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The effect of inhaled corticosteroids on CD27⁺ T-cells in patients with allergic asthma

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submitted for publication
Chapter 7

Abstract

T lymphocytes play an important role in the regulation of the chronic inflammation of the airways in patients with allergic asthma. We have performed a double blind, randomized, parallel-group study of the effect of 12 wk treatment with inhaled fluticasone propionate (FP) or salbutamol on CD25 and CD27 expression on CD4+ and CD8+ T lymphocytes in BAL fluid, and the soluble CD25 (sCD25) and sCD27 in the peripheral blood. Fluticasone propionate treatment significantly increased the percentage of CD27+ T cells in BAL fluid (p<0.01), indicating a decrease of antigen-activated T cells. FP treatment lowered the levels of sCD27 in the serum, which was significantly different from the changes induced by salbutamol (p = 0.04). The increase of CD27+ T cells in BAL fluid correlated with the decrease of eosinophils in the blood (p = 0.03). The changes of CD8+ T cells in BAL fluid correlated with changes in the permeability of the respiratory membrane for proteins (p<0.01). The decrease of sCD27 in the serum correlated with the increase in the PC20 histamine (p = 0.033). We conclude that FP treatment decreased T-cell activation both in BAL fluid and peripheral blood.

Introduction

Patients with allergic asthma have bronchial hyperreactivity, reversible airway narrowing, and chronic inflammation of the airway wall. Cardinal features of this inflammation are the infiltration of inflammatory cells into the airway lumen, an abnormal local secretion of proteins, an increased leakage of plasma proteins into the airways, and damage of the airway epithelium [1]. T lymphocytes play an important regulatory role in the allergic inflammatory process.

Therapy with glucocorticosteroids (GCS) is effective in controlling asthma symptoms, reducing airway obstruction and bronchial hyperresponsiveness [2]. Their effects are attributed to their anti-inflammatory action [3]. Oral GCS were reported to decrease activation of CD4+ T cells, and expression of some (but not all) cytokine mRNA by CD4+ T lymphocytes in bronchial biopsies [4]. They also decreased the degree of activation of lymphocytes in peripheral blood [5,6] of subjects with severe asthma. High dose of the inhaled GCS fluticasone resulted in a reduction of the proportion of lymphocytes in bronchoalveolar lavage (BAL) fluid and a reduction of lymphocyte activation as measured by HLA-DR [7], but low dose inhaled fluticasone did not affect total cell numbers and BAL
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cell differentials [8]. The inhaled GCS beclomethasone dipropionate (in doses varying from intermediate to low) did not alter BAL fluid cell differentials but did reduce T-cell activation as measured by expression of CD25 (which is the α-chain of the receptor for IL-2) and HLA-DR [9]. Inhaled GCS reduced the CD3+, CD45RO+, CD4+, CD8+, and CD25+ cells in the lamina propria of asthma patients [3,7,10-12].

Until now the available literature described the effects of GCS on total lymphocyte subpopulations and on the expression of CD25 and HLA-DR. Information is lacking on effects on subpopulations expressing co-stimulatory molecules like CD27 that are important in the antigen-specific activation of T cells. In this study we focussed in particular on activated and differentiated T cells by analysing effects on CD25 and CD27 expression. The degree of CD25 expression is considered to reflect T-cell activation [13,14]. CD27 is a co-stimulatory molecule, and considered as a marker for antigen-specific T-cell activation. The expression of this molecule on the T-cell membrane is increased after antigen-specific stimulation [15], and shed from the T-cell membrane after repeated and/or chronic antigenic stimulation [16]. Thus, CD27+ cells are considered antigen-activated cells [17]. The shed CD27 may be measured as soluble CD27 (sCD27) in various body fluids.

