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Antigen-presenting capacity of alveolar macrophages and monocytes in pulmonary tuberculosis

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ABSTRACT: Using purified protein derivative of tuberculin (PPD) as an antigen, antigen-presenting capacity by monocytes (Mo) and alveolar macrophages (AM) was determined in 17 patients with pulmonary tuberculosis and nine healthy controls. All of the patients and healthy controls were positive for PPD skin test. Although Mo obtained from both the control and tubercular subjects revealed antigen-presenting capacity to autologous blood T-lymphocytes, no significant difference was observed between the two groups. In contrast, AM obtained from the tubercular patients, but not from the controls, showed antigen-presenting capacity to autologous blood T-lymphocytes and to lung T-lymphocytes. No significant difference was shown in HLA-DR antigen expression on AM between the control and tubercular patients. Besides, the exogenous addition of interleukin-1 (IL-1) did not induce antigen-presenting capacity by AM obtained from the controls. These results suggest that neither increased HLA-DR antigen expression on AM nor an increased release of IL-1 from AM is responsible for the enhanced antigen-presenting capacity in tuberculosis.

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Tuberculosis is a disease almost entirely regulated by the cell-mediated delayed-type immune response of the host against Mycobacteria. This immune response involves both macrophages as the effector cell and lymphocytes as the immuno-responsive cell [1–4]. Antigen presentation by antigen-presenting cells is important in the initial immune response against circulating foreign antigens. Briefly, antigen-presenting cells take up the foreign antigens and present them, in association with HLA class II antigens on the antigen-presenting cells, to T-lymphocytes [5–9]. These two kinds of antigens trigger activation of T-lymphocytes. In addition, antigen-presenting cells release interleukin-1 (IL-1) to T-lymphocytes in order to complete the activation. Consequently, T-lymphocytes are activated and subsequently release interleukin-2 (IL-2). At the same time, T-lymphocytes express IL-2 receptors on there surface. It is known that, in tuberculosis, activated T-lymphocytes and alveolar macrophages (AM) migrate into the lower respiratory tract and these migrated cells result in alveolitis. Subsequently, these migrated cells play an important role in the formation of granuloma [10].

Various cell types have been reported to have the capability to become antigen-presenting cells in humans [5, 11, 12]. Among those cells, monocytes (Mo) were reported to have such a function. In contrast, it is reported that AM obtained from healthy persons do not have such a function [13, 14]. To our knowledge, antigen-presenting capacity in tuberculosis has not been reported. Therefore, we attempted to determine the antigen-presenting capacity by Mo and AM in patients with pulmonary tuberculosis, using Mo and AM as antigen-presenting cells and purified protein derivative of tuberculin (PPD) as an antigen.

Materials and methods

Subjects

Seventeen patients with pulmonary tuberculosis (13 men and 4 women with a mean age of 47±17 (SD) yrs) were studied. Among these patients, 14 were non-smokers, one former smoker and two smokers. Twelve were taking anti-tuberculosis drugs (isoniazid, rifampicin and streptomycin), whilst the remaining five were untreated. In all patients at least one recent sputum was positive for acid-fast bacilli on microscopic examination and grew *Mycobacterium tuberculosis*. According to the NTA classification based on radiographic findings [15], seven patients had minimal advanced disease, eight moderately advanced and two far advanced disease. Patients who were taking

corticosteroids or had systemic diseases (*i.e.* diabetes mellitus) were excluded.

The control group consisted of nine healthy subjects, including five men and four women, with a mean age of 50±14 yrs. Among them, six presented to our hospital with complaints of haemosputum. None of them had a history of lung disease or any evidence of lung disease based on the physical, chest radiographic and bronchoscopic examinations. The remaining three were volunteers and free from any diseases. All were non-smokers and none were taking medication at the time of evaluation. All patients and control subjects were positive for the PPD skin tests.

