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Immunological Aspects

High expression of BTLA and B7-H4 on the surface of myeloid dendritic cells has a negative regulatory effect on their anti-tuberculosis immunity activity in pleural tuberculosis patients

Xiaozhen Cai [a,1,*], Nanhai Ge [a,1], Rong Rong [a], Yuanbin Lu [b], Junai Zhang [b], Junfa Xu [b,**]

[a] Department of Respiratory Medicine, Dongguan Houjie Hospital Affiliated to Guangdong Medical University, Dongguan, 523945, China
[b] Institute of Laboratory Medicine, Guangdong Medical University, Dongguan, 523808, Guangdong, China

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ABSTRACT

To investigate the effects of the surface markers B- and T-lymphocyte attenuator (BTLA) and B7 homologous body 4 (B7-H4) on expression of CD83, and Human Leukocyte Antigen–DR isotype (HLA-DR) that can activate dendritic cells (DCs). Flow cytometry was used to detect the co-expression of BTLA and B7-H4 on myeloid DCs (mDCs) in peripheral blood (PB) and pleural effusions (PE) in 15 volunteers and 20 tuberculous pleurisy (TP) patients. Co-expression of BTLA and B7-H4 (double positive (DP)) mDCs in PB and PE of TP patients were enhanced. The proportion of DP mDC in PB decreased markedly after 2 weeks treatment, but was still greater than in controls. Expression of CD83 and HLA-DR on DP mDCs was higher than on BTLA and B7-H4 double negative (DN) expressing mDCs in PB of different TP groups. Expression of CD83 on DP mDCs in PB and PE of TP patients was greater than that of controls. Expression of HLA-DR on DP mDCs in TP patient PB was lower than in TP PE and controls. In pleural tuberculosis (TB) patients, high expression of BTLA and B7-H4 promoted a high level of CD83 and HLA-DR, which had a negative regulatory effect on mDCs on anti-TB immunity.

1. Introduction

Tuberculous pleurisy (TP) is the most common form of extrapulmonary tuberculosis (TB). It is mainly manifested as systemic symptoms of tuberculosis and local symptoms caused by pleural effusion (PE). Currently, patients with TP are believed to have a highly sensitive immune response [1], which means γδT cell, αβCD25+CD4+T cell and CD25+CD8+T are very active in patients with this condition [2]. Although regulatory T cells significantly increased in numbers, they still cannot completely inhibit the functions of effector T cells [2,3].

Our previous study showed that the percentage of dendritic cells (DCs) and myeloid DCs (mDCs) in peripheral blood (PB) and PE of TB patients was much higher than in healthy controls, an effect that was positively correlated with the expression levels of interleukin (IL)-12 in PB [4]. B- and T-lymphocyte attenuator (BTLA) and B7 homologous body 4 (B7-H4) are recently discovered immune checkpoint inhibitors [5,6]. BTLA is mainly expressed on T cells, B cells, DCs, and on some myeloid cells. The interaction between BTLA and its ligand herpes virus entry mediator (HVEM) would inhibit the proliferation and activation of T cells and also inhibit the secretion of a number of cellular factors from them [7]. B7-H4 is inductively expressed on T cells [8,9], B cells [10,11], monocytes [12,13], macrophages [14–16] and DCs [17,18]. B7-H4 activation plays a role in the immune response in peripheral tissue cells, and inhibits the proliferation of T cells and IL-2 secretion via ERK, JNK, p38, and AKT activation interference [19]. The high expression of B7-H4 on DCs may be related to the increase of Tregs and it may also affect the differentiation of Naive T cells, thereby affecting the identification of *mycobacterium tuberculosis* (MTB) by the body's immune system and induction of anti-TB specific immune activation and other anti-tuberculosis immune responses [20]. We have previously demonstrated high expression levels of BTLA and B7-H4 in CD11c+antigen presenting cells (APCs) that are present in the peripheral blood of pulmonary tuberculosis patients. CD11c+APCs with BTLA and B7-H4 expression showed a decreased ability to activate the same T cells,

* Corresponding author. Department of Respiratory Medicine, Dongguan Houjie Hospital Affiliated to Guangdong Medical University, No. 21 Hetian Road, Dongguan, 523945, China.
** Corresponding author. Institute of Laboratory Medicine, Guangdong Medical University, Dongguan, 523808, Guangdong, China.
E-mail addresses: imcaixiaozhen@163.com (X. Cai), imxujunfa@163.com (J. Xu).
[1] Xiaozhen Cai and Nanhai Ge contributed equally to the article.

