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Impaired TNF, IL-1β, and IL-17 production and increased susceptibility to *Mycobacterium tuberculosis* infection in HTLV-1 infected individuals

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ABSTRACT

IFN-γ and TNF play critical roles in the control of *Mycobacterium tuberculosis* infection. Despite leading to an exaggerated production of inflammatory cytokines, HTLV-1 infection increases the risk of developing tuberculosis (TB). However, the immune mechanisms accounting for this phenomenon are still unclear. The aim of this study was to evaluate immunological aspects of the HTLV-1/*M. tuberculosis* co-infection. In this cross-sectional study, the levels of TNF, IL-1β, and IL-17 were determined by ELISA in the supernatants of either unstimulated or tuberculin purified protein derivative (PPD) stimulated peripheral blood mononuclear cells. Cells from HTLV-1 infected individuals produced lower levels of TNF following PPD stimulation compared to unstimulated cells. IL-1β and IL-17 production by cells from HTLV-1/*M. tuberculosis* co-infected individuals was lower than in cells from patients with TB. Impairment in TNF, IL-1β, and IL-17 production upon stimulation with mycobacterial antigens may contribute to the increased susceptibility to *M. tuberculosis* infection observed in HTLV-1 infected individuals.

1. Introduction

It is estimated that one third of the world's population is currently infected with *Mycobacterium tuberculosis*. Brazil figures amongst the 22 countries with the highest burdens of tuberculosis (TB), being the sole representative country of the Americas [1]. It is known that innate immunity cytokines play critical roles in *M. tuberculosis* infection outcome [2]. The tumor necrosis factor (TNF) is fundamental for granuloma formation and contributes to controlling bacterial multiplication and dissemination [3]. Furthermore, the use of TNF inhibitors has been strongly associated with the development of TB [4]. IL-1β is essential for the host control of this bacterial infection, demonstrated by the significantly impaired survival of IL-1β knockout (KO) and IL-1R KO mice infected with *M. tuberculosis* [5,6]. Furthermore, polymorphisms in the *IL1* gene cluster also predispose individuals to TB [7,8]. The IL-17 is also involved in the TB control, by recruiting neutrophils, although it may contribute to tissue damage in advanced TB [9,10]. So, infections that interfere with the production of cytokines necessary for *M. tuberculosis* infection control may impact the disease outcome.

The human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus that infects around 10 million people worldwide [11]. Salvador, the capital of the state of Bahia, in Brazil, is considered a high endemic area for both HTLV-1 and TB, with a prevalence of 1.8% of HTLV-1 infection in general population [12]. The majority of HTLV-1 infected individuals are HTLV-1 carriers and less than 5% develop HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP) [13]. About 20% have overactive bladder but do not fulfill the defined criteria for HAM/STP and are considered as having probable HAM/TSP [14]. HTLV-1 infects preferentially $CD4^+$ T cells, and both $CD4^+$ and $CD8^+$ T cells proliferate spontaneously and produce high levels of inflammatory cytokines including TNF and IFN-γ [15–17]. Despite the fact that HTLV-1 induces lymphocyte activation, it has been reported that HTLV-1 infection poses a 2–4 fold increased risk of developing TB [18–21]. The reasons for the increased susceptibility for tuberculosis infection in

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HTLV-1 infected individuals are still unclear. Lymphocytes from HTLV-1 infected individuals have impairment in the ability to respond to purified protein derivative (PPD) of *M. tuberculosis* and to recall antigens [22]. However, IFN-γ, the main cytokine that activate macrophage to kill *M. tuberculosis* [23], is produced in high levels during HTLV-1 infection [15,17,24]. Innate immunity is poorly studied in HTLV-1 infection and it is known that TNF and IL-1β participate in the defense mechanism against *M. tuberculosis* [3,4,25,26]. Moreover, IL-17 is also involved in the defense mechanisms against the *M. tuberculosis* [9,27,28]. In the present study, we investigated the immunological aspects of the HTLV-1 and *M. tuberculosis* co-infection.