Preparation of lung and blood effector cells

Bronchoalveolar lavage (BAL) was performed using four aliquots (50 ml each) of sterile saline as described previously [16]. Briefly, sterile saline was introduced into the right 4th or 5th subsegmental bronchus. In cases of tuberculosis BAL was performed in five patients during the diagnostic bronchoscopy in the involved side of the lung. The lavage fluid was then recovered by gentle aspiration and pooled. The total cell count was evaluated on an aliquot of the pooled fluid using a haemocytometer. Differential cell counts were determined from cytocentrifuge preparations stained with the May-Giemsa stain. The remaining fluid was centrifuged at 600 × g for 5 min. The cell pellet was then washed sequentially in minimum essential medium (MEM) (Nissui Seiyaku Co. Ltd, Tokyo) containing 100 $U \cdot ml^{-1}$ penicillin G and 100 $\mu g \cdot ml^{-1}$ streptomycin and resuspended in RPMI-1640 (Gibco Laboratories, Grand island, NY) containing 10% fetal calf serum (FCS, Gibco) at 10^6 $cells \cdot ml^{-1}$.

The total recovered cell numbers were $50\pm19\times10^6$ and $52\pm11\times10^6$ cells in the tubercular patients and controls, respectively. The percentages on AM and lymphocytes were 76±18% and 20±11% in the tubercular patients, and 85±6% and 14±5% in the controls, respectively. In all cases, more than 98% of the recovered cells were viable.

Blood mononuclear cells were obtained from heparinized venous blood which was obtained just prior to BAL. They were purified by a density gradient centrifugation using a Ficoll-Paque gradient (Pharmacia, Piscataway, NJ). The cells were then washed sequentially and resuspended in RPMI-1640 medium containing 10% FCS at a concentration of 10^6 $cells \cdot ml^{-1}$.

Purification of alveolar macrophages, monocytes and T-lymphocytes

Lung and blood mononuclear cells were incubated in plastic culture dishes (Falcon ≠1005, Oxnard, CA) at 37°C in a humidified atmosphere of 5% CO_2 in air to permit the attachment of AM and Mo. After one hour of incubation, the cells were washed vigorously to remove the nonadherent cells. Adherent cells were then removed from the dishes by gentle scraping with a rubber policeman. This procedure increased the numbers of cells morphologically compatible with AM and Mo, resulting in a more than 95% purity.

The nonadherent cells from plastic culture dishes were resuspended in RPMI-1640 containing 10% FCS and incubated in nylon wool columns (Fenwall Laboratories, Peerfiels, IL) for 45 min at 37°C, and then eluted at 2 $ml \cdot min^{-1}$ using a warm medium. The final cell preparation contained more than 95% of T-lymphocytes as determined by rosette formation with sheep red blood cells.

Assay for antigen presentation by AM and Mo

To pulse the cells obtained from the adherent cells, the cells ($1 \times 10^6 \cdot ml^{-1}$) were incubated for 60 min at 37°C in RPMI-1640 containing 10% FCS in the presence of PPD ($100\ \mu g \cdot ml^{-1}$) and mitomycin-C (MMC, $50\ \mu g \cdot ml^{-1}$, Kyowa Hakko,Tokyo). As a control, cells were treated with MMC only. Following the treatment, cells were washed three times with phosphate-buffered saline (PBS) and then resuspended in RPMI-1640 containing 10% human antigen-binding (AB) serum at a concentration of $2 \times 10^4 \cdot ml^{-1}$, unless otherwise stated.

