among the seven subjects with COPD and antibodies against the 130-kD autoantigen, compared with the 28 patients lacking humoral responses to this particular antigen.

Another series of analyses was performed to evaluate the possibility that the presence of antibodies against specific cellular autoantigens (characterized by molecular weights) might be associated with selected demographic features and disease manifestations. There were no apparent associations between presence or absence of antibodies against the 62-, 75-, and 115-kD autoantigens and the demographic features and clinical parameters denoted in Table 1. However, the subjects with COPD and autoantibodies against the 130-kD antigen had significantly decreased body mass index (BMI) compared with those patients that did not have this particular autoantibody (Figure 2B). Although the 130-kD autoantigen-positive subjects tended to have slightly (albeit insignificantly) more airflow obstruction (see Table E4), the reduction in their BMI was disproportionately more extreme, and may be indicative of a systemic effect (e.g., weight loss and/or muscle wasting) mediated by these particular autoreactive immunoglobulins.

Several COPD samples simultaneously coprecipitated two or more of these, or other, less frequently seen, autoantigens. None of the COPD samples recognized known antigens associated with conventional connective tissue diseases (i.e., systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, and polymyositis), including centromere, ribonucleoprotein complexes (RNP), Scl70 (also known as topoisomerase I), RNA polymerases, Ku, polymyositis-scleroderma, Th/To, Smith (Sm), SS-A or Ro, SS-B or La, aminoacyl-tRNA synthetases, signal recognition particle (SRP), and 5' 2,2,7-trimethyl guanosine (TMG) cap (data not shown). Plasma specimens from healthy normal subjects (never-smoked control subjects) (n = 12) were

negative for autoantigens (Figure 2A), as was seen in previous studies (18). One of the eight smoking control subjects (also positive for antiepithelial antibodies) had an autoantibody (or autoantibodies) against the 62-kD antigen.

IgG Deposition in Lung Tissue

The deposition of IgG complexes in human lung tissues were examined using sections of pulmonary explants from six randomly selected patients with severe COPD who underwent pulmonary transplantations (see Table E5). Lung tissues from six random normal donor lungs that were not used for transplantation were used as controls. IgG deposition was detected in six of six (100%) of the patients with COPD, within alveolar septa and small airway walls, but in none of the normal lungs (Figure 3).

C3 Deposition in Lung Tissue

Complement fixation is a potentially important mechanism of antibody-mediated cell injury. We found substantial C3 deposition in five of the six COPD lung explants described above, most typically in alveolar septa (Figure 4A). Conversely, only minimal C3 staining was apparent in one of the six normal lung specimens.

Antibody-dependent Cell-mediated Cytotoxicity

The potential for autoantibodies of patients with COPD to induce or contribute to cytolysis of lung cells was also ascertained by antibody-dependent cell-mediated cytotoxicity (ADCC) assay. Preincubating human primary pulmonary epithelial cells

Figure 3. IgG deposition in lung explants. Immunohistochemical images of explanted sections to evaluate IgG deposition (dark red–brown). Left panels: photomicrographs of representative chronic obstructive pulmonary disease (COPD) lungs showing IgG deposition within alveolar septa and small airway walls. Top right is a normal control. Bottom right is an isotype antibody control. Images are $\times 20$ original magnification.

with plasma from subjects with COPD enhanced cytotoxicity of allogeneic PBMNC–epithelial cell cocultures by 46%, relative to effects of the incubations with normal plasmas (Figure 4B).

DISCUSSION

These data show that circulating autoantibodies are prevalent in patients with COPD. In contrast, autoantibodies were much less frequently found among age-matched healthy control subjects in concurrent, blinded analyses, and these particular prevalences are comparable to those previously reported in normal populations (21). Moreover, while cigarette smoking *per se* may exert immunologic effects, including decreased immunoglobulin production and increased frequencies of autoantibodies (22), the findings here do not seem either confounded or conditional on current smoking status. These autoantibodies have avidity against cells in the diseased organ (i.e., pulmonary epithelium and/or endothelium), and properties that render them potentially pathogenic (e.g., ability to mediate ADCC). Other data presented here show immune complexes and complement deposition *in situ* within severely diseased lungs. Altogether, the present findings fulfill conventional criteria that define the presence of antibody responses against self-antigens as “autoimmunity” (23, 24).

The identity and nature of the antigen or antigens that drive production of autoantibodies in patients with COPD remain unknown. Substances in cigarette smoke can chemically modify proteins and other molecules (25), thus potentially generating neoantigens or haptens that fuel primary autoreactive immune responses. In addition, autoantibodies with primary specificity against self-epitopes can result from aberrant adaptive immune responses directed against putative antigens for which tolerance has been lost or was never acquired (e.g., anatomically sequestered determinants newly exposed to immune surveillance as a result of other injuries) (26). A recent report shows that subjects with COPD frequently have T-cell reactivity and autoantibodies against elastin (27), perhaps generated after *de novo* exposure of elastin fragments by proteolytic enzymes from activated neutrophils and/or macrophages. The role of these particular antibodies in the pathogenesis of COPD remains

uncertain, however, and antielastin antibodies are common among normal individuals and patients afflicted with a variety of other extrapulmonary disorders (28–30).

