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Peripheral T Cell Functions Correlate with the Severity of Chronic Obstructive Pulmonary Disease

Xuehai Zhu, Aneal S. Gadgil, Rachel Givelber, M. Patricia George, Michael W. Stoner, Frank C. Sciurba, and Steven R. Duncan

Adaptive immune processes have been implicated in the pathogenesis of chronic obstructive pulmonary disease (COPD). We hypothesized that peripheral T cell abnormalities may be present in afflicted patients. We tested this hypothesis by characterizing circulating T cells in COPD patients and correlated these findings with disease severity, smoking status, and use of inhaled glucocorticosteroids (ICS). Compared with normal controls, a lesser proportion of peripheral CD4 T cells from COPD subjects produced IL-10, whereas the CD8 T cells from these patients were more often activated and more frequently produced both IFN-γ and IL-4. COPD severity was significantly and inversely associated with the proportion of circulating CD4 T cells and directly correlated with CD4 production of IL-2, as well as frequency of CD8 T cell activation and CD8 IFN-γ production. Adjustments for current smoking status and ICS use by linear regression showed independent, and generally inhibitory, effects of these clinical variables on the abnormal T cell functions of these patients. We conclude that circulating T cells from COPD patients are abnormally activated and elaborate proinflammatory mediators with admixed features of Th1 and Th2 responses. Furthermore, many of these effector processes are significantly correlated with disease severity. These findings further implicate adaptive immune processes in COPD progression and indicate that facile assays of peripheral lymphocytes may provide useful insights into disease mechanisms. Current smoking and ICS use had independent effects on T cell functions among the COPD subjects, illustrating the importance of controlling for clinical parameters as covariates in immunological studies of patients afflicted with this disease. The Journal of Immunology, 2009, 182: 3270–3277.

Chronic obstructive pulmonary disease (COPD) is a leading cause of death in the United States, and one of the few major diseases in which mortality continues to increase worldwide (1). A growing body of evidence suggests that adaptive immune responses play an important role in the pathogenesis and progression of COPD, as evidenced by correlations of lung histological and morphometric measurements with the characteristics of intrapulmonary lymphocyte infiltrations (2–10). Moreover, activated T cells can cause a variety of the tissue injuries that typify COPD by direct cytopathic effects, elaboration of diverse proinflammatory and deleterious mediators, and/or recruitment and activation of other immune and parenchymal effector cells (11, 12).

Most previous studies have examined functions of intrapulmonary T cell populations in situ or after isolation of these cells from the lungs of patients with COPD (2–10). However, it is also widely appreciated that lymphocytes readily traffic between inflammatory sites (including lungs), regional lymph nodes, and the systemic circulation, where they can be easily sampled (13). The ability to study disease phenomena using specimens procured by minimally invasive means could be a boon for subsequent biological and clinical investigations.

The characteristics of circulating lymphocytes in COPD patients have not yet been comprehensively defined, and the limited numbers of these previous studies are notable for often discrepant results (8–10, 14–16). We undertook an evaluation of peripheral blood lymphocytes from COPD patients for the purpose of determining whether characteristics of these cells could be reflective of the pulmonary physiological abnormality (expiratory airflow obstruction) that defines this disease (1). We found that circulating T cells of COPD patients are abnormally activated and elaborate proinflammatory cytokines that likely have relevance in the pathogenesis of this disease. Moreover, some measurements of T cell effector functions are significantly correlated with disease severity and, at least in some cases, appear to be independently affected by smoking status and inhaled glucocorticosteroid (ICS) use.

These data provide further evidence for a role of adaptive immunity in the progression of COPD and raise possibilities that focused immunomodulation could eventually be used as a specific treatment for this disease. In addition, these findings imply that easily procured circulating lymphocytes could be useful for study of disease pathogenesis and/or possibly utilized as surrogate biomarkers in early phase trials of novel therapeutics for COPD. The identification here of multiple significant clinical covariates also illustrates the importance of controlling for disease severity and other relevant parameters in immunological studies of afflicted patients.

