

BRIEF COMMUNICATION

Increased Allergen-Specific, Steroid-Sensitive gamma delta T Cells in Bronchoalveolar Lavage Fluid from Patients with Asthma

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Objective: To test the hypothesis that allergen-specific, steroid-sensitive gamma delta T lymphocytes are increased in bronchoalveolar lavage fluid of patients with asthma.

Design: Case series.

Setting: The outpatient allergy services at the University of Perugia, Perugia, Italy.

Patients: 12 untreated atopic patients (6 children and 6 adults) with mildly symptomatic chronic asthma were studied. Bronchoalveolar lavage fluid from 10 healthy nonsmoking volunteers and age-matched children with cystic fibrosis (n equals 5) or anatomic malformation of the airways (n equals 4) served as control samples.

Intervention: Three patients received treatment with deflazacort, 60 mg twice daily, for 1 week.

Measurements: CD3^{plus}, CD4^{plus}, and CD8^{plus} T cells from patients and controls were examined by two-color flow cytometry for coexpression of V delta 1 and V delta 2 isoforms of the gamma delta T-cell receptor. In vitro pulmonary gamma delta T-cell proliferation in response to a specific allergen, the apoptotic death of these cells after incubation with 10^{minus} 7 M dexamethasone, and bronchoalveolar lavage fluid T-lymphocyte composition before and after 1 week of deflazacort therapy were evaluated in 3 Dermatophagoides pteronyssinus-sensitive patients.

Results: The proportion of gamma delta T lymphocytes, primarily CD4^{plus} or CD4^{minus} CD8^{minus} cells, was higher in asthmatic patients than in controls (P less than 0.05 by one-way analysis of variance). Most lung gamma delta CD4^{plus} lymphocytes expressed the gamma delta T-cell receptor V delta 1 chain. These cells proliferated in response to allergen stimulation, underwent steroid-induced apoptosis in vitro, and disappeared after systemic steroid treatment.

Conclusions: Allergen-specific, steroid-sensitive gamma delta T cells may be one of the cellular components involved in the airway inflammation that characterizes allergic bronchial asthma.

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Macrophages are the main cellular component in bronchoalveolar lavage fluid specimens obtained from normal patients. Other cell types, including T lymphocytes (CD3^{plus}) of both helper (CD4^{plus}) and suppressor-cytotoxic

(CD8^{plus}) T-cell subsets, are also present, but the percentage of these cell types usually does not exceed 10%. Eosinophils, basophils and mast cells, and T lymphocytes have been found to be increased in bronchoalveolar lavage fluid samples in studies that have attempted to quantify the magnitude of the airway inflammatory response in patients with asthma [1,2].

Recent findings suggest that T lymphocytes play a fundamental role in the induction of allergic inflammation. In fact, these cells not only recruit other specialized cells, such as eosinophils, by secreting interleukin-5 [1], they also promote local and systemic synthesis of IgE through the production of interleukin-4 [3,4]. Lymphocytes with such functional activities are currently termed T-helper 2 (Th2), whereas the non-overlapping cell counterpart that secretes interferon-gamma or interleukin-2 or both is termed T-helper 1 (Th1) and is involved in the delayed hypersensitivity immune reactions [3].

Although Th2-like activated T lymphocytes have been detected in the lungs of atopic asthmatic patients [5], it is still unclear whether these cells bear the alpha beta or the less common gamma delta T-cell receptor for antigen on their surface. This doubt is legitimated by the fact that many CD3^{plus} intraepithelial lymphocytes found in the nasal mucosa of patients with allergic rhinitis are T cells that display the gamma delta T-cell receptor heterodimer [6].

These findings prompted us to determine whether allergen-specific gamma delta T lymphocytes are present in the bronchoalveolar lavage fluid of asthmatic patients and that, in these patients, they will be the major T-cell subset to disappear after systemic steroid treatment. Interestingly, our in vivo and in vitro studies provide evidence that apoptosis is the basic mechanism through which corticosteroid treatment acts on this T-lymphocyte type, thereby confirming the results of our previous investigations [7].

