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B7-DC induced by IL-13 works as a feedback regulator in the effector phase of allergic asthma

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Abstract

B7-DC is a costimulatory molecule belonging to the B7 family. We previously found that treatment with anti-B7-DC mAb during the effector phase enhances asthma phenotypes in mice. We investigated the mechanisms of B7-DC induction and how B7-DC regulates asthma phenotypes. In allergen-challenged IFN-γ-deficient mice, anti-B7-DC mAb failed to enhance the asthma phenotypes although the induction of B7-DC on dendritic cells of the mice was comparable with that on dendritic cells of wild-type mice. B7-DC on dendritic cells was up-regulated by IL-13 *in vitro*. The induction of B7-DC on dendritic cells after allergen challenge was attenuated by blockade of IL-13 *in vivo*. The asthma phenotypes were enhanced in B7-DC-deficient mice, more than in wild-type mice. The enhancement was concurrent with the down-regulation of IFN-γ and up-regulation of IL-13. These results suggest that B7-DC induced by IL-13 works as a feedback regulator by up-regulating IFN-γ production during the effector phase of allergic asthma.

Keywords: Costimulatory molecule; Dendritic cell; Allergy; Mouse; IFN-γ

Allergic asthma is characterized by Th2-biased immune responses to an inhaled antigen. The process of acquired immune responses is composed of the antigen sensitization phase and the effector phase following recall antigen exposure. From a therapeutic point of view, for established asthma, it is a rational approach to focus on understanding the mechanism of effector phase reactions. Both sensitization and effector phases depend on coordinated interactions between dendritic cells and antigen-specific T cells. In addition to the interaction between antigen-loaded MHC molecules and the T cell receptor (TCR), interactions between lines of costimulatory molecules are required to activate T cells [1,2]. B7 family molecules, such as B7-1 and B7-2, are representative costimulatory molecules expressed in dendritic cells. Recent investigations have shown that several B7 family molecules may work as regulators of immune responses [1].

B7-DC/PD-L2 shares its receptor, PD-1, with B7-H1/PD-L1 [3–6]. PD-1 is inducibly expressed on T cells and B cells during their activation, and its ligation to B7-H1 or B7-DC results in the suppression of the activated status [4,5,7]. B7-H1 and B7-DC are expressed constitutively or inducibly on antigen-presenting cells [8–10]. In addition, B7-H1 is substantially expressed on the peripheral tissues

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of diseased organs, and treatment with anti-B7-H1 mAb leads to exacerbation of the disease phenotype [11–15]. Thus, B7-H1 may play an important role in the induction and maintenance of peripheral tolerance.

On the other hand, treatment with anti-B7-DC mAb has shown to exacerbate the phenotypes of allergic diseases [16–19]. We previously found that the treatment of BALB/c mice with anti-B7-DC mAb during the effector phase, but not the sensitization phase, enhances typical asthma phenotypes, airway hyperresponsiveness (AHR), and eosinophilia [18]. The selective effect of mAb on the effector phase implies that B7-DC may work as a feedback regulator. If so, the arising question is what is an inducer of B7-DC in allergic asthma. We herein explore the mechanism of B7-DC induction and how B7-DC regulates the asthma phenotypes.

Materials and methods

Animals. BALB/c mice were purchased from Charles River Japan (Kanagawa, Japan). IFN-$\gamma^{-/-}$ mice on a BALB/c background were provided by Dr. Y. Iwakura (University of Tokyo, Japan). B7-DC$^{-/-}$ mice on a BALB/c background have been described by Shin et al. [20]. Their wild-type littermates were prepared as control animals. Mice were housed under specific pathogen-free conditions until 7–10 wks of age. The procedures and protocols were approved by the Animal Research Ethics Committee at Kyushu University.