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which implied that BTLA and B7-H4 on APCs had a large influence on anti-TB immune functions [21]. mDC, as one of the primary CD11c+ APCs [22], is the only APC that can activate native T cells in the human, where it plays a vital role in adaptive and innate TB immunity [23]. Therefore, in the present study, we analyzed the effects of expression of the checkpoint inhibition molecules BTLA and B7-H4 on the maturity of mDC in patients with tuberculous pleurisy, as well as the expression of the antigen-presenting molecule Human Leukocyte Antigen–DR isotype (HLA-DR).

2. Patients and methods

2.1. Patients

We retrospectively analyzed 20 patients with TP in the Houjie Hospital Affiliated to Guangdong Medical University and also 15 healthy control subjects. Exclusion criteria were: pregnancy, alcoholism, < 16 years old, > 65 years old, HIV-positive, other infectious diseases and chronic diseases (such as diabetes), and those individuals who had been taking hormones or immunomodulators for nearly 1 month. In the present study, the patients with tuberculous pleurisy were divided into prior anti-MTB treatment (PRT) and post anti-MTB treatment (POT) according to the treatment status of anti-TB drugs. Among them, those who were treated for < 3 days were considered as PRT and those who were treated for 2 weeks were considered as POT. The ethics committee of Dongguan Houjie Hospital Affiliated to Guangdong Medical University approved this study, and the subjects' informed written consent was obtained.

2.2. Reagents and instruments

Antibodies for flow cytometry included Lin1-FITC (mixed antibodies, containing FITC marked CD3, CD14, CD16, CD19, CD20 and CD56 antibodies, clone numbers are SK7, MϕP9, 3G8, SJ25C1, L27, NCAM16.2) (BD Company). BTLA-APC (MIH26) and CD83-PerCP-Cy^{TM}5.5 (HB15) were purchased from Biolegend, whereas B7-H4-PE (H74), CD11c-APC-eFluor780 (BU15) and HLA-DR-PE-Cyanine7 (LN3) were purchased from eBioscience. Lymphocytes Separation Medium was purchased from the GE Company. The FACS – Canto II flow cytometry instrument was purchased from the BD Company.

2.3. Isolation of peripheral blood mononuclear cells (PBMC) and pleural effusion mononuclear cells (PEMC)

The isolation method used was that reported by Sica et al. [8]. For PBMC, 5 mL of heparin sodium anticoagulant was first centrifuged at 1500 rpm for 5 min and the supernatant serum decanted and preserved at −80 °C for subsequent analysis. The bottom cells were mixed with phosphate buffer isolated by density gradient centrifugation over Ficoll-Hypaque (GE Healthcare Life Sciences, MA, US). For PEMC, 200 mL of heparin sodium anticoagulative pleurisy PE was centrifuged first. Some of the supernatant was preserved at −80 °C. The precipitate was mixed with 2% fetal bovine serum in phosphate buffer and then isolated using Ficoll-Hypaque (GE Healthcare Life Sciences, MA, US) lymphocyte separation medium.

2.4. Expression of BTLA and B7-H4 on mDCs and expression of CD83 and HLA-DR in 3 different phenotypes of mCDs by flow cytometry

PBMC or PEMC (1×10^6 cells in 100 μL) were placed in a flow tube and mixed with fluorescence marked antigens (CD83$^-$ PerCP-Cy^{TM}5.5, HLA-DR- PE-Cyanine7, CD11c- APC-eFluor780, Lin1-FITC, BTLA-APC, B7-H4-PE). Another tube with a corresponding antibody served as the control. After vortexing and incubation for 30 min, avoiding light, 2 mL of fluorescence activated cell sorter (FACS) washing buffer was added twice to wash the cells. Paraformaldehyde solution (200 μL of 10 g/L) was gently mixed with the cells, which were preserved at 4 °C in a light free environment. Measurements were performed within 24 h and FlowJo 7.6.1 software was used to analyze relevant populations and mean fluorescence intensity (MFI) of HLA-DR expression.