2. Material and methods

2.1. Study design and population

This was a cross-sectional study evaluating HTLV-1 infected individuals without tuberculosis (HTLV-1 without TB group, n = 20) or co-infected with *M. tuberculosis* (HTLV-1 and TB group, n = 15), individuals with only tuberculosis (TB without HTLV-1 group, n = 11), and HTLV-1 seronegative healthy subjects (HS group, n = 10). HTLV-1 infected individuals enrolled in this study were from HTLV-1 Clinic at the Complexo Hospitalar Universitário Professor Edgard Santos, Federal University of Bahia, Brazil. The diagnosis of HTLV-1 infection was established by antibody detection by ELISA (Murex HTLV-I + II, Abbot, Dartford, UK) and confirmed by Western blot (HTLV blot 2.4, Genelabs, Singapore). The patients with only TB were from The Brazilian Institute for TB Investigation (IBIT), Bahia, Brazil. Patients with active or pasty history of TB had the diagnosis made by documentation of acid-fast bacilli by microscopy in the sputum. All individuals had negative serology for HIV, hepatitis B, hepatitis C viruses, cytomegalovirus, and syphilis. The study was approved by the Ethics Committee of the Medical School of Federal University of Bahia and an informed consent was obtained from all participants.

2.2. Case definitions

HTLV-1 without TB group: HTLV-1 infected subjects without evidence of active or history of TB and with negative tuberculin skin test (TST). HTLV-1 and TB group: HTLV-1 infected subjects with active or history of TB. TB without HTLV-1 group: patients with active TB prior to therapy, not infected with HTLV-1. HS group: individuals not infected with HTLV-1, without history of TB, and with negative TST.

2.3. Separation and culture of peripheral blood mononuclear cells (PBMCs)

PBMCs were obtained from heparinized blood and separated by density gradient with Ficoll-Hypaque (GE Healthcare Bio – Sciences, Uppsala, Sweden). The cells were seeded at 3×10^6 cells/ml/well into 24-well plates containing RPMI 1640 (Gibco BRL, Grand Island, NY), supplemented with 2 mM L-glutamine, 25 mM HEPES, 10% heat-inactivated fetal bovine serum (Sigma, St. Louis, MO), and 0,05% gentamicin at 10 mg/ml (Gibco BRL, Grand Island, NY). PBMCs were incubated without stimulus or stimulated with tuberculin purified protein derivative (PPD, 1 μg/ml; Statens Serum Institut, Dinamarca), tetanus toxoid (TT, 0.5 Lf/ml; Connaught Laboratories, Willowdale, Canada), phytohemagglutinin (PHA, 1:100 v/v; Gibco BRL, Grand Island, NY), and *Escherichia coli* lipopolysaccharide (LPS, 0.1 μg/ml; Sigma, St. Louis, MO), at 37 °C in an atmosphere of 5% CO_2. Culture supernatants were collected 72 h after stimulation and stored at −20 °C until used for determination of cytokines production.

2.4. Cytokine measurement

The TNF, IL-1β, IL-17, IL-10, and IFN-γ levels were determined in PBMCs culture supernatants by enzyme-linked immunosorbent assay (ELISA) using commercial kits and according to the manufacturer's instructions. The reagents for TNF, IL-10, and IFN-γ measurement were purchased from BD Bioscience Pharmingen (San Jose, CA, USA), and the reagents for IL-1β and IL-17 were from DuoSet R & D Systems (Minneapolis, MN, USA).