The PPD-pulsed cells were co-cultured with column-purified T-lymphocytes in triplicate in round bottomed microtitre plates (Corning ≠25850, Corning, NY) containing 200 µl of RPMI-1640 with 10% human AB serum. To evaluate the optimal ratio of Mo or AM to T-lymphocytes, these T-lymphocytes were co-cultured with various concentrations of PPD-pulsed Mo or AM. The cells were incubated for six days at 37°C in a humidified atmosphere of 5% CO_2 in air. To quantify T-lymphocyte proliferation, 16–18 h prior to harvesting, 0.2 µCi of ^{3}H-thymidine was added to each well. Triplicate samples were harvested using a multiple sample harvester and counted in a liquid scintillation counter. Antigen-presenting capacity was expressed as Δcpm (cpm in PDD-pulsed antigen-presenting cells - cpm in PPD-nonpulsed antigen-presenting cells). Antigen-presenting capacity in the present study was determined using autologous blood T-lymphocytes as responder cells.

Quantification of AM and Mo expressing HLA-DR surface antigen

AM and Mo were incubated with appropriate dilution of monoclonal antibodies I_2 (Coulter Immunology, Hialean, FD) for 30 min at 4°C. After washing with PBS, 30 µl of fluorescence isothiocyanate-conjugated goat $F(ab')_2$ anti-mouse (immunoglobulin G + immunoglobulin M) (IgG +IgM) antibody (× 15) was added and incubated for an additional 45 min at 4°C. After washing, the cells were assayed by a fluorescence-activated flow cytometry with a fluorescence-activated cell sorter (FACS) 3 (Beckton Dickinson, Mountain View, CA). Data analysis was based on reading 5,000 cells per sample. In all assays, an excess of normal

human IgG (250 μg·ml^{-1}) was simultaneously added to the first antibody to block crystallizable fragment (Fc) receptors on AM and Mo [17]. Results were expressed as both mean fluorescence intensity (MFI) and percentage of HLA-DR antigen positive cells.

Effect of exogenous IL-1 on antigen presentation

To assess the effect of exogenous IL-1 on antigen-presenting capacity, PPD-pulsed antigen-presenting cells were co-cultured with T-lymphocytes in the presence of a serial concentration of exogenous IL-1, ranging from 0.1–1 U·ml^{-1}.

Statistics

Statistical analysis was performed by using Student's t-test. A p value of <0.05 was considered as a significant difference.

Results

Antigen-presenting capacity

The antigen-presenting capacity of Mo from the controls and tuberculosis to autologous blood T-lymphocytes are summarized in figure 1. When the Mo to T-lymphocyte ratio was 1:5, the antigen-presenting capacity was optimal in both groups. Therefore, in the following studies, the antigen-presenting capacity by Mo was determined in co-culture of Mo to T-lymphocyte ratio of 1:5.

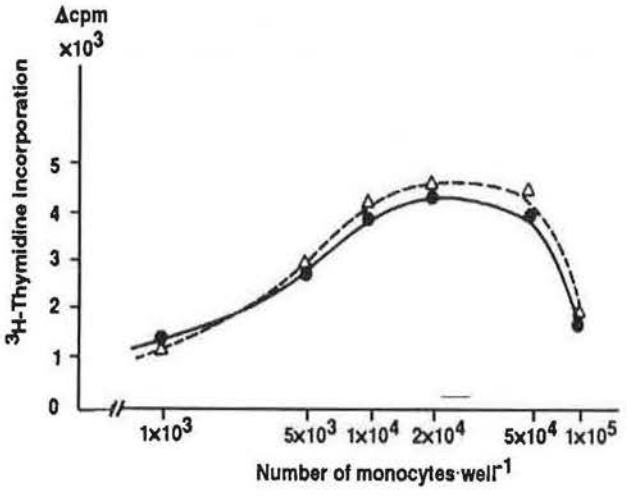

Fig. 1. – Antigen-presenting capacity by blood monocytes. T-lymphocytes (1×10^5) were co-cultured with various numbers of blood monocytes (ranging from 1×10^3 to 1×10^5) for six days and then the antigen-presenting capacity was determined. When the cell concentration of monocytes was 2×10^4·well^{-1} (*i.e.*, the monocyte to T-lymphocyte ratio was 1:5), the antigen-presenting capacity was optimal in both the controls and tubercular patients. cpm: counts per minute; ●——●: control; Δ——Δ: tuberculosis.