Sensitization and challenge. Mice were sensitized by an i.p. injection of 10 μg of chicken ovalbumin (OVA) (Sigma–Aldrich, St. Louis, MO) and 0.3 mg of $Al(OH)_3$ (SERVA Electrophoresis, Heidelberg, Germany) on days 1 and 11 and then challenged with 5% OVA in saline mist for 20 min on days 19, 21, and 23, as described previously [18]. Control mice received 0.9% saline sensitization and challenges and are referred to as naive mice. Subgroups of animals received i.p. injections (250 μg/animal) of anti-mouse B7-DC mAbs (TY25, rat IgG2a, or MIH37, rat IgG1) or control rat IgG (Sigma–Aldrich) 6 h before each OVA challenge. In some experiments, mice received i.p. injections of 330 μg/animal of recombinant mouse IL-13 receptor alpha 2/Fc chimeric protein (rmIL-13Rα2-Fc) (R&D Systems, Minneapolis, MN) or control human IgG1 (Sigma–Aldrich) 3 h before OVA challenges on days 19, 21, and 23 [21–23]. Unless otherwise noted, outcome measurements were conducted on day 24.

Measurement of airway responsiveness. Mice were anesthetized, and their tracheas were cannulated via tracheostomy. Animals were ventilated to measure airway responsiveness to ACh aerosol, as described previously [18]. The data were expressed as the provocative concentration 200 (PC_{200}), i.e., the concentration at which airway pressure was 200% of its baseline value. Values of PC_{200} were expressed as log ($PC_{200} \times 100$).

Bronchoalveolar lavage (BAL) and cytokine measurements. Lungs were gently lavaged with 1 ml of 0.9% saline via a tracheal cannula. Cell counts were performed as previously described [18]. IL-5, IL-13, and IFN-γ in the supernatants were quantified using ELISA kits (IL-5 and IFN-γ: BioSource International, Camarillo, CA; IL-13: R&D Systems).

Collection of lung cells and lymph node cells. The single-cell suspensions were prepared from whole lung tissues as previously described [18]. DLN cells were collected from thoracic lymph nodes and dissociated into a single-cell suspension.

Preparation of dendritic cells. Bone marrow-derived dendritic cells (BMDCs) were prepared by culturing bone marrow cells from BALB/c mice in the presence of recombinant mouse GM-CSF (R&D Systems) at 10 ng/ml for 4–6 days. Non-adherent cells were removed, and a fresh medium containing GM-CSF was fed at days 2, 4, and 6 after the initiation of culture. On day 7, BMDCs were stimulated with or without recombinant mouse IL-13 (Sigma–Aldrich) at 100 ng/ml or IL-5 (R&D Systems) at 50 ng/ml for 24 h.

Flow cytometric analysis. To detect dendritic cells, cells were incubated with FITC-labeled anti-CD11c (HL3, hamster IgG1), PE-labeled anti-B7-DC (TY25, rat IgG2a), and PerCP-labeled anti-CD8α (53-6.7, rat IgG2a). Several samples were incubated with biotinylated anti-B7-1 (16-10A1, hamster IgG2), or anti-B7-2 (GL1, rat IgG2a) (eBioscience, San Diego, CA) and followed by staining with PE-labeled streptavidin. After fixation with a 4% paraformaldehyde-containing solution (Fix/Perm Buffer, eBioscience), the cells were assessed using a FACSCalibur (BD Biosciences). The absolute numbers of dendritic cells were calculated by multiplying the total cell count of lungs or DLNs with the frequency of each subset. All mAbs and isotype IgGs were purchased from BD Biosciences.

Data analysis. Values were expressed as the means ± SEM. Parametric data were analyzed using the unpaired *t* test or ANOVA with Bonferroni's correction. Non-parametric data were analyzed using the Mann–Whitney *U* test or the Kruskal–Wallis test. *P*-values less than 0.05 were accepted as being statistically significant.