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4 Abbreviations used in this paper: COPD, chronic obstructive pulmonary disease; ICS, inhaled glucocorticosteroid; GOLD, Global Initiative for Obstructive Lung Disease; FEV1/FVC, forced expiratory volume in 1 s, as a percent of predicted values.

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Materials and Methods

Subjects

Current and former smokers (n = 81) with no history of asthma and at least a 10-pack-year tobacco smoking history were recruited through the Em-physema-COPD Research Registry at the University of Pittsburgh (Pitts-

burgh, PA). All subjects included in these analyses were stable at the time of the examination and had no current clinical evidence of active infections or current or previous diagnoses of rheumatological, malignant, or other systemic inflammatory disease. COPD subjects with a dominant restrictive impairment by spirometry, a significant allergic history, completely revers-

ible airflow obstruction, a history of clinical asthma, or current use of oral steroids were excluded. Exsmokers herein denotes COPD subjects who quit smoking and to use ICS. The ages of normal controls (56 ± 1 years old) were similar to those of COPD subjects. All of the subjects studied here were Caucasian except one African American with COPD (GOLD 2).

Comparisons of circulating T cells among COPD subjects and normal subjects

Quantitative assays of peripheral T cells were initially performed to test for global differences between COPD subjects and healthy volunteers.

The proportion of CD4 T cells among PBMCs was slightly, albeit significantly, decreased in the COPD subjects compared with normal subjects, whereas proportions of CD8 T cells were equivalent in both groups (Fig. 2A). These decrements in CD4 T cells were reflected by a possible (albeit insignificant) trend for decreased CD4:CD8 ratios in the COPD subjects (3.3 ± 0.3 vs 4.3 ± 1.0, for COPD and normal subjects, respectively).

Results

Subjects

COPD patient characteristics are shown in Table I. There were no systematic associations between either age or smoking duration and the magnitude of physiological impairments. Subjects with the most severe physiological impairments, however, were more likely to have quit smoking and to use ICS. The ages of normal controls (56 ± 1 years old) were similar to those of COPD subjects. All of the subjects studied here were Caucasian except one African American with COPD (GOLD 2).

Comparisons of circulating T cells among COPD subjects and normal subjects

Quantitative assays of peripheral T cells were initially performed to test for global differences between COPD subjects and healthy volunteers.

The proportion of CD4 T cells among PBMCs was slightly, albeit significantly, decreased in the COPD subjects compared with normal subjects, whereas proportions of CD8 T cells were equivalent in both groups (Fig. 2A). These decrements in CD4 T cells were reflected by a possible (albeit insignificant) trend for decreased CD4:CD8 ratios in the COPD subjects (3.3 ± 0.3 vs 4.3 ± 1.0, for COPD and normal subjects, respectively).
We further hypothesized that if T cells were involved in ongoing inflammatory responses in the COPD patients, there might be evidence of activation among the circulating lymphocytes. Peripheral CD8 T cells of the COPD subjects were more frequently activated than those among normal subjects, as ascertained by MHC class II expression (HLA-DR; Fig. 2B). There was a trend too for greater relative proportions of activated CD4 in the COPD patients, although this difference did not reach statistical significance.

Intracellular cytokine determinations also often showed intergroup differences of mediator elaborations in COPD peripheral lymphocytes. CD4 T cells of COPD subjects less frequently produced IL-10 than those of normal subjects (p = 0.009). IFN-γ and IL-4 production was more frequent in COPD CD8 T cells (n = 49) than in normal subjects (p = 0.0006 and p = 0.001, respectively). All intergroup comparisons were made using Mann-Whitney rank-sum tests.

Disease severity and immune parameters
We hypothesized that if adaptive immune mechanisms are important in COPD pathogenesis, associations of immunological assays with disease severity may be evident. Moreover, the presence of correlations between T cell functions would not only implicate these immune responses in disease progression but also show that immunological assays in heterogeneous COPD populations could be confounded by the particular case-mix of disease severities.