Methods

Patients

We studied 12 mildly symptomatic patients (6 children and 6 adults) with chronic asthma (FEV₁ 70% of that predicted for persons of their age and height) who were not receiving therapy with inhaled or oral corticosteroids, sodium cromoglycate, theophylline, or beta₂-agonists. Results of skin prick tests with purified Dermatophagoides pteronyssinus, D.

farinae, and Parietaria judaica allergen extracts (Neo Abello, Madrid, Spain) were positive; results of an enzyme-linked immunosorbent assay (DPC Corporation, Los Angeles, California) for circulating allergen-specific IgE were also positive. None of the patients was a smoker or had had antecedent upper respiratory tract infection. Bronchoalveolar lavage fluid collection and fiberoptic bronchoscopy were done as previously described [8]. Ten healthy non-atopic, nonsmoking volunteers and patients diagnosed as having pulmonary sarcoidosis (n equals 5) or extrinsic allergic alveolitis (n equals 4), two pathologic conditions known to be associated with over-expanded lung CD4^{plus} or CD8^{plus} T-cell populations, were used as adult control groups. Age-matched uninfected children with cystic fibrosis (n equals 5) or anatomic malformation (n equals 4) of the airways served as controls for the cohort of asthmatic children. Bronchoalveolar lavage was repeated in 3 asthmatic patients after 1 week of therapy with deflazacort (Flantadin, Lepetit, Milano, Italy), 60 mg twice daily (a dose equivalent to 50 mg of prednisone), and then 3 weeks after therapy. We administered corticosteroids to these patients for exacerbation of their disease. We obtained informed consent from all study participants, and the clinical research was conducted in accordance with the local ethical committee guidelines.

Lymphocyte Typing

Pulmonary T cells were phenotyped with the following monoclonal antibodies: phycoerythrin-conjugated anti-CD3 (Ortho Pharmaceutical Corporation, Raritan, New Jersey), which recognizes up to 90% of T cells bearing the alpha beta or gamma delta T-cell receptor heterodimer; anti-CD4 and anti-CD8 (Ortho), which stain helper/inducer and

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cytotoxic T-cell subsets; and fluorescein-conjugated anti-TCR delta 1, anti-delta V1(a), and anti-delta V2(a) (T Cell Sciences, Cambridge, Massachusetts), which identify all gamma delta T lymphocytes and the reciprocal subtypes expressing V delta 1^{plus} and V delta 2^{plus} gene products. In the analysis of two-color cytofluorimetric data (FACScan, Becton-Dickinson, Mountain View, California), we used the Lysis II program (Becton-Dickinson) to optimize gating of lymphocytes and to provide an objective means of excluding both debris and other cell types.

gamma delta T-Cell Enrichment

In accordance with the manufacturer's instructions (DynaL, A. S., Oslo, Norway), pulmonary mononuclear cells from 3 D. pteronyssinus-sensitive patients were enriched in TCR delta 1-reactive T-cell subsets by negative magnetic immunoselection, using a mixture of anti-alpha beta T-cell receptor monoclonal antibodies. This procedure yielded a gamma delta^{plus} T-cell population of greater than 85%, which was used for culture and apoptotic cell death experiments.

Proliferation Assay

To assess the allergen-specificity of bronchoalveolar lavage gamma delta T cells, 1.2 times 10⁵ mononuclear cells and 4 times 10⁴ gamma delta-enriched lung T cells (the latter co-cultured with 8 times 10⁴ autologous macrophages) from three D. pteronyssinus-sensitive patients and, because of the very small percentage of gamma delta T cells in normal bronchoalveolar lavage fluid, 1.2 times 10⁵ mononuclear cells from three controls were seeded in microplates and cultured in medium alone (RPMI-1640 [Gibco, Grand Island, New York] supplemented with fetal calf serum, L-glutamine, Hepes buffer, and antibiotics) or in the presence of 1 mug/mL purified D. pteronyssinus (Neo Abello, Madrid, Spain) or unrelated allergen *Lolium perenne* (purified L. perenne, Neo Abello) from the Gramineae family. After 60 hours of culture, the cells were pulsed for 16 hours with 0.5 muCi [(³) H]-thymidine and were harvested, and the radioactivity was measured by liquid scintillation. Results are expressed as net cpm (counts per minute) [(³) H]-thymidine incorporation and reflect absolute cpm [(³) H]-thymidine uptake minus background cpm (cpm incorporated in the absence of allergen).

Evaluation of Apoptotic Cell Death

Apoptotic cells were qualitatively evaluated by agarose gel DNA electrophoresis [7] and quantitatively assessed as described previously [9]. Briefly, 1 times 10⁶ TCR delta 1^{plus} pulmonary T cells were incubated for 24 hours with medium alone or dexamethasone (10^{minus} 7 M), resuspended in 1.5 mL hypotonic propidium iodide solution and propidium iodide fluorescence of individual nuclei measured in a FACScan flow cytometer (Becton-Dickinson). We carried out control experiments using macrophage-depleted pulmonary T cells from healthy persons.