Results

B7-DC is induced but fails to suppress asthma phenotypes in IFN-γ-deficient mice

In anti-B7-DC mAb (TY25)-treated BALB/c mice, the absolute counts of eosinophils in BAL fluid (BALF) and AHR were significantly higher than those of control IgG-treated mice (Fig. 1A). The concentrations of IL-5 and IL-13 in the BALF of TY25-treated mice were significantly higher than those in the controls. IFN-γ is a potent cytokine capable of inducing the expression of B7-DC [8–10,24]. In IFN-$\gamma^{-/-}$ mice on a BALB/c background, the eosinophilia in BALF and AHR did not differ between TY25-treated mice and control mice. The concentrations of IL-5 and IL-13 did not differ between the two groups either.

To determine whether the dendritic cells in the lungs and DLNs might fail to induce B7-DC in the absence of IFN-γ, the expression of B7-DC was compared in IFN-$\gamma^{-/-}$ mice and wild-type mice. When sensitized wild-type mice were challenged with OVA, the expression of B7-DC in the CD8α$^-$ dendritic cells of DLNs was markedly induced, while that in naive mice was not (Fig. 1B). The induction peaked on day 1 following the last OVA challenge and returned to the baseline on day 8. A similar kinetics was found for the expression of B7-DC in CD8α$^-$ dendritic cells of OVA-challenged lungs. The expression of B7-DC in CD8α$^+$ dendritic cells was negligible both in the DLNs and in the lungs over the time course. The frequencies and absolute numbers of B7-DC$^+$CD8α$^-$ dendritic cells in both the DLNs and the lungs of IFN-$\gamma^{-/-}$ mice on day 1 were not different from those of wild-type mice (Fig. 1C). Thus, B7-DC was substantially induced, but its regulatory effect on asthma phenotypes was lost in the absence of IFN-γ.

B7-DC on dendritic cells is induced by IL-13

Given that the induction of B7-DC is not affected in IFN-$\gamma^{-/-}$ mice, we hypothesized that Th2 cytokine(s) might induce B7-DC to turn on the negative-feedback sys-