Our analyses showed that significant correlations between several T cell parameters and disease extent were present in the COPD patients. The percentages of CD4 T cells among PBMCs decreased, and the frequency of their IL-2 production increased, in normal subjects (11.5 ± 1.8%), and this difference approached but did not reach significance (p = 0.06). Both IFN-γ and IL-4 were more frequently produced by the CD8 T cells of COPD patients than the corresponding cells from normal subjects (Fig. 2D).

FIGURE 2. Characteristics of circulating T cells in COPD patients. Comparisons between the aggregate COPD population (composed of subjects with varying disease severity; see Table I) vs healthy normal subjects. A, Proportions of CD4 among PBMCs (PBMNC) were decreased in COPD subjects (p = 0.009), whereas there were no significant differences in CD8 percentages. B, Activation (per MHC class II coexpression) of CD8 T cells were greater in COPD patients (n = 49) than in controls (p = 0.0002). There may also be a trend for increased activation of CD4 T cells among COPD subjects, but this comparison with controls did not reach statistical significance (p = 0.07). C, Circulating CD4 T cells in COPD patients less frequently produced IL-10 (n = 29) than those of normal subjects (p = 0.009). D, IFN-γ and IL-4 production was more frequent in COPD CD8 T cells (n = 49) than in normal subjects (p = 0.0006 and p = 0.001, respectively). All intergroup comparisons were made using Mann-Whitney rank-sum tests.

FIGURE 3. Immune functions of COPD peripheral T cells correlate with disease severity. Significant correlations (by linear regression analyses) were evident between pulmonary function (FEV1) of COPD patients and characteristics of circulating T cells in these subjects. The FEV1 values of individual COPD patients were significantly correlated with the proportions of CD4 T cells among their circulating PBMCs (PBMNC; A), the frequency of IL-2 production by their CD4 T cells (B), and the frequency with which their CD8 T cells expressed MHC class II (C) and produced IFN-γ (D).
proportion to the extent of pulmonary dysfunction (Fig. 3, A and B, respectively). Both HLA-DR expression and IFN-γ production of circulating COPD CD8 T cells were also directly associated with
disease severity (Fig. 3, C and D). There were no significant correlations between FEV\textsubscript{1}%/p and CD8 proportions among PBMCs, CD4 MHC class II or IFN-γ frequencies, CD8 IL-2 production, or IL-4 and IL-10 elaborated by either T cell subpopulation.

Effects of smoking

Although not extensively studied within COPD populations per se, cigarette smoking has been shown elsewhere to exert multiple effects on many adaptive immune functions (19). Moreover, in our population of COPD patients, those subjects with the most severe impairment in lung function were also less likely to have continued smoking. Therefore, to examine the potential that continued smoking may have confounded the relationship between pulmonary impairment and T cell functions among COPD patients, we performed multivariate analyses, using FEV\textsubscript{1}%/p and smoking status (current vs former) as independent covariates, in evaluations of those immune parameters that were associated with disease severity.

Direct comparisons of still smoking and ex-smoking cohorts stratified by disease severity suggested that current, continued smoking was associated with tendencies to blunt cytokine elaborations and CD8 T cell activation, particularly among those subjects with the most advanced disease (Fig. 4A). The addition of current smoking status as a second independent variable strengthened the associations between FEV\textsubscript{1}%/p with CD4 proportions among PBMCs (r = 0.35, p = 0.007) and CD8 activation (r = 0.42, p = 0.012; compare with Fig. 3, A and C, respectively). Post hoc regression analyses limited solely to exsmokers also showed that the correlations between productions of IL-2 (among T2 cells) and IFN-γ (by CD8 T cells) with disease severity tended to be stronger in this subpopulation (Fig. 4, B and C) than in the aggregate COPD cohort (compare with Fig. 3, B and D, respectively).