We have reported earlier on our double-blind, randomized, parallel-group study to evaluate the effect of FP and salbutamol (Sb) on inflammatory indices in BAL fluid and on bronchial hyperresponsiveness in patients with mild to moderate asthma [18,19]. In that study, 12 weeks treatment with FP resulted in an improvement of clinical symptoms, a decrease in BAL fluid eosinophils, and a decrease of plasma protein leakage into the airways. Sb treatment resulted in a significant increase in bronchial hyperresponsiveness and had no effect on inflammatory parameters. In the present study we have tested the hypothesis that FP affects antigen-specific activation of T cells. To this end we measured the effects on CD27 expression on T cells in BAL fluid, and on CD25 expression as a control. The primary outcomes of the study were the effects on CD3, CD4, CD8, CD25CD4, CD25CD8, CD27CD4, CD27CD8 lymphocytes in BAL fluid. Furthermore, we tested CD3, CD4, CD8, and CD25 in the peripheral blood. As soluble markers for T-cell activation we measured soluble CD25 (sCD25) and sCD27 in the serum of the patients. Furthermore, we studied the relations between primary outcomes and clinical- and other inflammatory-parameters.
Material and Methods

Patients
Thirty patients were included in the treatment study, the characteristics of whom are shown in Table 1. Asthma was diagnosed according to the American Thoracic Society criteria and included a history of recurrent episodes of wheezing, chest tightness and dyspnoea and a normal lung function between asthmatic attacks [20]. Asthma severity before institution of treatment ranged from Grade I (episodic) to Grade III (moderately persistent) [21].

Study design and lung function tests
The study design was as described before [18,19]. In short, the study was a double-blind, double dummy, single-center, parallel-group study in which patients were randomized to receive either FP 250 μg bid or Sb 400 μg bid via rotadisk powder inhaler (GlaxoWellcome, Zeist, The Netherlands) after having withheld inhaled corticosteroids for 6 weeks. The study was approved by the Internal Review Board of the Academic Medical Center, and was performed after written informed consent had been obtained.

The forced expiratory volume in one second (FEV₁) was measured as described [22]. Values are expressed as percentage of predicted. Bronchial reactivity to histamine was determined by a two-minute tidal-breathing method [23].

Fiberoptic bronchoscopy and immunologic analyses
Bronchoalveolar lavage (BAL) was performed with seven successive 20 ml aliquots of sterile, prewarmed NaCl (154 mM) [24]. The aliquots four to seven were combined and used for this study. The BAL fluid was centrifuged at 500 g and 4°C, and the supernatant stored at −80°C until analysis. Cell differentials were measured as described [18,19]. Peripheral blood mononuclear cells (PBMC) were obtained as described [25].

The cells were stained with specific antibodies [25]: anti-LeucoGateTM, anti-CD2, anti-CD3, anti-CD4, anti-CD8, anti-CD19, anti-CD25, anti-CD27 (all from Becton Dickinson, San Jose, CA). The antibodies were FITC, phyco-erythrin (PE) or PE-Cy5 labeled. The analysis was performed with a FACScan (Becton Dickinson) [25]. Lymphocytes were gated on the basis of forward and side light scatter (lymphogate). In all experiments, parallel incubations were performed with irrelevant antibodies matched for the isotypes of the detecting antibodies used. Vitality of the cells was checked by analyzing the cells after addition of propidium iodide.
Inhaled steroids and T-cells

Total and allergen-specific IgE [18], and albumin and alpha-2-macroglobulin (A2M) [26] were measured as described. sCD25 and sCD27 were measured by ELISA (OpteiaSet, Pharmingen, San Diego, CA, and CLB Sanquin blood supply foundation, Amsterdam, the Netherlands, respectively). The permeability of the respiratory membrane for proteins was assessed by the relative coefficient of excretion (RCE), which was calculated as follows: \((\text{A2M in BAL fluid}/\text{A2M in serum})/((\text{Albumin in BAL fluid}/\text{Albumin in serum}))\) [26].

Statistical analysis

The Mann Whitney U (MWU) test and Student’s t-test were used to evaluate differences between the FP and the Sb group. The Wilcoxon matched pair signed rank (WR) test was used to evaluate treatment effects and differences between cells within individuals. Spearman’s rank correlation and Pearson correlation were used to assess relationships between variables. Two-sided probability values less than 0.05 were considered significant. The statistical analysis was performed with GP Prism 3.01 [27].

Results

Thirty patients were randomized to receive FP \((n = 15)\) or Sb \((n = 15)\). At the start of the treatment period no significant differences were observed in baseline characteristics between the two treatment groups, with respect to patient demographics and pulmonary functions (Table 1). We have reported earlier that corticosteroid therapy was effective by decreasing bronchial hyperresponsiveness, decreasing plasma protein leakage into the airway lumen, and decreasing the percentage of eosinophils in BAL fluid [18,19].