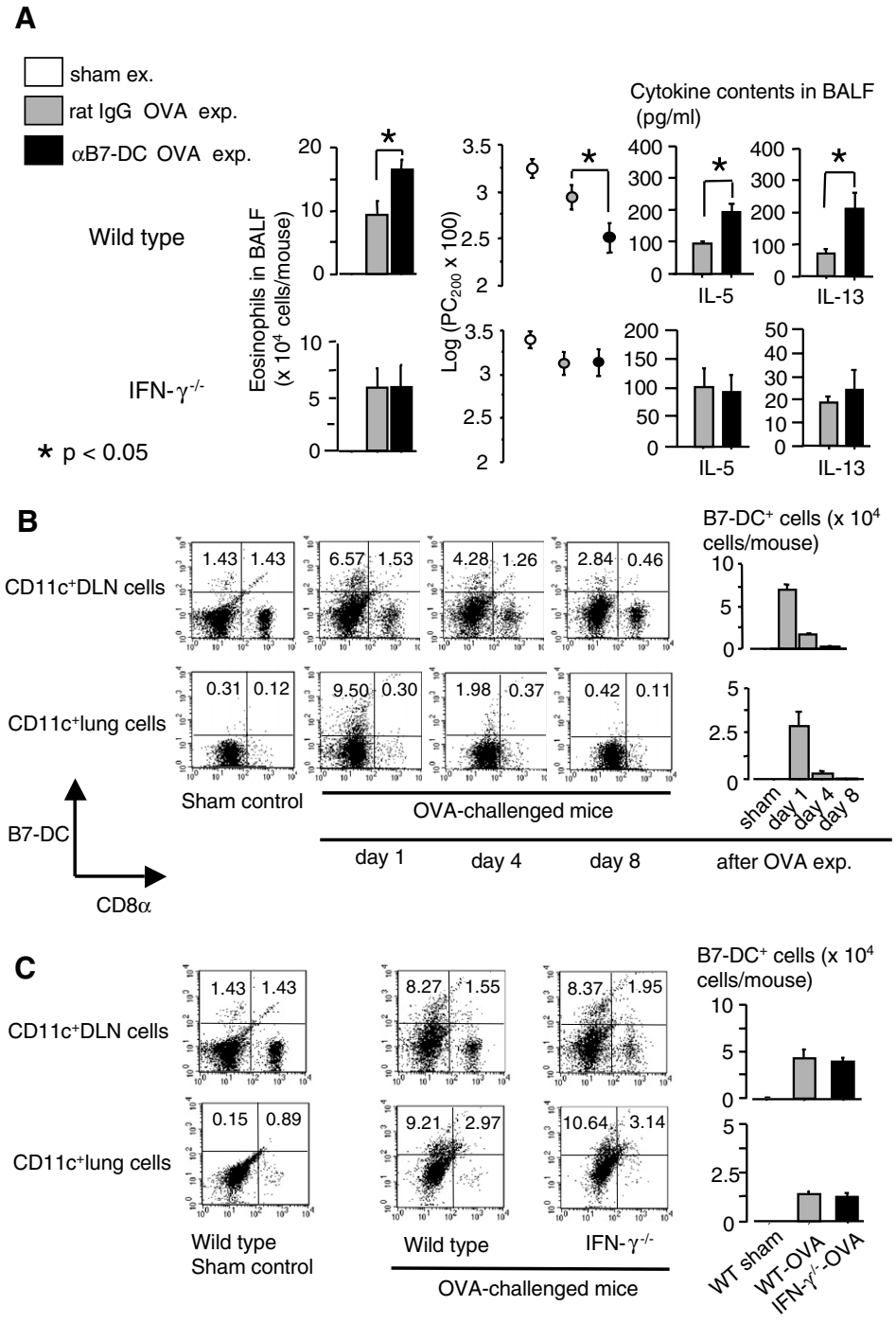

Fig. 1. Effect of anti-B7-DC mAb treatment on asthma phenotypes and profiles of B7-DC expression in IFN-$\gamma^{-/-}$ mice. (A) OVA-sensitized IFN-$\gamma^{-/-}$ mice and wild-type BALB/c mice were challenged with OVA and the subsequent asthmatic reaction was assessed by the eosinophil count in bronchoalveolar lavage fluid (BALF) and by measuring the airway hyperresponsiveness and the contents of IL-5 and IL-13 in BALF. The effect of anti-B7-DC mAb (TY25) treatment during OVA challenge on the asthmatic reaction was examined. Each group consisted of five to seven mice. Data are expressed as means ± SEM. Data are representative of two independent experiments. (B) OVA-sensitized BALB/c mice were challenged with OVA, and the expression of B7-DC in $CD11c^+$ dendritic cells of DLNs and the lungs was evaluated on day 1, 4, and 8 after the last OVA challenge. The numbers of dot plots indicate the typical percentage of B7-$DC^+CD8\alpha^-$ cells and B7-$DC^+CD8\alpha^+$ cells for $CD11c^+$ cells. (C) OVA-sensitized IFN-$\gamma^{-/-}$ mice and their wild-type mice were challenged with OVA, and the expression of B7-DC in $CD11c^+$ dendritic cells of DLNs and the lungs was evaluated 24 h after the last OVA challenge. Each group consisted of five mice. Data are expressed as means ± SEM.

tems. Among Th2 cytokines, IL-13 is particularly important for the pathogenesis of asthma. The administration of IL-13 to naive mice induces typical asthma phenotypes [23,25,26]. The blockade of IL-13 in allergen-challenged mice inhibits the development of asthma phenotypes [22,23]. To explore the direct effect of IL-13 on the expres-

sion of B7-DC *in vitro*, BMDCs were prepared from naive BALB/c mice (Fig. 2A). There were high expression of B7-1 and B7-2, and minimal expression of B7-DC on day 8 after the initiation of culture. When BMDCs were stimulated with IL-13 for 24 h, the expression of B7-1 and B7-2 was down-regulated, while that of unstimulated controls was not. In contrast, the expression of B7-DC was markedly up-regulated, while that of unstimulated controls was not. The up-regulation of B7-DC was not found for BMDCs treated with IL-5 (data not shown).