2.5. Fluorescence-activated cell sorter (FACS) analysis

For intracellular detection of TNF, PBMCs were adjusted to 4×10^5/well into 96-well plate. The cells were stimulated with PPD (1 μg/ml; Statens Serum Institut, Dinamarca) and *E. coli* LPS (0.1 μg/mL; Sigma, St. Louis, MO) at 37 °C for 20 h (lymphocyte staining) or 6 h (monocyte staining). Brefeldin A (10 μg/ml; Sigma, St. Louis, MO) was added for the last 4 h of culture. Cells were then stained for surface markers and intracellular cytokine. Briefly, cells were stained with monoclonal antibodies [anti-CD3-FITC, anti-CD4-PerCP (eBioscience, San Diego, CA), anti-CD8-APC, or anti-CD14-APC (BD Pharmingen, San Diego, CA)] for 20 min at 4 °C. Cells were washed, fixed using a 2% formaldehyde solution, and permeabilized with a 0.5% saponin solution in PBS. Cells were stained with anti-TNF-PE (eBioscience, San Diego, CA) for 30 min at room temperature. Cells were washed with permeabilization solution and resuspended in PBS. Cells (150,000 events) were collected using a II FACSCanto flow cytometer (Becton Dickinson, San Jose, CA), and data were analyzed using the FlowJo Software version 7.6 (Tree Star, Ashland, OR). The monocyte or lymphocyte populations were selected according size and granularity.

2.6. Statistical analyses

GraphPad Prism 5 Software (San Diego, CA) was used to carry out the statistical evaluation and P-value < 0.05 was considered to indicate a significant difference. Data was expressed as median and interquartile (IQ) range. Mann Whitney test was used to compare cytokine production between two groups. Wilcoxon T test was used to compare differences between unstimulated and stimulated cells.

3. Results

3.1. Demographic characteristics and production of cytokines

The demographic finding and spontaneous production of IFN-γ and TNF from participants of the study are on Table 1. There was no significant difference in gender between the participants. Comparing the age distribution, the HTLV-1 group was older than HS group, and HTLV-1 and TB group were older than TB group. Regarding the clinical status of HTLV-1 infection, in the HTLV-1 group there were 17 HTLV-1

Table 1
Demographic characteristics and spontaneous cytokine production.

	Healthy Subjects (n = 10)	HTLV-1 without TB (n = 20)	HTLV-1 and TB (n = 15)	TB without HTLV-1 (n = 11)	p-value
Age (years), median (range)	30.5 (25–37)	51.5 (35–75)	62.0 (33–75)	35.0 (18–60)	< 0.0001[a]
Females, n (%)	8 (80)	14 (70)	11 (73)	8 (73)	0.95[b]
IFN-γ levels (pg/ml), median (range)	0	1933 (0–3701)	691 (0–3599)	0	< 0.0001[a]
TNF levels (pg/ml), median (range)	0	199 (0–866)	100 (0–849)	0	< 0.0001[a]

[a] Kruskal-Wallis.
[b] Chi-square test.