The percentage recovery of the BAL fluid before and after treatment was, mean ± SEM: FP group before, 66.5 ± 15.2; after, 74.2 ± 12; Sb group before, 71.1 ± 18.9; after, 69.0 ± 14.5, without a significant difference between treatment and groups [18,19].

In the FP group total cell numbers in BAL fluid increased from 106 ± 19 x 10^6/L (mean ± SEM) before treatment to 128 ± 15 x 10^6/L after treatment \((p < 0.04)\). This increase was mainly caused by an increase in alveolar macrophages. There were no significant changes in the cell differentials, nor in the absolute numbers of lymphocytes, eosinophilic granulocytes and neutrophilic granulocytes.
Table 1. Summary of the patients characteristics at the start of the treatment period

<table>
<thead>
<tr>
<th></th>
<th>FP group</th>
<th>Sb group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y; median, range)</td>
<td>36 (20 - 52)</td>
<td>32 (27 - 49)</td>
</tr>
<tr>
<td>M/F</td>
<td>8/7</td>
<td>8/7</td>
</tr>
<tr>
<td>Smoking (ex-smokers)*</td>
<td>4/15 (1/15)</td>
<td>2/15 (5/15)</td>
</tr>
<tr>
<td>Total IgE (GM/GSD, IU/mL)</td>
<td>224 (4.9)</td>
<td>169 (6.0)</td>
</tr>
<tr>
<td>Allergy (RAST positive)</td>
<td>13/15</td>
<td>13/15</td>
</tr>
<tr>
<td>PC20 histamine (GM/GSD, mg/mL)</td>
<td>0.65 (4.7)</td>
<td>0.54 (3.2)</td>
</tr>
<tr>
<td>FEV₁ (% predicted; mean (sd))</td>
<td>92.7 (17.6)</td>
<td>83.8 (21.2)</td>
</tr>
<tr>
<td>FEV₁/FVC (mean (sd))</td>
<td>0.74 (0.10)</td>
<td>0.71 (0.13)</td>
</tr>
<tr>
<td>Inhaled glucocorticosteroids</td>
<td>before study</td>
<td>9/15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9/15</td>
</tr>
</tbody>
</table>

GM/GSD, geometric mean, geometric standard deviation; RAST, radio-allergen-sorbent-test; FVC, forced vital capacity.

* Median pack years in smokers and ex-smokers (n = 12): 4.5 (IQR 2.3-12.8).

Figure 1. A: CD27 expression on T cells in BAL fluid before and after 12 weeks therapy with the inhaled corticosteroid fluticasone propionate (FP) or the inhaled β2-agonist salbutamol (Sb). There was a significant increase of CD27⁺CD3⁺ cells after FP therapy (WR: p<0.01). B: The increase of CD27⁺ cells resided mainly in the CD8⁺ T cell population. FP: WR, p = 0.014; Sb: WR, p = 0.037.
**Lymphocyte subpopulations in BAL fluid**

The results for lymphocyte subpopulations are shown in Table 2. From some patients we did not obtain enough cells to perform all analyses. Paired analyses could be done for 12 to 13 individuals in the FP group and for 9 to 11 individuals in the Sb group. Before treatment there were no differences between the two groups for all the parameters depicted. FP treatment resulted in a statistically significant increase of the percentage CD27+ (% of CD3+) T cells in BAL fluid from 42% ± 4.5% (mean ± SEM) before to 51% ± 3.9% after therapy (Figure 1A; MWU, p<0.01). The changes of CD27+CD3+ in the GCS group were not significantly different from changes in the Sb group (MWU, p = 0.17). When analyzed for CD4 and CD8 separately, it appeared that increase of CD27+ cells resided mainly in the CD8+ T cells (Figure 1B; MWU, p = 0.014). Sb treatment had no significant effect on the percentage CD27+ (% of CD3+), and there was a slight but significant increase of the percentages CD27+ (% of CD8+) T cells (p = 0.04). CD25 expression on BAL fluid T cells was not affected by either treatment (Table 2).