As shown in figure 2, when purified T-lymphocytes were cultured alone or with nonpulsed-Mo, the amount of incorporated ^{3}H-thymidine in the controls as well as tuberculosis was minimal. However, co-culture of T-lymphocytes with PPD-pulsed Mo from the controls as well as tubercular subjects induced marked increase in T-lymphocyte proliferation. Thus, Mo from the controls and tubercular subjects showed antigen-presenting capacity to autologous blood T-lymphocytes. However, no significant difference was observed between the two groups.

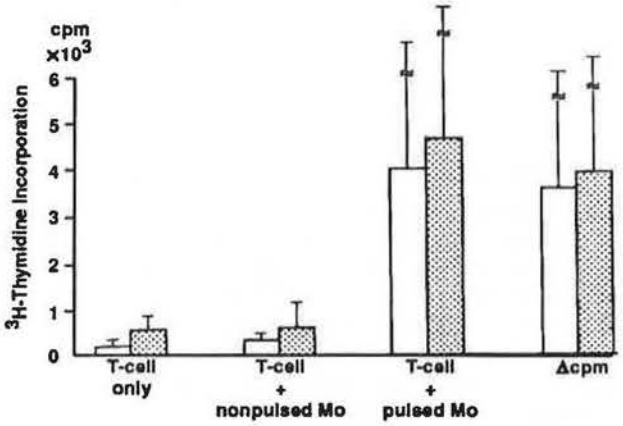

Fig. 2. – Antigen-presenting capacity by blood monocytes. T-lymphocytes (1×10^5) were cultured alone or with PPD-nonpulsed or PPD-pulsed blood monocytes (Mo; 2×10^4) for six days and then the antigen-presenting capacity was determined. In the control ^{3}H-thymidine incorporation in T-lymphocytes, T-lymphocytes plus PPD-nonpulsed Mo, and T-lymphocytes plus PPD-pulsed Mo was 264±130 cpm, 315±186 cpm, and 4,005±3,276 cpm, respectively. In tuberculosis ^{3}H-thymidine incorporation in T-lymphocytes, T-lymphocytes plus PPD-nonpulsed Mo, and T-lymphocytes plus PPD-pulsed Mo was 500±441 cpm, 590±635 cpm, and 4,578±4,668 cpm, respectively. No significant difference was observed in the antigen-presenting capacity by Mo between the controls and tubercular subjects. PPD: purified protein derivative (tuberculin); Mo: monocytes; cpm: counts per minute; ▭: control (n=9); ▨: tuberculosis (n=15).

The antigen-presenting capacity by AM is summarized in figure 3. As reported previously [8, 9], AM from the controls were hardly capable of functioning as antigen-presenting cells. In contrast, AM from tuberculous patients showed antigen-presenting capacity to autologous blood T-lymphocytes. Again, the antigen-presenting capacity was optimal in a condition of AM to T-lymphocyte ratio of 1:5 (fig. 3). Thus, in the following studies, antigen presenting capacity by AM was determined in the same condition as that by Mo (*i.e.* AM to T-lymphocyte ratio of 1:5).

As shown in figure 4, the antigen-presenting capacity by pulsed AM to T-lymphocytes in tuberculous patients was significantly higher than that in controls ($p<0.05$).

The source dependence of T-lymphocytes on response to antigen presentation by AM and Mo is summarized in table 1. The antigen-presenting capacity by AM and Mo to autologous lung T-lymphocytes was not significantly different from that to autologous blood T-lymphocytes. Besides, autologous mixed lymphocyte reaction (AMLR) was seldom observed during this study.