To explore the role of endogenous IL-13 in the induction of B7-DC *in vivo*, OVA-sensitized BALB/c mice received a treatment of rmIL-13Rα2-Fc or control human IgG1 in the phase of OVA challenge. The number of eosinophils in the BALF and AHR of rmIL-13Rα2-Fc-treated mice was significantly lower than that in human IgG1-treated control mice (data not shown). Importantly, the frequencies and absolute numbers of B7-DC^{+}CD8α^{-} dendritic cells in both the DLNs and the lungs of rmIL-13Rα2-Fc-treated mice were significantly lower than those in control mice (Fig. 2B). These results indicate that IL-13 is a cytokine responsible for inducing B7-DC on the dendritic cells.

B7-DC up-regulates IFN-γ but down-regulates IL-13

Finally, the downstream pathway of B7-DC induction was explored by comparing the asthma phenotypes between B7-DC$^{-/-}$ mice and their wild-type controls (Fig. 3). When B7-DC$^{-/-}$ mice were sensitized and challenged, the number of eosinophils in their BALF was significantly higher than that in the controls. The AHR of B7-DC$^{-/-}$ mice was significantly higher than that of the controls. The concentrations of IL-5 and IL-13 in the BALF of B7-DC$^{-/-}$ mice were significantly higher than those in the controls, while the concentration of IFN-γ was significantly lower than that in the controls. Consistent results were obtained from the experiments using anti-B7-DC mAb (MIH37) treatment other than TY25 (data not shown). These results indicate that B7-DC up-regulates the production of IFN-γ and down-regulates the production of IL-5 and IL-13.