Autoantibodies can also arise in the course of immune responses that are initially and more appropriately targeted against exogenous antigens (e.g., inhaled proteins or microbes), if molecular characteristics of the inciting antigen sufficiently “mimic” those of self-determinants (31). In addition, initially specific responses against these and other foreign antigens can generalize and spread to include targeting of quiescent self-antigens by “epitope spreading” (32). The lower airways of patients with COPD, including those with early/mild disease, or even asymptomatic smokers, are frequently colonized and/or infected with various microbes (33–36) that are capable of eliciting antibody responses (37). Thus, and in keeping with current paradigms regarding pathogenesis of other autoimmune disorders (13, 23), adaptive immune responses to eradicate these organisms could ultimately progress, at least in some patients, to self-reactivity via processes of microbial mimicry and/or epitope spreading (31, 32, 38).

By whatever mechanism they arise, antibodies directed against self-antigens are often important causal factors in the pathogenesis of autoimmune diseases (13, 23, 38). Autoantibodies can exert their pathogenic effects directly, by cross-linking cell-surface receptors or modifying cytokine productions (39), or by cell injuries mediated by antigen–antibody complexes (Figure 3), complement fixation (Figure 4A), and/or ADCC (Figure 4B) (19). The present findings that autoantibodies of subjects with COPD have avidity against human pulmonary epithelial and endothelial cells (*see* Figures E1 and E2) also increase the likelihood that these immunoglobulins could mediate disease pathogenesis. Moreover, the intracellular (and nucleolar) locations of the target antigens exclude the possibility that these responses are simply attributable to recently described antielastin reactions (27), because this matrix component is typically an extracellular elaboration of mesenchymal rather than epithelial (or K562) cells (40). The current findings of intrapulmonary IgG and C3 deposition in diseased lungs, and the overt potential of these self-reactive immunoglobulins to mediate ADCC, are highly consistent with analogous findings in conventional autoimmune

Figure 4. Complement (C3) deposition and antibody-dependent cell-mediated cytotoxicity mediated by chronic obstructive pulmonary disease (COPD) autoantibodies. (A) C3 stains red against the blue cellular background in alveolar septa of two representative COPD lung sections (*left panels*) compared with those from normal subjects (*right panels*). (B) Incubation of human primary airway epithelial cells with plasmas from COPD patients ($n = 10$) enhances allogeneic cytotoxicity compared with effects of plasmas from normal control subjects ($n = 8$).

syndromes (13, 22), and implicate autoantibodies in the etiology of COPD.

The pathogenesis of most autoimmune syndromes is generally believed to be the result of complex interactions between environmental factors (e.g., cigarette smoke and/or possibly microbes) and genetic backgrounds (13, 23). If this autoimmune paradigm is also true in COPD, previously reported familial predilections (41) and interindividual differences in susceptibility for the disease (2, 4) could plausibly be explained. In addition, classical autoimmune responses tend to be self-perpetuating, and this characteristic may also account for long-term persistence of pulmonary inflammation in patients with COPD after smoking cessation (36). Moreover, autoimmune disorders frequently manifest with widespread systemic effects and involvement of multiple organ systems. Several clinical features in cohorts of patients with COPD may be a consequence of a systemic (and autoreactive) immune response (5), including increased risks of cardiovascular disease not accounted for by cigarette smoking *per se* (42), as well as muscle wasting (and/or decrements of BMI; see Figure 2B).

Indirect immunofluorescence assays can simultaneously detect heterogeneous autoantibodies that may have highly varied avidities, immunochemical properties, and cellular targets. Therefore, although positive test results denote the presence of an abnormality (24, 26), autoantibody levels (e.g., titers or intensity of fluorescent stains) are often not closely correlated with disease activity (or stage) *per se* (43). The association between autoantibody prevalence and disease stage in the subjects with COPD here has similarly limited precision (Figure 1B). However, identification of particular autoantibodies within a defined disease cohort can help in many cases to distinguish subgroups of afflicted patients with distinctive clinical syndromes and prognoses. For example, in systemic sclerosis, the presence of anti-Scl70 antibodies is associated with the development of pulmonary fibrosis, whereas findings of anti-RNA polymerase antibodies are more predictive of renal disease (43, 44). The present findings also suggest that particular autoantibodies in patients with COPD could be associated with unique clinical manifestations (Figure 2B), and the exploration of further clinical correlations with particular immunoglobulins in these patients is an area of ongoing investigation.

The data here corroborate and extend a series of reports that implicate adaptive immune mechanisms in the pathogenesis of COPD (5–11, 27). The potential that these particular immune responses may have an autoimmune component has also been previously hypothesized (5, 6), and the development of emphysema in an animal model of T-cell-dependent autoantibody production was recently described (45). Other reports show B-cell aggregates are present in COPD lungs (10, 46, 47) and immunoglobulin light-chain deposition in humans has previously been linked to progressive emphysema-like disease (48).

In summary, we have established that COPD is associated with autoantibodies that have avidity against pulmonary airway epithelial and, perhaps somewhat less frequently, pulmonary endothelial cells. The pathogenicity of these autoantibodies is supported by findings of *in situ* IgG and C3 depositions in diseased human lungs and an *in vitro* demonstration that these immunoglobulins can mediate ADCC. The present data are consistent with emerging paradigms that suggest that adaptive immune processes likely play a role in COPD progression (5–11, 27). These findings could have substantial relevance for future development of diagnostic and management modalities, and raise the potential that new approaches, possibly including directed immune modulation, could ultimately be beneficial in treatment of this disease.

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