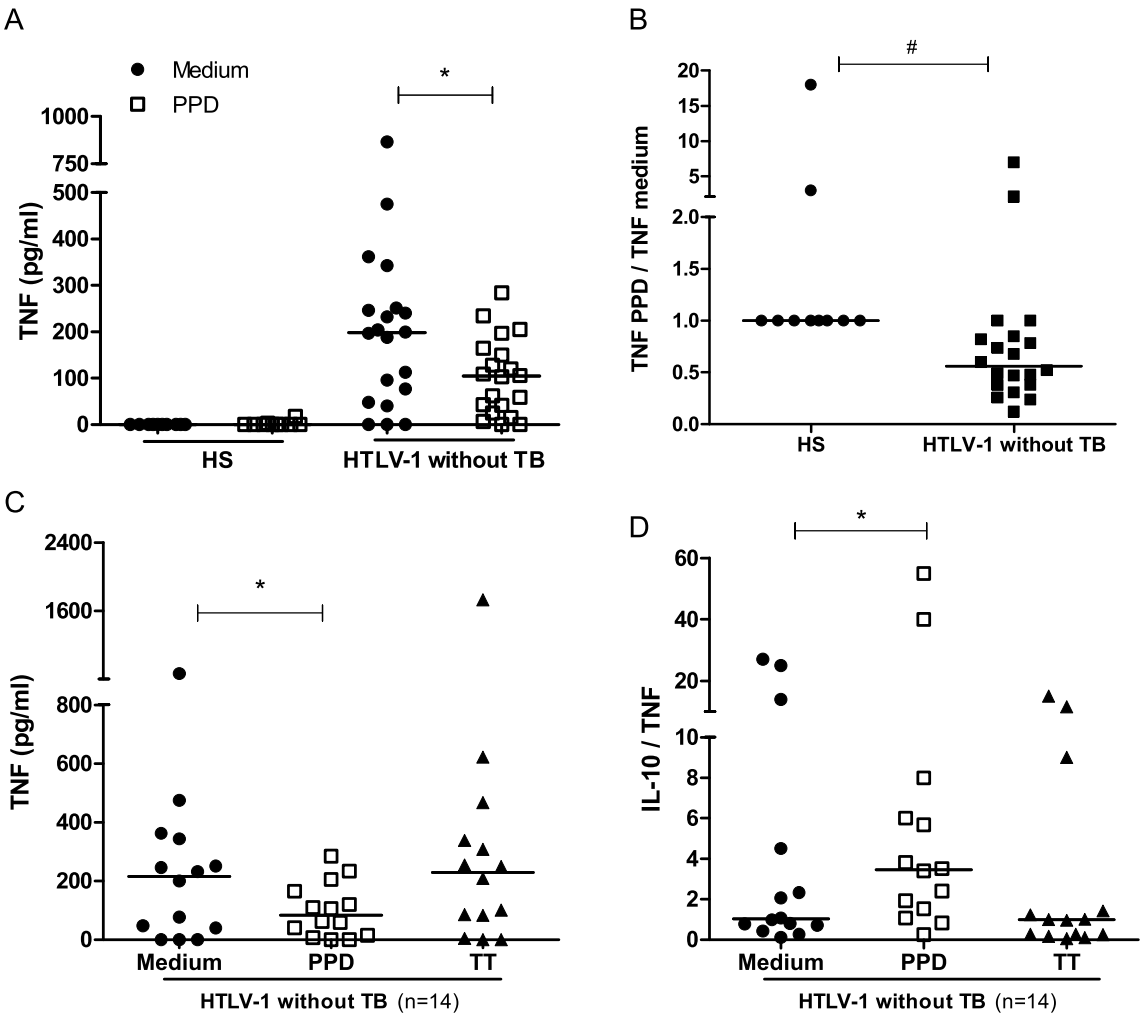

Fig. 1. HTLV-1 infection leads to a decrease in TNF production in response to PPD. PBMCs from healthy subjects (HS) and HTLV-1 infected individuals without TB were stimulated with PPD (1 μg/ml) or TT (0.5 Lf/ml) for 72 h. Levels of TNF and IL-10 in supernatants were assayed by ELISA. (A) TNF production by PPD stimulated cells. (B) Relative levels of TNF under PPD (PPD stimulated cells/unstimulated cells ratio). (C) TNF production by PPD or TT stimulated cells. (D) The ratio IL-10 production/TNF production by cells from HTLV-1 infected individuals without TB. Bars represent the median of each group. Statistical analyses were performed using Wilcoxon T test (*$p < 0.05$) and Mann Whitney test (#$p < 0.05$).

carriers, 1 probable HAM/TSP, and 2 HAM/TSP. In the HTLV-1 and TB group, 7 individuals were HTLV-1 carriers, 4 were probable HAM/TSP, and 4 were HAM/TSP.