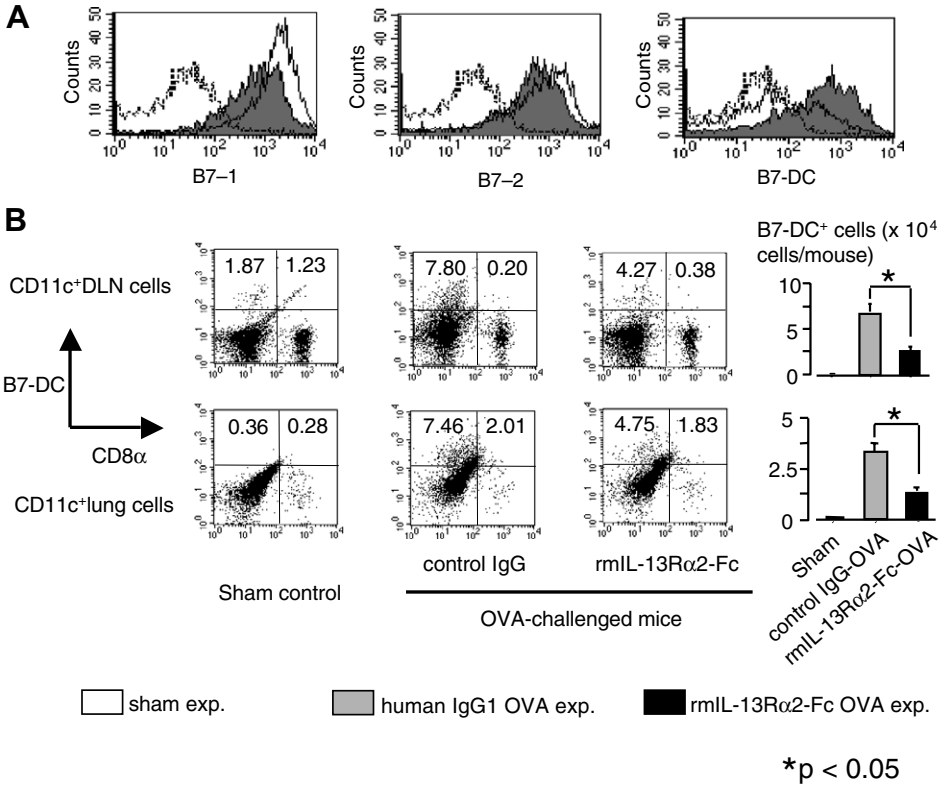

Fig. 2. Effect of IL-13 on the expression of B7-DC in dendritic cells. (A) Bone marrow-derived dendritic cells (BMDCs) were prepared by culturing bone marrow cells from BALB/c mice in the presence of GM-CSF for 4–6 days. On day 7, BMDCs were stimulated with or without IL-13 at 100 ng/ml for 24 h and then processed for flow cytometric analysis to evaluate the expression of B7-1, B7-2, and B7-DC. The shaded histograms indicate IL-13-treated samples and the open histograms indicate untreated samples. Both histograms indicate staining with mAbs against the indicated B7 family molecules. The dotted histograms indicate background staining with control IgGs. Data are representative of three independent experiments. (B) OVA-sensitized BALB/c mice were challenged with OVA. A subgroup of mice received i.p. injections of recombinant mouse IL-13 receptor alpha 2/Fc chimeric protein (rmIL-13Rα2-Fc) or control human IgG1 before each OVA challenge. The expression of B7-DC in CD11c^{+} dendritic cells of DLNs and the lungs was evaluated at 24 h after the last OVA challenge. The numbers of dot plots indicate the typical percentage of B7-DC^{+}CD8α^{-} cells and B7-DC^{+}CD8α^{+} cells for CD11c^{+} cells. Each group consisted of five to seven mice. Data are expressed as means ± SEM.

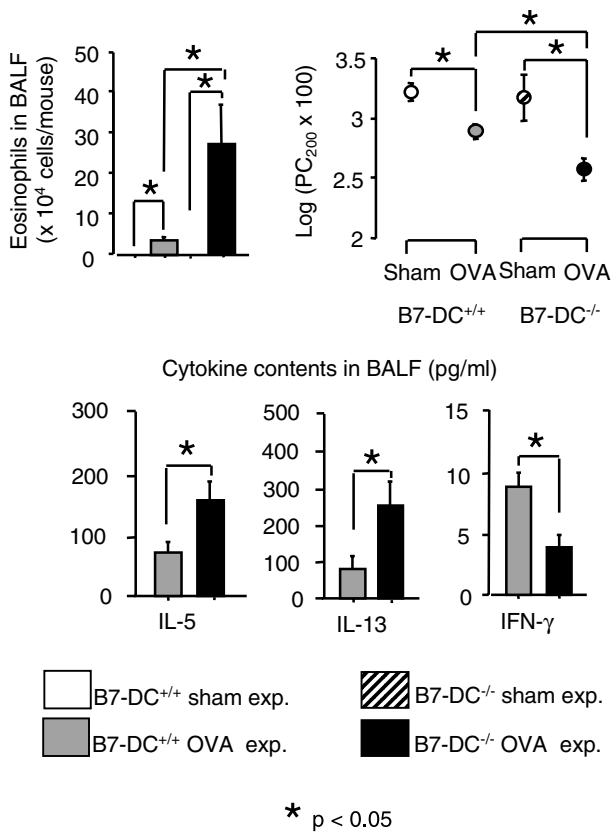

Fig. 3. Effect of B7-DC deletion on asthma phenotypes. OVA-sensitized B7-DC$^{-/-}$ mice and their wild-type mice were challenged with OVA, and the subsequent asthmatic reaction was assessed by the eosinophil count in BALF and by measuring the airway hyperresponsiveness and the contents of IL-5, IL-13, and IFN-γ in BALF. Each group consisted of six to eight mice. Data are expressed as means ± SEM. Data are representative of two independent experiments.