**Serum sCD25 and sCD27, and blood lymphocyte subpopulations**

At baseline there were no differences between the groups for the levels of sCD25 and sCD27 in the serum. FP treatment resulted in a decrease of the levels of sCD27 in the serum of most patients, which was significantly different from the changes in sCD27 in the Sb group (Figure 2A, p = 0.04). FP nor Sb had effect on the levels of sCD25 (Figure 2B). For blood lymphocytes, paired analyses could be done for 13 individuals in the FP group and for 13 individuals in the Sb group. Neither treatment had any statistically significant effect on the CD4, CD8, CD25CD4+ or CD25CD8+ subpopulations.

**Correlation of outcomes with clinical and other inflammatory parameters**

To investigate whether the effects of therapy on CD27 expression, and on the levels of sCD27 were correlated with effects on clinical- and inflammatory- parameters, we analyzed whether changes in those parameters were correlated with changes in the FEV₁, PC₂₀, histamine, eosinophilic granulocytes in the BAL fluid and blood, and changes in the permeability of the respiratory membrane for plasma proteins, expressed as the relative coefficient of excretion, the RCE.
Figure 2. A) The decrease of sCD27 in the serum was significantly larger after treatment with fluticasone (GCS) than after treatment with Salbutamol (t-test, \( p = 0.04 \)). B) The changes in sCD25 in serum were not different between GCS and salbutamol treatment.

Table 2. Lymphocyte subpopulations in BAL fluid

<table>
<thead>
<tr>
<th></th>
<th>FP group (n = 15)</th>
<th>Sb group (n = 15)</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>CD3(^+) (% of lymphgate)</td>
<td>71.7 (43.3-91.7)</td>
<td>85.7 (17.9-95.7)</td>
</tr>
<tr>
<td>CD4(^+) (% of CD3)</td>
<td>45.4 (10.8-90.6)</td>
<td>45.0 (12.7-87.0)</td>
</tr>
<tr>
<td>CD8(^+) (% of CD3)</td>
<td>38.4 (12.8-82.6)</td>
<td>47.1 (15.5-76.9)</td>
</tr>
<tr>
<td>CD25(^+)CD4(^+) (% of CD4)</td>
<td>20.8 (5.4-46.5)</td>
<td>17.9 (5.8-39.8)</td>
</tr>
<tr>
<td>CD25(^+)CD8(^+) (% of CD8)</td>
<td>5.0 (0-23.3)</td>
<td>4.7 (1.2-22.1)</td>
</tr>
<tr>
<td>CD27(^+)CD4(^+) (% of CD4)</td>
<td>38.7 (15.1-70.3)</td>
<td>45.3 (11.6-71.7)</td>
</tr>
<tr>
<td>CD27(^+)CD8(^+) (% of CD8)</td>
<td>64.2 (28.8-81.8)</td>
<td>73.2 (55.5-84.1)(*)</td>
</tr>
</tbody>
</table>

Depicted are percentages of cells; median and range. *: WR, \( p = 0.014 \); **: WR P = 0.037.

The increases of CD27\(^+\)CD3\(^+\) T cells in the BAL fluid correlated with the changes in eosinophils in the blood (Figure 3; all patients: \( r = -0.42 \), \( p = 0.03 \)). So, the decrease of antigen-activated cells in BAL fluid paralleled the decrease of eosinophils in the blood. In the separate treatment groups this correlation was statistically significant in the Sb group (\( \rho = -0.61 \), \( p = 0.03 \)).

With the analysis of the relation between T-cell parameters and the RCE we observed that in the FP-treated group the lowering of the CD8\(^+\) (% of CD3\(^+\)) T cells in BAL fluid significantly correlated with the decreases in the RCE: FP group, \( \rho = 0.77 \) (\( p < 0.01 \)) (Figure 4); Sb group, not significant. Similarly, but measured independently, the changes in CD4 (% of CD3\(^+\)) were correlated with the changes in RCE (Figure 4, \( \rho = -0.91 \), \( p < 0.001 \)); in the Sb-treated group there were no significant correlations.
The changes in sCD27 in the serum were significantly correlated with the changes in the PC_{20} histamine: $r = -0.42$ ($p = 0.033$), shown in Figure 5.