Lin1$^-$ HLA-DR$^+$ CD11c$^+$ cells comprised the mDCs, in which the effect of BTLA and B7-H4 co-expressions (as double negative (DN) or double positive (DP)) on CD83 and HLA-DR expressions were further characterized (Fig. S1).

Table 1
Characteristic information about the study participants.

	TB pleurisy (TP) n = 20	Healthy control (HC) n = 15	*P*-value
Age (years)	32 ± 7	25 ± 8	>0.05
Gender (male/female)	14/6	8/7	>0.05
TB duration (days)	45	-	-
Hemoglobin (g/dL)	128.0 ± 6.0	132.0 ± 5.0	>0.05
Neutrophils (%)	46.12 ± 4.09	50.25 ± 0.71	<0.05
Monocytes (10^9/L)	0.90 ± 0.42	0.50 ± 0.30	<0.05
Lymphocytes (%)	45.36 ± 10.60	40.83 ± 5.26	<0.05
Platelets (10^9/L)	329 ± 28	256 ± 40	>0.05
MTB treatment	20	0	-

Note. MTB, mycobacterium tuberculosis; TB, tuberculosis.

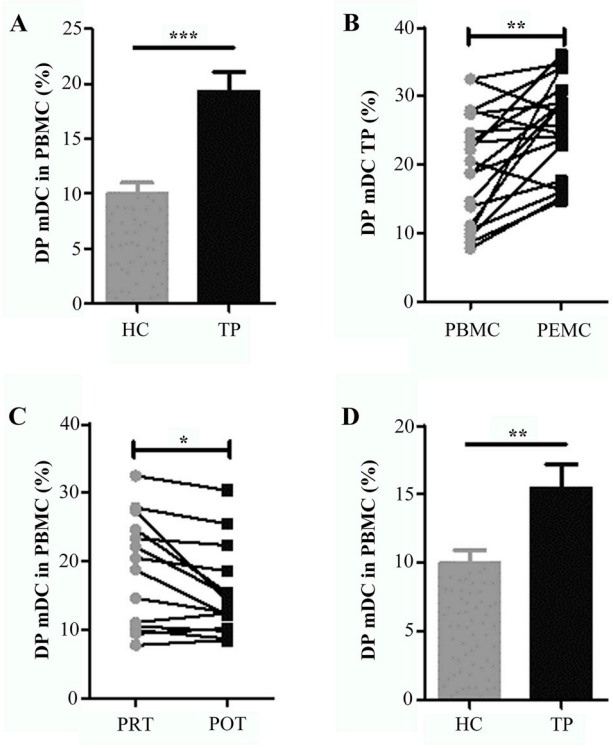

Fig. 1. Double co-expression of BTLA and B7-H4 (DP) on mDCs isolated from peripheral blood (PB) and pleural effusions (PE) of patients with tuberculous pleurisy (TP). A: comparison of DP mDC percentages from peripheral blood between TP patients and the healthy controls (HC); B: comparison of DP mDCs percentage between PB and PE of TP patients (PBMC and PEMC); C: comparison of DP mDC percentages from TP peripheral blood prior to and post treatment (PRT and POT); D: comparison of DP mDCs percentages between HC and TP patients after two weeks treatment. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

2.5. Statistical analysis

GraphPad Prism 5.0 was used for data analysis. Measurement data are expressed as mean ± *SD*. A *t*-test was used for data analysis between two groups with a normal distribution. ANOVA was used for data