3.2. HTLV-1 infection leads to a decrease in TNF production in response to PPD

To investigate whether HTLV-1 infection interferes with immune responses to *M. tuberculosis* antigens, PBMCs from HS and individuals from HTLV-1 without TB group were stimulated with PPD and levels of TNF, IL-10, IL-1β, and IL-17 were measured by ELISA. As expected, unstimulated cells from HTLV-1 infected individuals showed a high spontaneous TNF production (199 pg/ml, IQ range 55–250 pg/ml). However, after PPD stimulation, these individuals had a decrease in TNF production (105 pg/ml, IQ range 29–161 pg/ml), $p < 0.001$. In unstimulated and PPD stimulated cells from HS, there was no significant TNF production (Fig. 1A). When the data were normalized (ratio between stimulated and unstimulated cells), TNF levels in HTLV-1 without TB group were significantly lower than in HS, $p < 0.001$ (Fig. 1B). In order to test if the reduced TNF production by PBMCs from HTLV-1 infected individuals was PPD specific, PBMCs from these individuals were also stimulated with TT, a non-related antigen. While there was no difference in TNF production by unstimulated cells (199 pg/ml, IQ range 55–250 pg/ml) compared to TT stimulated cells (229 pg/ml, IQ range 64–370 pg/ml), $p = 0.08$, there was a decrease ($p < 0.05$) in TNF production in cultures stimulated with PPD (Fig. 1C). Since IL-10 regulates proinflammatory cytokines, IL-10 production was determined. No difference was observed in IL-10 production in unstimulated and PPD stimulated cells (data not shown). Nevertheless, the median IL-10/TNF ratio was higher in PPD stimulated cells than in unstimulated cells from HTLV-1 infected individuals (Fig. 1D).

In order to evaluate the source of cells producing TNF, the frequency of monocytes and lymphocytes expressing TNF was determined by flow cytometry. There was a slight, but no significant, increase in $CD14^+TNF^+$ monocytes after PPD stimulation. No difference was observed in frequency of $CD4^+TNF^+$ and $CD8^+TNF^+$ lymphocytes stimulated or unstimulated with PPD (Fig. 2).

IL-1β and IL-17 production by cells from HS and HTLV-1 infected individuals after PPD stimulation and their respective controls (*E. coli* LPS and PHA) were assayed. There was no significant difference in IL-1β production between unstimulated and PPD stimulated cells from both groups (Fig. 3A). Regarding IL-17, only cells from HS showed an increased IL-17 production following PPD stimulation (0 pg/ml, IQ range 0–11 pg/ml in unstimulated cells versus 15 pg/ml, IQ range 2–44 in PPD stimulated cells, $p = 0.01$), Fig. 3B.

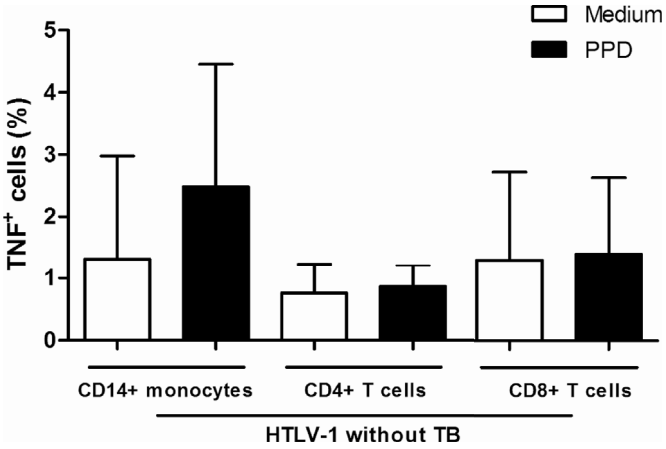

Fig. 2. Frequencies of TNF producing cells from HTLV-1 infected individuals after PPD stimulation. PBMCs from HTLV-1 infected individuals without TB (n = 5) were stimulated with PPD (1 μg/ml) for 16 h (lymphocyte staining) or 6 h (monocyte staining). Cells were stained for CD3, CD4, CD8, CD14 and TNF and collected using II FACSCanto flow cytometer. To analyze the data, the monocyte or lymphocyte populations were selected according size and granularity. Results are presented as means ± standard deviations. Statistical analyses were performed using Wilcoxon T test.

3.3. Impairment in IL-1β and IL-17 production in individuals co-infected with M. tuberculosis and HTLV-1 and in patients with tuberculosis without HTLV-1