Effects of ICS use

Comparisons of cohorts stratified by disease severity indicated that current ICS use tended to diminish cytokine elaborations and CD8 T cell activation among severely afflicted subjects (Fig. 5A). Multivariate analyses, with current ICS usage as an independent variable, strengthened the association between FEV\textsubscript{1}%/p and IL-2 production by CD4 T cells of COPD patients (r = 0.39, p = 0.017; compare with Fig. 3B). Additional post hoc analyses, limited solely to the COPD subjects not currently taking ICS agents, again showed that the correlation between CD8 IFN-γ production and FEV\textsubscript{1}%/p was strengthened by exclusion of ICS-treated subjects (Fig. 5B). Although there were too few subjects to rigorously analyze and adjust for combinations of independent variables, the potential for complex, simultaneously confounding effects of both smoking status and ICS use could be indicated by the stronger correlations between immune functions and disease severity in analyses limited to exsmoking COPD subjects who also were not using ICS (Fig. 5C).

Discussion

The primary focus of these investigations was to determine whether peripheral adaptive immune functions in COPD patients correlated with the severity of airflow obstruction. Indeed, we observed several associations between circulating T cell characteristics and pulmonary physiology in these patients (Fig. 3). These correlations are consistent with, and further implicate, a role of adaptive immune processes in COPD progression.

COPD is a complex heterogeneous syndrome with an incompletely understood pathogenesis (2–10, 13–16, 20–27). Long-term exposure to tobacco smoke is unquestionably the primary risk factor for development of the abnormal expiratory airflow obstruction that characterizes this disease (1). Nonetheless, severe COPD occurs in only a minority of long-term cigarette smokers, and illness susceptibility appears to be highly variable, even among subjects with similar ages and smoking histories (Table I), indicating that superimposed processes are the final determinants of disease development and/or progression (1, 20). Furthermore, abnormal intrapulmonary inflammation persists, and COPD typically progresses, long after smoking cessation (21). In addition, numerous systemic disease manifestations with a potential inflammatory basis have been associated with COPD, including skeletal muscle wasting and osteoporosis, as well as increased risks of cardiovascular disease that cannot be fully accounted for by cigarette smoking per se (22).

The potential importance of adaptive immunological processes in COPD has lately become a focus of considerable attention (2–10, 13–16, 23–29). Among other observations, T lymphocytes are the most numerous inflammatory cell within alveolar walls of COPD patients, and the extent of intrapulmonary lymphocyte infiltrations in situ is closely correlated with various morphometric and physiological measures of disease severity (2–6). In general, CD8 T cells predominate in the diffuse parenchymal infiltrates within COPD lungs, although large numbers of CD4 lymphocytes are present proximate to focal lymphoid aggregates (6, 23). Findings of oligoclonal expansions among lymphocytes from COPD patients show these cells are activated and undergo proliferations in response to conventional peptide Ags (23–25). The identity(ies) of the Ag(s) that trigger and fuel these immune processes has not yet been established, although microbes that frequently (and/or chronically) colonize or infect COPD lungs have been indirectly implicated as potential initiators of immune responses (21, 28, 29). In turn, these antimicrobial responses could possibly generalize via processes of mimicry and/or epitope spreading (30). Autoreactive cellular and humoral responses directed against lung endothelium, epithelium, and connective tissue elements appear to be frequent in COPD patients (26, 27), and these processes could also conceivably contribute to or cause systemic manifestations of the disease (22).

Functional characterizations of intrapulmonary lymphocytes in situ, or among cells directly isolated from pulmonary specimens of diseased patients, include observations of activation and specific, and usually Th1 predominant, mediator elaborations, most consistently and notably including production of IFN-γ (2–7). However, contrary findings have also been reported (8, 10).

Only a limited number of previous investigations have specifically examined the characteristics and functions of circulating T cells among COPD patients, and findings of these studies are often considerably disparate (8–10, 13–16). However, direct comparisons of these reports may be complicated by their considerable differences of experimental methodologies, frequent use of small COPD subject cohorts, and variable extents of controlling for clinical parameters, including disease severities.