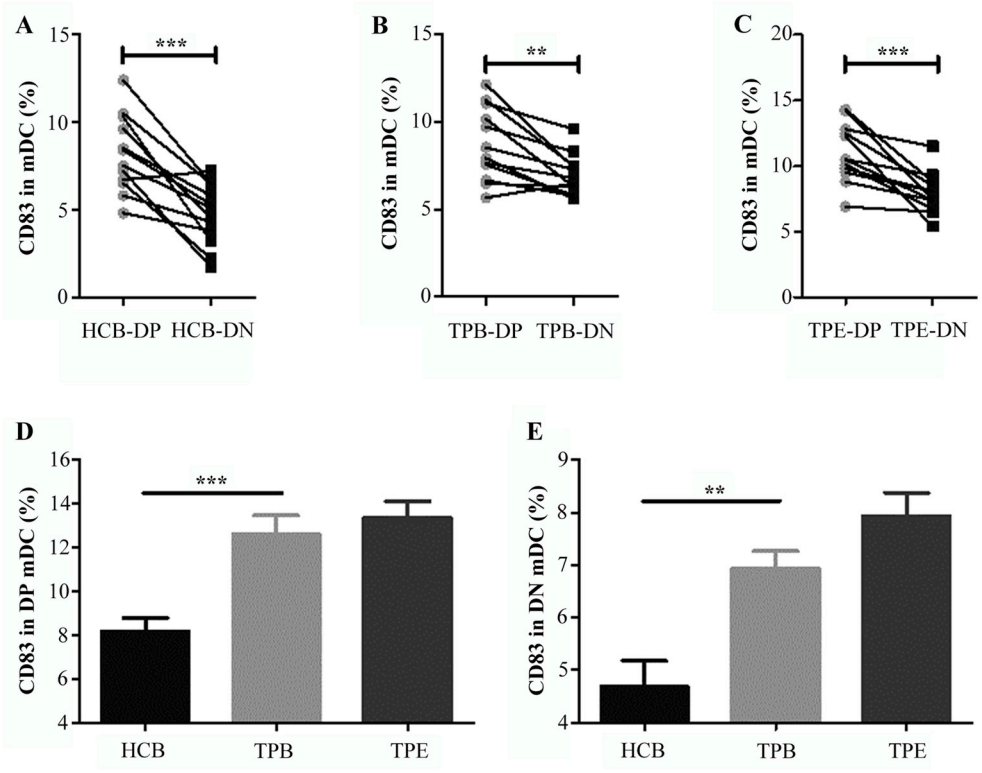

Fig. 2. Effects of co-expression of BTLA and B7-H4 on CD83 in mDCs. A~C: comparison of the CD83 expression rates between DP mDCs and DN mDCs obtained from healthy control peripheral blood (HCB), tuberculous pleurisy (TP) peripheral blood (TPB) and TP pleural effusions (TPE). D: comparison of the CD83 expression rate in DP mDCs in HCB, TPB and TPE. E: comparison of the CD83 expression rate in DN mDCs in HCB, TPB and TPE. $^{**}P < 0.01$, $^{***}P < 0.001$.