To assess whether IL-1β and IL-17 production differs among patients with only TB and those with HTLV-1 and TB, PBMCs from TB patients without HTLV-1 and HTLV-1 and TB co-infected individuals were stimulated with PPD and the levels of these cytokines were measured by ELISA. There was an increase in IL-1β production in response to PPD in TB without HTLV-1 group (0 pg/ml, IQ range 0-0 pg/ml in unstimulated culture versus 87 pg/ml, IQ range 14–160 pg/ml versus PPD stimulated culture, p = 0.009) and in the HTLV-1 and TB group (4 pg/ml, IQ range 0–26 pg/ml in stimulated culture versus 10 pg/ml, IQ range 0–85 pg/ml PPD stimulated culture, p = 0.02), Fig. 4A. Although there was no significant difference (p = 0.06) in IL-1β production between PPD stimulated cells from both groups, when the data were normalized (ratio between PPD stimulated and unstimulated cells), the production of this cytokine was lower in co-infected individuals than in patients with only TB (Fig. 4B). Similarly, there was an increase in IL-17 production in unstimulated versus PPD stimulated culture in TB without HTLV-1 group (0 pg/ml, IQ range 0–1 pg/ml versus 43 pg/ml, IQ range 13–150 pg/ml, respectively, p = 0.002) and in the HTLV-1 and TB group (3 pg/ml, IQ range 0–58 pg/ml versus 41 pg/ml, IQ range 0–124 pg/ml, respectively, p = 0.04), Fig. 4C. However, when the data were normalized (ratio between PPD stimulated and unstimulated cells), IL-17 production in response to PPD by HTLV-1 and TB co-infected individuals was lower than in patients with TB without HTLV-1 (Fig. 4D).

4. Discussion

The HTLV-1 infection influences the development of infectious diseases, such as strongyloidiasis [29], scabies [30] and TB [18–20,31,32]. The association between HTLV-1 and TB is well documented. In a population based study, it was demonstrated that TB is more frequent in HTLV-1 infected individuals than in seronegative controls [18]. Moreover, the frequency of HTLV-1 infection was higher in TB patients admitted to a referral pulmonary disease hospital than in individuals with other pulmonary diseases [20]. However, the mechanisms accounting for the high susceptibility to infection with *M. tuberculosis* in HTLV-1 infected individuals are still unclear.

The immune response against *M. tuberculosis* primarily involves the Th1 arm of the immune response [33]. However, even though the spontaneous productions of IFN-γ and TNF are immunological hallmarks of HTLV-1 infected individuals, TB has been seen to be more frequent in HTLV-1 infected individuals than in seronegative controls [20,34]. Studies evaluating the immune response to mycobacterial antigens by HTLV-1 infected individuals have shown controversial results. It was reported that the positivity of tuberculin skin test (TST) was lower in HTLV-1 infected individuals than in seronegative controls [35,36]. However, these studies evaluating the TST were performed in elderly Japanese subjects, after more than 3 decades of TB control in Japan. Additionally, a previous study demonstrated that PBMCs from HTLV-1 infected individuals have a lower capacity to proliferate in response to recall antigens, including PPD, suggesting that these individuals present immunosuppression [22]. Nevertheless, these studies were performed in individuals without documentation of active TB, history of TB or vaccination with BCG. Moreover, when the frequency of responders to TST, as well as the size of induration, was compared between patients with TB co-infected with HTLV-1 and patients with only TB, no difference was observed [34].

To the best of our knowledge, the present study is the first that evaluated the immune response of HTLV-1 and TB co-infected individuals that were not hospitalized for treatment of tuberculosis. Herein we demonstrated that HTLV-1 infection leads to a decrease in TNF production in response to PPD. This data corroborated with a previous study by our group that demonstrated lower TNF production in PPD stimulated PBMCs from hospitalized TB patients co-infected with HTLV-1, when compared to hospitalized patients with only TB [34]. It is well known that HIV infection increase susceptibility for tuberculosis [37] and HIV and *M. tuberculosis* co-infected macrophages release less TNF than macrophages infected with only *M. tuberculosis* [38]. HIV also induces functional changes in *M. tuberculosis*-specific T cell response leading to a lower IFN-γ, TNF, and IL-2 production and cellular proliferation in HIV and *M. tuberculosis* co-infected individuals