Circulating CD4 T cells from 20 COPD patients (all were exsmokers) with highly varying disease severities (FEV\textsubscript{1}%/p range, 19–80), were reported in one study to more frequently elaborate IFN-γ, but less frequently produce IL-4, compared with normal preparations, whereas there were no apparent abnormalities of CD8 T cell cytokine productions among the former (14). In the largest previous study to date (n = 70), but limited to exsmoking subjects with GOLD stage II (FEV\textsubscript{1}%/p, 54 ± 8), the frequency of T cell IL-2 and IL-4 productions among the COPD patients were equivalent to those of normal subjects (16). These investigators...
also reported the seemingly paradoxical finding that CD8 T cells from their diseased subjects less frequently produced IFN-γ. More recently, analyses of circulating T cells from four exsmoking patients with predominantly severe COPD (median FEV1%pred 36) did not find significant differences of either IFN-γ or IL-4 production, in comparison with four subjects who had normal pulmonary function (two current smokers and two exsmokers; Ref. 10). Another study of 14 patients with moderate lung disease (FEV1%pred, 57 ± 2), none of whom had smoked within 12 h of testing (6 subjects were taking ICS), similarly did not find significant intergroup differences in elaborations of IL-2, IFN-γ, IL-4, or IL-10 by circulating COPD T cells, in comparison with specimens from healthy normal subjects (8). A characterization of peripheral T cell subsets among 20 currently smoking COPD subjects (FEV1%pred, 45 ± 3) found no overall changes in T cell expression of HLA-DR, proportions of CD4+ or CD8+ T cells, or the CD4:CD8 ratio (15).

We believe our study of circulating T cells in COPD subjects has several unique features. The use of a large number of COPD subjects increases the power of the present analyses to detect intergroup differences and minimize type II (β) errors. Inclusion here of subjects with a broad (and delineated) range of disease severities (Table I) also facilitates analyses of clinical-immunological correlations (Figs. 3, 4, B and C; and 5, B and C).

The findings here, showing that the magnitude of physiological abnormalities are associated with T cell functions, notably demonstrate that global analyses of adaptive immune parameters in COPD-affected patients can be heavily skewed by the case-mix distributions of disease severities in these study populations. As an example using the current data, the frequency of IL-2 production by CD4 T cells among the aggregate COPD population here with diverse disease severities was not significantly greater than that of the normal controls (28.3 ± 2.7%). However, CD4 IL-2 production was directly correlated with COPD severity (Figs. 3A and 4B). Hence, study here of a patient cohort composed of only those with severe disease (i.e., GOLD 3 and 4) would have resulted in assertions that 37.8 ± 3.3% of circulating CD4 T cells among COPD subjects produce IL-2, and this value is significantly and abnormally greater than that of healthy controls (p < 0.05). Conversely, however, study of a COPD subpopulation instead composed solely of those with mild-to-moderate disease severity (i.e., GOLD 1–2) would have resulted in finding the frequency of IL-2 production among their circulating CD4 T cells was 27.3 ± 2.5% and led us to an equally (albeit opposite) erroneous conclusion that the value for COPD patients is nearly identical with that of normal individuals (16). Thus, attempts to define particular immunological measures as a constant or meaningful function for all COPD patients seem problematic and possibly misleading. The potential ascertainment biases due to differences of disease severities among their experimental populations may explain at least some of the discrepant results of earlier COPD studies (8–10, 13–16).

The present data showing generally increased activation among circulating T cells in COPD subjects (Fig. 2B) also appear to be an unprecedented finding and a possible result of the power afforded by study of comparatively greater subject numbers. Moreover, this particular observation is also consistent with previous findings of increased activations of in situ T cells within COPD lungs (2, 3, 7, 9). Proportions of circulating CD4 T cells were also seen here to decrease among those more severe COPD (Fig. 3A), a possible result of these cells being sequestered within the bronchus-associated lymphoid aggregates most often found in patients with advanced disease (6). The present findings of increased IFN-γ production by circulating COPD CD8 T cells, although distinctly contrary to results of an analysis limited to GOLD 2 subjects (16), is consistent with most in situ observations (2, 5, 7). The likely singular importance of IFN-γ in COPD pathogenesis is underscored by the many demonstrable proinflammatory effects of this mediator, including activation and recruitment of epithelial and inflammatory cells, up-regulation of matrix metalloproteases and other injurious mediators (2, 12), as well as inferences derived from animal models (31).