Figure 3. The increase of CD27^+CD3^+ cells in BAL fluid significantly correlated with the decrease of eosinophils in the blood. Open symbols, FP group; filled symbols, Sb group.

Figure 4. In the asthma patients who were treated with fluticasone, the changes in the % CD8^+ and CD4^+ T cells in BAL fluid were significantly correlated with the change in the permeability of the respiratory membrane. Open circles: CD8^+ T cells: $\rho = 0.77$, $p < 0.01$; filled squares: CD4^+ T cells: $\rho = 0.91$, $p < 0.001$.

Figure 5. The changes in serum sCD27 were significantly correlated with the changes in PC_{20} histamine doubling doses ($r = -0.42$, $p = 0.033$).
Chapter 7

Discussion

We have reported earlier that glucocorticosteroid (GCS) treatment in the patient group studied here resulted in statistically significant decreases in the bronchial hyperreactivity, plasma protein leakage into the airways, and the percentage of eosinophilic granulocytes in BAL fluid [18,19]. Here we show that treatment with FP increased the percentage of CD27+ T cells in BAL fluid. FP treatment also resulted in a decrease of the levels of sCD27 in the serum of most patients. The changes of sCD27 in serum correlated negatively with the increase of PC_{20} histamine.

CD27- cells are considered to represent antigen-activated cells [17]. This is based on the observations that 1) CD27 was released from the membrane of T cells after activation of the cells via the TCR/CD3 complex [15], and 2) the T-cell clones derived from the CD27- cells were enriched for antigen- and allergen-specific T cells in comparison to those derived from the CD27+ cells [16]. Therefore, the increase of the percentage of CD27+ T cells in BAL fluid points to a decrease of antigen-activated T lymphocytes in the BAL fluid. This may result either from a decrease of antigen-specific activation of BAL-fluid T cells and/or from an influx of cells that have not recently been in contact with antigen. The downregulation of antigen-specific T-cell activation might be the result of a downregulation of the production of activating cytokines and/or antigen-presenting cell functions. It is widely accepted that GCS exert such effect [28]. The observation that these effects occur in CD8+ T cells in allergic asthma is unexpected. T-cell activation in allergic asthma is thought to result mainly from allergen contact. Allergens are soluble proteins and their fragments are presented in the context of MHC II, which results in CD4+ T cell reactions. We did find a trend for a decrease of CD4+ T cell-activation on the basis of CD27 expression. However, the changes on CD8+ T cells were more clear. Either allergens react with CD8+ T cells to some extent [29] or the CD8+ cell reactions are secondary, reflecting regulatory cellular reactions with as yet unknown antigenic specificity. Allergen-induced activation or accumulation of CD8+ T cells in the lungs in asthma patients has earlier been demonstrated by Wahlström et al. [30].

A subset of CD27-CD8+ T cells, defined as CD27-CD45RA-CD8+, was characterized as memory-effector cells and contains the antigen-specific effector cells [31]. It would be important to focus in further studies on effects of GCS on this subpopulation.

In another group of patients with allergic asthma we studied the expression of another co-stimulatory molecule that is involved in antigen-specific activation of T lymphocytes, CD28. There we observed higher percentages of CD28-CD8+ cells (in % of
CD45R0^CD8^ and of CD45RA^CD8^) in the blood of asthmatic patients compared to healthy subjects [32] which suggests increased antigen-specific activation of CD8^+ T cells in the blood of asthmatic patients not treated with inhaled GCS. Though it is believed that CD8^+ T cells preferentially interact with fragments from intracellular pathogens, in several model systems CD8^+ T cells have been shown to interact with antigenic fragments from soluble antigens as well [29].

The decrease of T-cell activation in BAL fluid was concluded on the basis of the increase in CD27 expression on BAL fluid T cells. The lowered activation was not apparent from any decrease of another T-cell activation marker, the CD25 expression on BAL fluid T cells. It is not known, however, whether the asthma patients in this study had an increased CD25 expression in comparison to healthy subjects. The lack of changes in CD25 expression confirms results in other studies on the effect of GCS treatment in mild asthmatics [33].