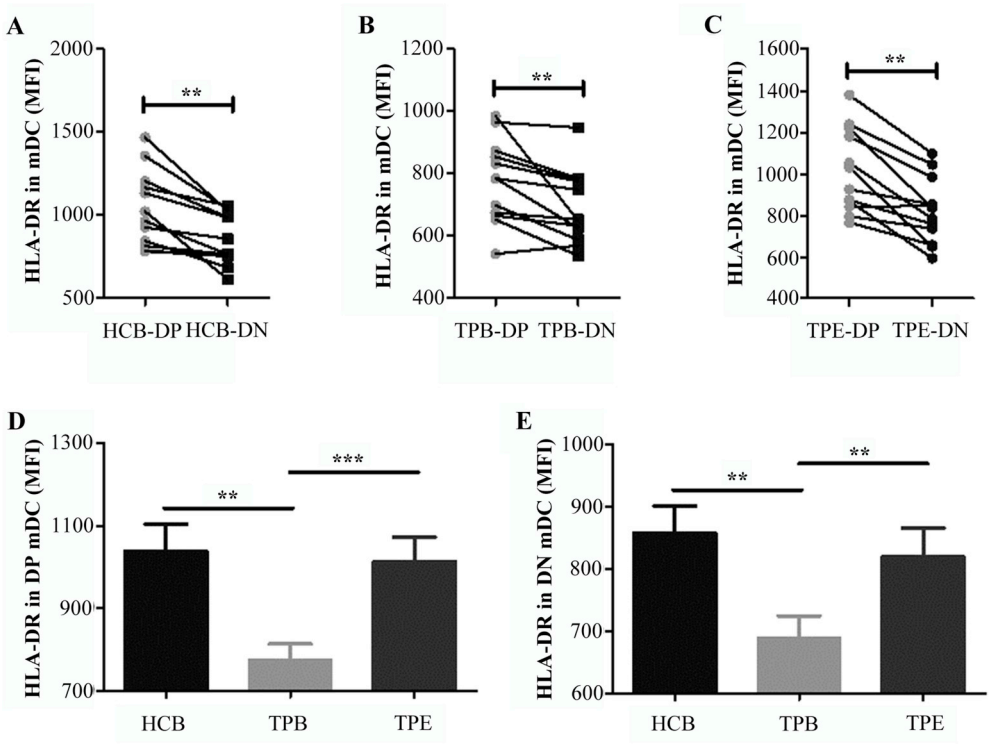

Fig. 3. Effects of co-expression of BTLA and B7-H4 on HLA-DR in mDCs. A~C) comparison of the mean fluorescence index (MFI) of HLA-DR expressed between DP mDCs and DN mDCs obtained from healthy control peripheral blood (HCB), tuberculous pleurisy (TP) peripheral blood (TPB) and TP pleural effusions (TPE). D) comparison of the MFI of HLA-DR expressed in DP mDCs in HCB, TPB and TPE. E) comparison of the MFI of HLA-DR expressed in DN mDCs from HCB, TPB and TPE. $^{**}P < 0.01$, $^{***}P < 0.001$.

comparison between multiple groups. $P < 0.05$ was considered to be a statistically significant result.

3. Results

3.1. Basic information about TP patients and healthy control subjects

In this study, 20 TP patients and 15 healthy controls (HC) were enrolled and their age was from 16 to 65 years old. There were significant differences in neutrophil, monocyte and lymphocyte counts between TP patients and healthy control subjects (Table 1).

3.2. High expression of BTLA and B7-H4 on mDCs obtained from PB and PE of TP patients

Co-expression of BTLA and B7-H4 on mDCs obtained from PB and PE of TP patients was measured by flow cytometry. The results showed that the co-expression level of BTLA and B7-H4 on mDCs isolated from PB of infected patients was significantly higher than in the control group (Fig. 1A, Fig. S2A, $P < 0.001$). Moreover, the co-expression levels of BTLA and B7-H4 on mDCs isolated from the PE of patients were significantly higher than in PB (Fig. 1B, Fig. S2B, $P < 0.01$). After 15 days treatment of the 12 patients, the expression levels of BTLA and B7-H4 on mDC from peripheral blood were significantly decreased (Fig. 1C, Fig. S2C, $P < 0.05$), but still higher than in the healthy control group (Fig. 1D, Fig. S2D $P < 0.01$).

3.3. DP mDCs expressed high levels of CD83, the percentage of high expression CD83 DP mDC being higher in patients than in controls

The analysis of CD83 expression in BTLA and B7-H4 co-expression mDCs revealed that the CD83 positive rate in DP mDCs was much higher than in DN mDCs, no matter whether they were obtained from PB or PE in both groups (Fig. 2A–C, Figs. S3A–C, $P < 0.01$ or $P < 0.001$). The results confirmed the high percentage of mature mDCs in DP mDCs. In addition, the expression of CD83 in both DP mDCs and DN mDCs from PB of patients was higher than in the control group of healthy subjects (Fig. 2D–E, $P < 0.01$ or $P < 0.001$). There was no significant difference between the PB and PE of patients. The results demonstrated that the maturity of mDCs is similar in the PB and PE of TP patients and that both were higher than in the healthy control group (all $P < 0.01$ or $P < 0.001$). The maturity of mDCs was highly related to the co-expression of BTLA and B7-H4.