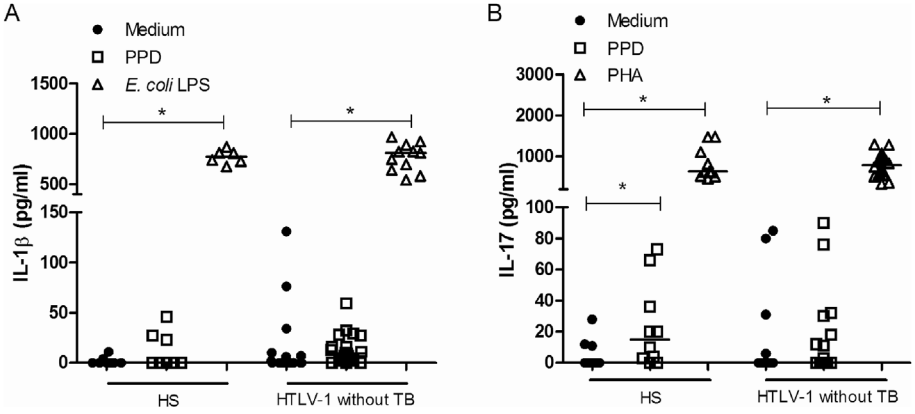

Fig. 3. IL-1β and IL-17 production by PBMCs from healthy individuals and HTLV-1 infected individuals after PPD stimulation. PBMCs from healthy subjects (HS) and HTLV-1 infected individuals without TB were stimulated with PPD (1 μg/ml), *E. coli* LPS (0.1 μg/ml) or PHA (10 μl/ml) for 72hs. Levels of (A) IL-1β and (B) IL-17 in supernatants were assayed by ELISA. Bars represent the median of each group. Statistically significant differences between unstimulated and stimulated cells were indicated by an asterisk (Wilcoxon T test, *p < 0.05).

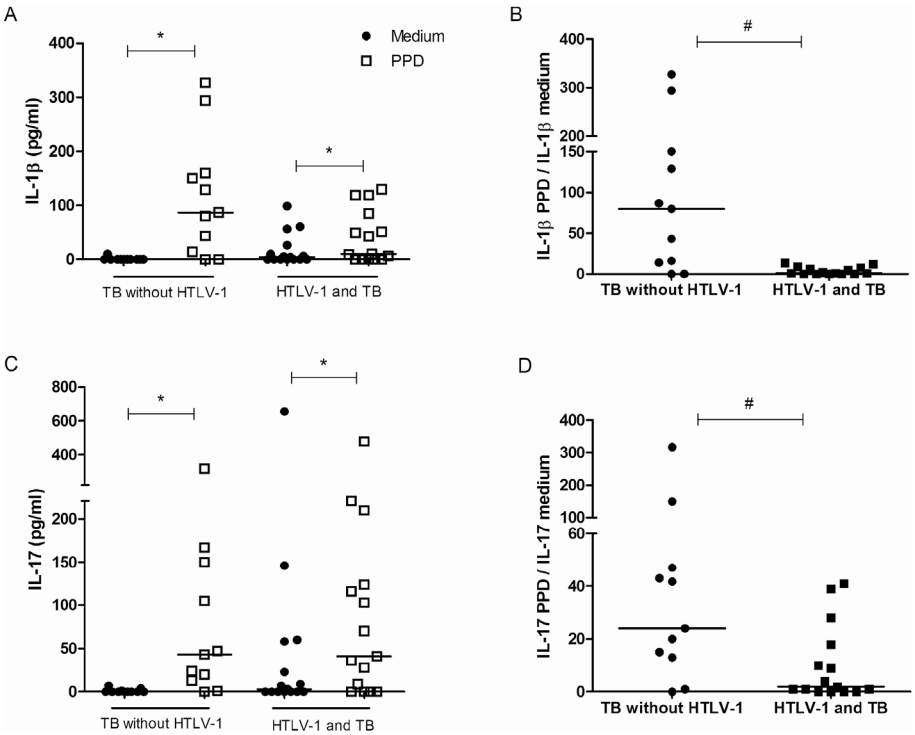

Fig. 4. IL-1β and IL-17 production by PBMCs from patients with TB and HTLV-1 and TB co-infected individuals after PPD stimulation. PBMCs from TB without HTLV-1 and HTLV-1 and TB co-infected individuals were stimulated with PPD (1 μg/ml), *E. coli* LPS (0.1 μg/ml, data not shown) for 72hs. Levels of (A) IL-1β and (C) IL-17 in supernatants were assayed by ELISA. The ratio PPD stimulated cells/unstimulated cells for (B) IL-1β and (D) IL-17 production was evaluated. Bars represent the median of each group. Statistical analyses were performed using Wilcoxon T test (*$p < 0.05$) and Mann Whitney test (#$p < 0.05$).