In our study on BAL fluid T cells in patients with systemic sclerosis we also observed a divergence between the expression of CD25 and CD27 as markers for T-cell activation in the BAL fluid [34]. Patients with systemic sclerosis without signs of pulmonary fibrosis showed abnormal T-cell activation on the basis of a decreased CD27 expression on BAL fluid CD4^+ T cells, whereas CD25 expression was normal. Patients with systemic sclerosis who had signs of pulmonary fibrosis, and can therefore be classified as being in the more chronic phase of the disease, showed BAL fluid T-cell activation on the basis of an increased CD25 expression on BAL fluid CD4^+ T cells, whereas CD27 expression was normal.

In the present study, the increase in the CD27 expression on T cells in BAL fluid was significantly correlated with a decrease in % eosinophilic granulocytes in the blood. This may be related to a decrease of antigen-specific activation of T cells and a decrease of the production of chemoattractants or chemokines and cytokines that activate eosinophils. Candidates in this respect are for example IL-4, IL-5, Rantes and eotaxin. Indeed, a decrease of IL-5 expression in the airway compartment was shown to result from GCS therapy [35]. Lung allergen-challenge models have shown that local T-cell activation indeed signals the bone marrow to release eosinophil precursors and resulted in increased eosinophils in the blood [36].

The changes in the total CD8^+ T cells (% of CD3^+) in BAL fluid were significantly correlated with the RCE, decreases of CD8^+ cells paralleled decreases of the RCE. This correlation with total CD8^+ T cells was much stronger than correlations between changes in subpopulations of T cells, like CD25^+ or CD27^+, and the RCE. The RCE is considered
as a surrogate parameter of airway inflammation in the airways of patients with asthma, a high RCE indicating an increased leakage of plasma proteins from the blood into the airway space as a consequence of epithelial cell damage [24,26]. The correlation between impairment of airway epithelial cell integrity and relatively high CD8+ T-cell numbers may reflect mechanisms in which CD8+ T cells directly damage airway epithelial cells. It may be hypothesized that chronic inflammatory stimuli induce airway epithelial cells to express targets for CD8+ T cells. GCS may inhibit the inflammatory stimuli thereby lowering CD8+ targets and lowering the damage to the epithelial cells. As a consequence the CD8+ T cell number may become lower. This whole process may involve cytotoxic activity towards virus infected cells [37,38]. However, other explanations invoking the regulation of CD8+ and CD4+ T-cell migration by cytokines and chemokines [39] may explain the correlation as well. Furthermore, our results indicate that an increase of the percentage CD4+ T cells in the lungs parallels a decrease of the permeability of the respiratory membrane. This finding makes it unlikely that CD4 T cells are directly involved in the processes causing epithelial cell damage. In our study we also have found systemic effects of inhaled GCS as is clear from the reduction of sCD27 in the blood. It is unlikely that this decrease was the result of the less antigen-specific activation of T cells and shedding of CD27 in the airway compartment since the levels of sCD27 in BAL fluid were not higher than those in the serum. Neither were the levels of sCD27 in the epithelial lining fluid higher than those in the serum. Thus, we conclude that inhaled GCS have systemic effects on the T lymphocytes. Another explanation may be that lung T cells migrate into peripheral lymph nodes after they have been locally activated, and that they then shed the sCD27 in the systemic compartment. In such concept, it is not necessary to assume that inhaled GCS exert their effects in the systemic compartment. Interestingly, the decrease of sCD27 in the serum was correlated with the increase of PC20 histamine.

In conclusion, therapy of mild asthmatic patients with inhaled GCS decreased T-cell activation both in BAL fluid and in the systemic compartment. In BAL fluid, the effects of FP were observed on CD27 expression by CD4+ and CD8+ T cells pointing at either a decrease of antigen-specific activation of BAL fluid T cells and/or an influx of cells which have not recently been in contact with antigen. The therapy thus lowers activity of the cells that are considered orchestrating the airway inflammation in asthma patients. In studies in severe asthma, therapy that was specifically targeted at T cells was found to beneficial [40,41], though it could not always be continued because of deleterious side-effects. Future
therapies in allergic asthma may be successful if they modulate antigen specific T-cell activities to prevent symptoms leaving the immune system intact for its normal function.

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References


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