Overall, the current data suggest that a complex cytokine network process is mediated by the T cells of COPD patients. A Th1 bias is indicated here by findings of increased IFN-γ- and IL-2-producing lymphocytes, along with concurrent decreases of IL-10-producing cells in the COPD subjects, and these observations are consistent with previous observations of a Th1 predominance in situ (2, 5, 7). However, the increased frequency of IL-4-producing CD8 T cells in the COPD patients also reflect a Th2-associated process and corroborates a trend reported previously (10). This particular observation is also concordant with earlier reports of heightened productions of IL-4 and/or other Th2 cytokines among COPD bronchoalveolar lavage T cells (8, 10) and could have important pathogenic implications, given the diverse, but generally profibrotic, and other injurious effects of this cytokine (32). Present data showing that IL-10 is less frequently elaborated by circulating COPD CD4 T cells could also have implications relevant to modulation (e.g., down-regulation) of adaptive immune responses among the diseased subjects (33). Corroboration and further study of potential immunoregulatory mechanisms in COPD seem indicated, including more definitive numerical and functional ascertainties of regulatory T cell subpopulations (26, 34).

Our analysis of smoking effects on T cell functions among a population of afflicted COPD patients also appears to be a novel approach. Tobacco smoking has been previously shown, by in vitro investigations and comparative studies of other subject populations (e.g., individuals with normal pulmonary function), to depress a variety of T cell functions, putatively due to toxicities of acrolein and/or other constituents of complex smoke aerosols (19, 35). Associations between disease severity and T cell parameters here were generally more rigorous in post hoc analyses limited to the nonsmoking COPD patients (Figs. 4, B and C; and 5C), suggesting that current smoking has substantial confounding effects on some measurements of immune parameters. Results of the multivariate linear regression models here also confirm an independent influence of smoking status on immunological processes in COPD patients, even after adjusting for disease severity, including decrements in the proportion of circulating CD4 T cells and frequency of CD8 T cell activation.

The present study is also relatively unique in evaluations of inhaled corticosteroid effects by use of comparatively large numbers of afflicted COPD patients, with adjustments for disease severity. Previous investigations of ICS have yielded conflicting results regarding systemic immunological effects of these drugs (36–39). We found statistically significant effects of ICS use on the frequency of IL-2 production among circulating CD4 T cells of COPD patients. In addition, possible trends for other systemic immunological effects of these agents were also indicated (Fig. 5), suggesting a possible focus for future and more powerful studies with even larger numbers of subjects that also need to incorporate considerations for confounding by disease severity and smoking status.

Assays using relevant immune effector cells from blood may ultimately prove to be a facile methodology for study of COPD pathogenesis, particularly in exploratory investigations of disease mechanisms, or in patients from whom more invasive specimen procurements are not feasible (e.g., those with severe and/or unstable pulmonary dysfunction). These particular measures may be
especially useful for replicating, serial assays among individual subjects in longitudinal cohort studies. The correlations of immune functions with disease severity imply that certain of these assays could possibly be useful as clinically relevant biomarkers. As an example, the central importance of IFN-γ in modulating key pathophysiological processes in COPD patients seems increasingly likely (2, 5, 7, 12, 31), and longitudinal determinations of this cytokine production by peripheral T cells might eventually be used as indications of treatment efficacy in early-phase therapeutic trials (e.g., changes of IFN-γ production with therapy) and hence be a valuable adjunct to other clinical and physiological end-point determinations.

In summary, these data show that numerous, pathologically relevant immunological functions of circulating T cells are abnormal and correlated with COPD severity and thus further support paradigms that posit that adaptive immune processes contribute to progression of this disease. These findings also show that immunological assays using COPD patient specimens can be heavily influenced by the distribution of disease severities, as well as smoking status and ICS use. Hence, studies to define immunological responses among patients with this complex disease need to incorporate appropriate considerations for these confounding clinical factors, and/or inclusion of much larger subject numbers than has been typical in most previous investigations. Ultimately, better understanding of the role(s) that adaptive immune mechanisms play in COPD progression will likely lead to development of novel treatments that could have greater therapeutic efficacy for patients with this otherwise inexcusable disease.

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