than in individuals with TB alone [37]. Although IFN-γ is produced in high concentration by unstimulated PBMC culture of HTLV-1 infected individuals, no difference in IFN-γ production was found in cultures of cells from TB and TB and HTLV-1 co-infected patients [34]. Furthermore, our previous study demonstrated no difference in the size of induration in TST when TB and TB and HTLV-1 co-infected patients were compared [34].

It is already known that IL-1β produced by human macrophages is negatively regulated by type I IFNs [39]. Besides, a recent study reported that IL-1 dependent prostaglandin E_2 confers host resistance through limiting excessive type I IFN production and restricting the intracellular growth of *M. tuberculosis* [25]. Herein, we observed that HTLV-1 and TB co-infected individuals exhibit lower production of IL-1β when compared to only TB infected individuals.

During early *M. tuberculosis* infection, IL-17 may have beneficial effects by recruiting neutrophils and promoting secretion of tissue-specific homing chemokines [9]. It has been demonstrated that Tax protein of HTLV-1 induces IL-17 gene expression in HTLV-1 infected T-cell lines [40]. Moreover, it has been suggested that IL-17 participates in the pathogenesis of neurological disease related to HTLV-1 infection [41,42]. In this study, we demonstrated that cells from HTLV-1 infected individuals did not increase IL-17 production following PPD stimulation, as observed in HS. In addition, IL-17 production in response to PPD by HTLV and TB co-infected individuals was lower than in patients with only TB. These data suggest that HTLV-1 infection appears to interfere with IL-17 response after PPD stimulation.

We recognize that the present study has a few limitations. Individuals of the HTLV-1 groups, with TB and without TB, were older then the HS and TB without HTLV-1 group. This may account for the low TNF, IL-1β, and IL-17 production in response to PPD. However, HTLV-1 infected individuals produce high spontaneous TNF and IFN-γ levels (Table 1) and the decrease was observed only when PPD was added to the cultures. Moreover, the production of TNF in TT stimulated culture was higher than in PPD stimulated cultures indicating that rather than age, cells stimulated with PPD had a decrease in the production of TNF. The high spontaneous production of cytokines in HTLV-1 infected individuals sometimes makes difficult the interpretation of results of antigen stimulated cultures. Therefore, in the present study, in addition to the results obtained after antigen stimulation we normalized the data by calculating the ratio between PPD stimulated culture and unstimulated cultures. Indeed the mechanisms involved in the decrease of IL-1β and IL-17 were not studied. Regarding the decrease in TNF production from HTLV-1 infected individuals, the possible mechanism is an inhibitory effect of IL-10. Actually, we have previously demonstrated the ability of IL-10 in decreasing IFN-γ [43] and TNF production (unpublished data) in HTLV-1 infected subjects. Additionally, the role of regulatory T cells in down-modulation of cytokine production can not be ruled out.

The association between HTLV-1 and TB is a highly relevant subject in areas where both HTLV-1 and *M. tuberculosis* infection are endemic. As the production of cytokines involved in the defense mechanisms against TB are up-regulated in HTLV-1 infected individuals due to the virus infection it is difficult to explain the increasing susceptibility to HTLV-1 infected individuals to TB. Here we showed that impairment in TNF, IL-1β, and IL-17 production upon stimulation with mycobacterial antigens may explain the higher susceptibility to *M. tuberculosis* infection in HTLV-1 infected individuals.

Conflicts of interest

The authors declare that there is no conflict of interests involved.

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