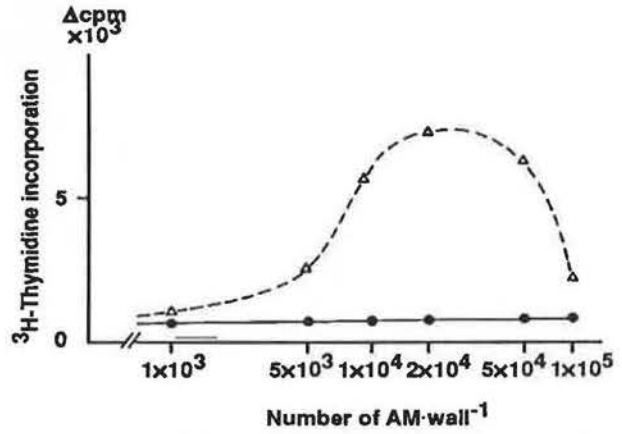

Fig. 3. – Antigen-presenting capacity by alveolar macrophages. T-lymphocytes (1×10^5) were co-cultured with various concentrations of alveolar macrophages (AM) (ranging from 1×10^3 to 1×10^5) for six days and then the antigen-presenting capacity was determined. As reported previously, no significant antigen-presenting capacity was observed in the controls, whereas in tubercular patients, when the cell concentration of AM was 2×10^4·well^{-1} (*i.e.* the AM to T-lymphocyte ratio was 1:5), the antigen-presenting capacity was optimal. ●——●: control; Δ----Δ: tuberculosis; cpm: counts per minute.

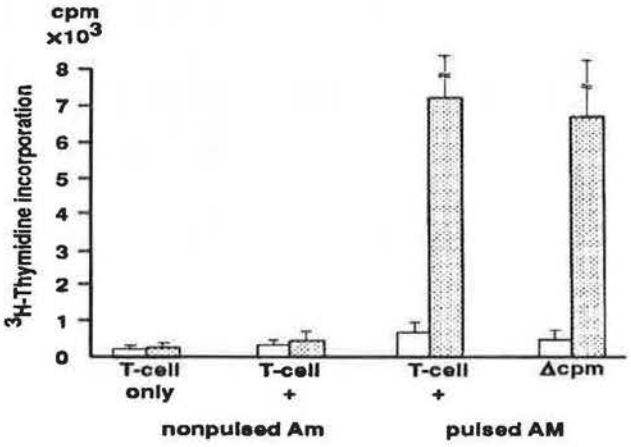

Fig. 4. – Antigen-presenting capacity by alveolar macrophages. T-lymphocytes (1×10^5) were cultured alone or with PPD-nonpulsed or pulsed alveolar macrophages (AM; 2×10^4) for six days and then the antigen presenting-capacity was determined. In the control ^{3}H-thymidine incorporation in T-lymphocytes, T-lymphocytes plus PPD-nonpulsed AM, and T-lymphocytes plus PPD-pulsed AM was 269±114 cpm, 296±191 cpm, and 597±281 cpm, respectively. In the tuberculosis ^{3}H-thymidine incorporation in T-lymphocytes, T-lymphocytes plus PPD-nonpulsed AM, and T-lymphocytes plus PPD-pulsed AM was 278±172 cpm, 478±265 cpm, and 7,201±1,916 cpm, respectively. There was a significant difference in the antigen-presenting capacity by AM between the controls and tubercular subjects ($p<0.05$). PPD: purified protein derivative (tuberculin); cpm: counts per minute; ▭: control (n=6); ▨: tuberculosis (n=5).

HLA-DR antigens on the surface of AM and Mo

HLA-DR antigen expression on the surface of AM and Mo is summarized in table 2. Not only the density of HLA-DR on AM and Mo, but also the percentage of HLA-DR antigen positive cells was not significantly different in controls and tubercular patients.