Statistical Analysis

Study populations were stratified according to age class. We used the Kruskal-Wallis one-way analysis of variance (with a significance level of 0.05) for statistical evaluation of the differences in bronchoalveolar lavage gamma delta T-lymphocyte subset distributions. Pairwise comparisons for measuring the significance of the differences among mean values (plus minus SE) calculated in the various groups (asthmatic patients compared with controls) were done with the Mann-Whitney U-test. In asthmatic patients (n equals 12), the overall relation between serum IgE levels (IU/mL) and the percentages of pulmonary gamma delta T cells was analyzed using the Spearman correlation test. The Statistical Package for the Social Sciences (SPS, Chicago, Illinois), version 4.0, was used for all statistical computations.

Results

As shown in [Table 1](#), a significant proportion of CD3^{plus} T lymphocytes in patient samples double-stained for the TCR

delta 1 monoclonal antibody, which defines gamma delta^{plus} T lymphocytes. More than half of these gamma delta T cells were CD4^{plus}, primarily of the V delta 1^{plus} subset, whereas the remainder of gamma delta T cells found in the lung of our asthmatic patients were CD4^{minus} CD8^{minus}, as shown by the fact that they never reacted with anti-CD8 monoclonal antibody. In addition, the percentage of gamma delta T cells expressing the V delta 2 isoform of the gamma delta T-cell receptor was negligible in all samples tested (data not shown). Statistically significant differences were also obtained when the absolute numbers of pulmonary gamma delta T cells from patients with asthma (mean count in adults, 29.6 plus minus 2.5 times 10⁴; in children, 23.2 plus minus 3.1 times 10⁴) were compared with those of the corresponding controls (mean count in adults, 0.2 plus minus 0.1 times 10⁴; P less than 0.001; in children, 0.3 plus minus 0.1 times 10⁴; P less than 0.001).

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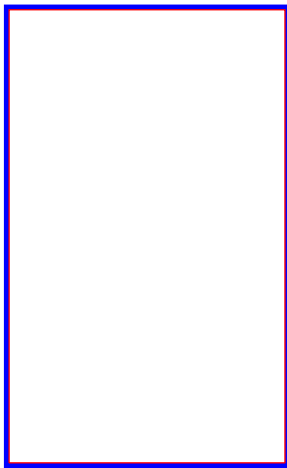
View this table: [\[in this window\]](#) [\[in a new window\]](#) **Table 1. Bronchoalveolar Lavage gamma delta T-Lymphocyte Subset Distribution in Patients with Allergic Asthma***

The bronchoalveolar lavage gamma delta T-cell concentration was not correlated with either specific serum IgE levels or any other clinical or functional (spirometric) variables (data not shown). In contrast, a relation was found between total serum IgE concentrations and pulmonary gamma delta T-lymphocyte numbers, but this did not reach statistical significance (r equals 0.21; P equals 0.06).

In the three in vitro experiments that we carried out, pulmonary gamma delta T cells from D. pteronyssinus-sensitive patients proliferated in response to the specific allergen, with a net [(³) H]-thymidine incorporation ranging from 2400 to 4850 cpm, but did not proliferate in the presence of unrelated (L. perenne) allergen extract, with a [(³) H]-thymidine incorporation ranging from 120 to 450 cpm.

Furthermore, lung gamma delta T cells abruptly decreased and alpha beta (^{plus}) CD4^{plus} and CD8^{plus} T lymphocytes increased in these patients after 1 week of treatment with glucocorticoids. Interestingly, the absolute numbers of gamma delta T cells did not increase again when therapy was discontinued [Figure 1](#). The gamma delta T-cell subpopulation was sensitive to steroid-induced programmed cell death in vitro. In fact, 24-hour dexamethasone incubation followed by flow-cytometric analysis with propidium iodide staining showed that the propidium iodide fluorescence profiles of apoptotic nuclei increased from 7% to 35% in dexamethasone-treated bronchoalveolar gamma delta-enriched T cells, but not in control cultures set up in medium alone. DNA agarose gel electrophoresis revealed the typical ladder of fragmented DNA in experiments performed in parallel (data not shown).