3.4. The MHCII member HLA-DR is highly expressed in DP mDCs but the expression of HLA-DR in TP patients was lower than that in healthy controls

The analysis of HLA-DR expression in DP mDCs showed that the HLA-DR positive rate in DP mDCs was much higher than in DN mDCs, no matter whether samples were obtained from PB or PE (Fig. 3A–C, $P < 0.01$ or $P < 0.001$). The expression levels of HLA-DR in DP mDCs and DN mDCs in PB of TP patients were significantly lower than in the control group (Fig. 3D–E, $P < 0.01$). Additionally, the expression levels of HLA-DR in DP mDCs and DN mDCs obtained from PE of TP patients were significantly higher than in the PB of these patients (Fig. 3D–E, $P < 0.01$ or $P < 0.001$). These findings revealed that in the same subject, the HLA-DR positive rate was higher in DP mDCs than in DN mDCs, whether sourced from PB or PE. When mDCs were sourced from different subjects, the HLA-DR positive rate was dependent on whether the mDCs came from the control group or PE, regardless of the expression levels of BTLA and B7-H4.

4. Discussion

The frequency of DP mDCs was higher in the PB of patients with TP compared to healthy control, higher in PE compared to PB of TP patients and higher in PB before treatment compared to 2 weeks after treatment. CD38 expressions correlated positively with percentages of mDCs in PB of healthy control, in PB and PE of TP patients and was higher in DP mCDs of TP patients' peripheral blood and pleural effusions than in healthy control blood. HLA-DR correlated positively with DP mDCs in healthy control blood and TP patients' PB and PE.

These findings imply that tubercle bacillus triggers the production of mDCs, However, with increasing number of mDCs, also their CD83, BTLA and B7-H4 surface expressions increase significantly. Han et al. [24] reported that bone marrow-derived DCs expressed high levels of BTLA under LPS stimulation. Our previous study reported high expression levels of BTLA in CD11c+ antigen presenting cells (APC) in PB of patients with pulmonary TB. CD11c+ APC with BTLA expression had a decreased ability to activate the same T cells, suggesting that BTLA expression on APC had a large influence on anti-TB immune functions [21]. BTLA is highly expressed not only in mature activated T cells, but also in mature DCs [7]. Kobayashi et al. [25] found that in BTLA-/- mice that LPS could induce DCs to produce a large number of cytoactive factors, and that such gene knockout mice are prone to LPS-induced endotoxin shock death. Yang et al. [26] found that the BTLA signal pathway can inhibit the immune activity of CD8+DC, resulting in its decreased immune response against *Listeria*, which has the characteristics of intracellular infection. Therefore, it is believed that the presence of BTLA can inhibit the overactivation of DCs [27], thus maintaining the self-stability of the body's immune response. B7-H4 is inductively expressed on DCs [17,18] with a negative regulation on the immune activity of T cells. It was found that B7-H4 was highly expressed in tumor-associated macrophages and was positively correlated with tumor progression, and also involved in tumor immune escape [14–16]. CD 83 expression levels in TB patients was significantly increased by tubercle bacillus, which further affected the immune function of mDC and reduced anti-TB immunity [28–30]. It was found that stimulation of DCs *in vitro* with tuberculous or bacterial antigens could induce maturity of DCs and a high expression of CD83 [31,32]. Mendelson et al. [33] found mature mDCs in TP with high CCR7 and Il-12 expression during *in vitro* stimulation and mature activated DCs express CD83 as well as negative immune molecules including BTLA and B7-H4 [34]. Taken together, high expression of CD83 induced by systemic or local maturation of DCs might correspond to a greater expression of inhibitory markers that modulate mDCs response, thereby avoiding an exacerbated response.

5. Conclusion

In conclusion, our study has shown the remarkable percentage increase in the co-expression of BTLA and B7-H4 in mDC from TP patients. The DP expression of BTLA and B7-H4 might influence the maturity of mDCs through high expression of CD83, which might be a mechanism avoiding exacerbated responses.

Author contributions

XC, NG, RR, YL, JZ and JX were responsible for the conception and design of the study. XC, NG, RR, YL, JZ and JX were responsible for acquisition and statistical analysis of data. XC, YL and JX drafted the manuscript; XC, YL and JX revised and commented the draft, and all authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tube.2019.101877.

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