Table 1. – Antigen presentation by Mo and AM to autologous lung and blood T-lymphocytes in tuberculosis

Culture condition	n	cpm (mean±SD)
Blood T-cell alone	3	271±170
+ PPD-nonpulsed Mo	3	601±291
+ PPD-pulsed Mo	3	10046±4100
+ PPD-nonpulsed AM	3	473±277
+ PPD-pulsed AM	3	7785±1677
Lung T-cell alone	3	264±151
+ PPD-nonpulsed Mo	3	470±171
+ PPD-pulsed Mo	3	3198±931
+ PPD-nonpulsed AM	3	137±21
+ PPD-pulsed AM	3	4572±1236

PDD-nonpulsed or PPD-pulsed antigen-presenting cells (2×10^4) were co-cultured with autologous blood T-cells or lung T-cells (1×10^5) for six days and then the antigen-presenting capacity was determined. Mo: monocytes; AM: alveolar macrophages; cpm: counts per minute; PPD: purified protein derivative (tuberculin).

Table 2. – HLA Class II antigens on Mo and AM

	Mo			AM		
	n	MFI	%	n	MFI	%
Control	8	57±16	64±10	4	142±56	96±3
Tuberculosis	9	69±15	69±7	5	171±68	98±3

Mean fluorescence intensity of HLA-DR antigen expression on Mo or AM was assessed by the indirect immunofluorescence method, using anti-HLA-DR monoclonal antibody. Results are expressed as mean±SD. There was no significant difference in the density of HLA-DR antigens or the percentage of HLA-DR antigen positive cells between the controls and tubercular patients. MFI: mean fluorescence intensity. For further abbreviations see legend to table 1.

Table 3. – Effect of exogenous IL-1 on antigen presentation

IL-1	T-cell only	Mo + T-cell	AM + T-cell
(-)	319±99	3010±810	404±94
(+)	338±166	2847±167	684±40

Values are expressed as mean±SD. To assess the effect of exogenous IL-1 on antigen-presenting capacity PPD-pulsed antigen-presenting cells were co-cultured with T-lymphocytes in the presence of serial concentrations of IL-1 (ranging from 0.1–1 U·ml^{-1}), and the antigen-presenting capacity was determined. This table shows representative data using 0.5 U·ml^{-1} of IL-1. Similar results were obtained in other two controls. IL-1: interleukin-1. For further abbreviations see legend to table 1.

Effect of IL-1 on antigen presentation

Table 3 shows the effect of exogenous IL-1 on the antigen presenting capacity during co-culture of antigen-presenting cells and T-lymphocytes. No significant effect on antigen presenting capacity by the addition of exogenous IL-1 was observed.

Discussion

Antigen-presenting cells play an important role in the recognition of foreign antigens by T-lymphocytes. The antigens taken up by antigen-presenting cells, in association with HLA class II antigens on the antigen-presenting cells, trigger the activation of T-lymphocytes [5, 9]. Many cells other than T-lymphocytes are known to function as antigen-presenting cells in humans. These cells include Langerhans cells, astrocytes and Mo [11, 12, 18, 19]. In the present study, we confirmed that Mo could act as antigen-presenting cells. However, the antigen-presenting capacity by Mo in tuberculosis is not significantly different from that in normal controls.

On the other hand, AM from normal subjects functioned insufficiently as antigen-presenting cells, as previously reported [13, 14]. In contrast, AM from patients with pulmonary tuberculosis functioned as potent antigen-presenting cells as shown in the present study, indicating an enhanced state of local immunity in pulmonary tuberculosis. The mechanism which induced the enhanced antigen-presenting capacity by AM in tuberculosis is unknown. Several possibilities have been considered as follows.

The first is that an increased density of HLA-DR antigen expression on AM or increased frequency of HLA-DR positive AM in tuberculosis might cause the enhanced antigen-presenting capacity. An optimal response of sensitized T-lymphocyte to antigens requires the combined recognition of the nominant antigen plus HLA-DR antigens on the surface of antigen-presenting cells [6, 7]. However, in the present study, not only the density of HLA-DR antigen on AM but also the percentage of HLA-DR antigen positive AM revealed no significant difference between the control and tubercular subjects.