Figure 1. Effects of systemic steroid therapy on bronchoalveolar lavage fluid T-cell composition and gamma delta T-cell survival in allergic bronchial asthma. After 1 week of deflazacort treatment (60 mg twice daily), the absolute numbers of bronchoalveolar lavage CD3^{plus} TCR delta 1^{plus} and CD4^{plus} V delta 1^{plus} T-cell values decreased abruptly (bottom), whereas the global TCR- alpha beta^{plus} T-cell compartment expanded, and did not increase again when therapy was discontinued (top). The absolute bronchoalveolar lavage lymphocyte numbers remained stable in all samples tested. Data depicted are from a single patient of the three studied.



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Discussion

In our study, we show, for the first time, that the percentage and absolute numbers of gamma delta T cells, which do not usually exceed 2% of the total T lymphocytes in the normal human lung [10], are increased in bronchoalveolar lavage fluid samples from untreated patients with asthma but not in samples from healthy controls or from persons with other pulmonary diseases. Previous findings that T lymphocytes recruited in the late-phase reaction induced by inhaled allergen are CD3^{plus} CD4^{minus} CD8^{minus} [11], a

phenotypical feature of gamma delta T cells, and that double-negative (CD4^{minus} CD8^{minus}) gamma delta T lymphocytes are increased in the nasal mucosa of patients with allergic rhinitis [6] are both consistent with our findings. The described increase in gamma delta T lymphocytes, either CD4^{plus} or double-negative, together with the finding that the gamma chain of the high-affinity IgE receptor (FcεRI) is a major functional subunit of murine CD3^{plus} cells bearing the gamma delta T-cell antigen receptor complex [12] indicate that these cells may contribute to the recognition of IgE-complexed allergens.

Our in vitro proliferation studies indicate that pulmonary gamma delta T cells from asthmatic patients are allergen-specific, a result that is consistent with the results obtained in experiments carried out on gamma delta T-cell clones established from the nasal mucosa of D. farinae-sensitive patients with allergic rhinitis [13].

During the past few years, significant progress has been made toward identifying the histopathologic picture of bronchial asthma [1,2] and understanding the molecular mechanisms that regulate human IgE synthesis [4]. Testimony continues to mount in support of the hypothesis that, in the airway mucosa of asthmatic patients, the release of cytokines by activated T lymphocytes (that is, interleukin-5) leads to the local accumulation of eosinophils, their activation, and the secretion of eosinophil-derived proteins with subsequent epithelial damage and bronchial hyper-responsiveness [2]. Among the many kinds of cytokines, interleukin-4 is the sole inducer of IgE synthesis [14,15], but additional signals, which are provided by T cells, are required for induction of IgE switching in naive B cells [16]. In vitro studies have shown that gamma delta T cells, like conventional alpha beta T lymphocytes, help in the production of IgE in the presence of interleukin-4 [17]. Furthermore, human gamma delta T-cell clones that produce high levels of interleukin-4 and interleukin-5 but lack detectable production of interferon-gamma (Th2-type T lymphocytes) have recently been described [18].

The proliferation of lung gamma delta T cells in response to the specific allergen and their in vitro and in vivo apoptotic

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death after corticosteroid treatment show not only that gamma delta T lymphocytes are involved in the generation of airflow inflammation in asthmatic patients, but also that they may be one of the cellular components on which steroids exert their anti-inflammatory activity. We documented substantial modifications in the bronchoalveolar lavage fluid cellular component of three patients sampled at the end of short-term therapy with corticosteroids. After 7-day therapy with deflazacort, eosinophils and CD4^{plus} and CD4^{minus} CD8^{minus} gamma delta T lymphocytes almost completely disappeared and the global alpha beta^{plus} T-cell compartment expanded. That pharmacologic doses of glucocorticoids suppress the production of interleukin-4 by T lymphocytes [19] and that exogenous recombinant interleukin-4 protects T cells from steroid-induced death [20] may partially explain the susceptibility of T cells to apoptosis. Our findings that the reduced corticosteroid-receptor binding affinity on T cells, which is a relevant feature in steroid-resistant asthma, can be induced in normal lymphocytes after in vitro interleukin-2 and interleukin-4 incubation [21] raises the intriguing hypothesis that this subtype of asthma may be the end result of poorly controlled ongoing pulmonary immune activation of T lymphocytes refractory to steroid-induced apoptosis.

The exact mechanism of action of drugs widely and long used in the treatment of bronchial asthma is now becoming clearer for both glucocorticoids [22] and theophylline [23] with respect to the survival of various cell types (eosinophils, neutrophils, mast cells, and T lymphocytes) involved in the tissue damage. Our results could have important implications at a time when the safety of therapy with long-term inhaled corticosteroids and regular beta-agonists is still a matter of debate.

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