Another possible explanation for the enhanced antigen-presenting capacity by AM in tuberculosis is that the production of IL-1 from AM in this disease may be greater than that in controls. It is reported that IL-1 production from AM is less than that from Mo in normals [20–22]. However, in the present study, the exogenous IL-1 failed to induce any antigen presenting capacity by AM obtained from the healthy controls. Therefore, at least in tuberculosis, the amount of IL-1 may not play an important role in the antigen-presenting capacity by AM.

Other possibilities include the difference of the density of lymphocyte function associated antigens-1 (LFA-1) on AM, structural differences of HLA-DR antigens, and an increased recruitment of Mo into the lungs. Among them, LFA-1 was first reported as the antigen relating the attachment of killer cells against target cells [23, 24]. It has recently been reported that AM could not function as antigen-presenting cells because of the small amounts of LFA-1 on AM in normals [25]. Although in the present study, we have not studied LFA-1, an increased LFA-1 may be responsible for the enhanced antigen-presenting capacity in tuberculosis. Concerning HLA-DR antigens, we demonstrated that there was no significant difference in the density of HLA-DR antigens on AM between the controls and tubercular subjects. However, antigen-presenting capacity may possibly be enhanced in this disease because of the structural changes of HLA-DR antigens on AM. It has been reported that in mice, antigen-presenting cells bearing less sialylated HLA-DR antigens functioned more efficiently as antigen-presenting cells than those bearing sialylated HLA-DR antigens [26]. In addition, since differences in carbohydrate of HLA-DR molecules synthesized by AM and Mo have been reported in humans [27], the different glycosylation of HLA-DR molecules in AM and Mo may be related to the difference of antigen-presenting cell function in humans.

Patients with sarcoidosis have recently been demonstrated to have enhanced antigen-presenting capacity by AM [28–30] and, based on the studies of phenotype of AM, have also been reported to have increased recruitment of Mo from blood to lung [31]. Therefore, the increased recruitment of Mo to the lungs may be responsible for the enhanced antigen-presenting capacity in sarcoidosis. In tuberculosis, antigen-presenting capacity was also possibly enhanced by this mechanism.

The precise mechanisms responsible for the enhancement of antigen-presenting capacity by AM in tuberculosis as shown in the present study should be explored in the future.

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Capacité de présentation des antigènes par les macrophages alvéolaires et les monocytes dans la tuberculose pulmonaire. Y. Ina, K. Takada, M. Yamamoto, M. Morishita, K. Yoshikawa.
RÉSUMÉ: Chez 17 patients atteints de tuberculose pulmonaire, et chez 9 sujets contrôle, nous avons étudié la capacité de présentation des antigènes des monocytes et des macrophages alvéolaires, en utilisant la "protéine purified derivative" (PPD) de tuberculine comme antigène. Tous les patients et les contrôles sains avaient un test cutané à la PPD positif. Quoique les monocytes obtenus à la fois chez les sujets contrôle et les sujets tuberculeux ont démontré une capacité de présentation des antigènes aux lymphocytes sanguins T autologues, aucune différence significative n'a été observée entre les deux groupes. Au contraire, les macrophages alvéolaires obtenus chez les patients tuberculeux, mais non ceux des contrôles, ont montré une capacité de présentation des antigènes aux lymphocytes T du sang autologue et aux lymphocytes T pulmonaires. Nous n'avons observé aucune différence significative dans l'expression des antigènes HLA-DR sur les macrophages alvéolaires entre les sujets contrôle et les tuberculeux. Par ailleurs, l'addition exogène de IL-1 n'a pas induit une capacité de présentation des antigènes par les macrophages alvéolaires obtenus chez les contrôles. Ces résultats suggèrent que ni l'augmentation de l'expression de l'antigène HLA-DR sur le macrophage alvéolaire, ni une libération accrue de IL-1 par les macrophages alvéolaires, ne sont responsables de l'accentuation de la capacité de présentation des antigènes dans la tuberculose.
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