Discussion

Immune responses are regarded as an integrated process of various positive- and negative-feedback mechanisms, and the latter is important for preventing excessive outcomes. Several cytokines that contribute to the effector phase of Th2 responses may be a trigger of negative-feedback regulation in allergic asthma. In the present study, exogenously applied IL-13 markedly up-regulated the expression of B7-DC in dendritic cells. In addition, the treatment of rmIL-13Rα2-Fc inhibited the up-regulation of B7-DC in dendritic cells. The default enhancement of asthma phenotypes by anti-B7-DC mAb in IFN-γ$^{-/-}$ mice suggests that the regulation of asthma by B7-DC is dependent on the IFN-γ-mediated pathway. The Th1 cytokine, IFN-γ, is known as a regulator of asthma, by its suppressive effect on the production of Th2 cytokines [27–29]. Collective evidence leads us to the conclusion that IL-13-induced up-regulation of B7-DC may result in the down-regulation of IL-5 and IL-13 production from effector Th2 cells via up-regulation of IFN-γ production. These findings suggest that a critical Th2 cytokine, IL-13, triggers a negative-feedback regulation for asthma through the up-regulation of a costimulatory molecule, B7-DC.

The blockade of IL-13 inhibited but did not completely abolish the up-regulation of B7-DC in the present study. It has been reported that GM-CSF, IL-12, and IL-4 also had potency to induce B7-DC in dendritic cells in mice [24]. IL-4 is known as a crucial cytokine for the development of Th2-biased allergen sensitization. Although the contribution of IL-4 in the effector phase of asthma remains to be established, the up-regulation of B7-DC independently of IL-13 might be induced by IL-4.

The issue to be discussed is the possible mechanism whereby B7-DC may up-regulate the production of IFN-γ. The ligation of PD-1 by B7-DC is known to inhibit T cell responses, which cannot explain the stimulatory effect of B7-DC on IFN-γ production. In addition to PD-1, there may be a second receptor for B7-DC that is capable of delivering a stimulatory signal [6,30,31]. B7-DC^{+} dendritic cells may activate several types of cells to produce IFN-γ. We have shown that the production of IFN-γ by purified DO11.10 CD4^{+}T cells being cultured with OVA$_{323–339}$ peptide-loaded BMDCs from B7-DC$^{-/-}$ mice was reduced in comparison with that from wild-type mice [20]. Taken together with the results of experiments using IFN-γ$^{-/-}$ mice, our results indicate that B7-DC may augment IFN-γ production, presumably from Th1 and Tc1 cells.

The cross-regulation between cytokines and other immune molecules, including costimulatory molecules, may be an important component that enables the cytokine-mediated actions to be retained within a self-limited fashion. Considering that the IL-13-B7-DC axis works during the effector phase, the manipulation of B7-DC activity may provide a new therapeutic modality for the control of allergic asthma.

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References

[1] R.J. Greenwald, G.J. Freeman, A.H. Sharpe, The B7 family revisited, Annu. Rev. Immunol. 23 (2005) 515–548.
[2] S. Wang, L. Chen, T lymphocyte co-signaling pathways of the B7-CD28 family, Cell. Mol. Immunol. 1 (2004) 37–42.
[3] H. Dong, G. Zhu, K. Tamada, L. Chen, B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion, Nat. Med. 5 (1999) 1365–1369.
[4] G.J. Freeman, A.J. Long, Y. Iwai, K. Bourque, T. Chernova, H. Nishimura, L.J. Fitz, N. Malenkovich, T. Okazaki, M.C. Byrne, H.F. Horton, L. Fouser, L. Carter, V. Ling, M.R. Bowman, B.M. Carreno, M. Collins, C.R. Wood, T. Honjo, Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation, J. Exp. Med. 192 (2000) 1027–1034.

[5] Y. Latchman, C.R. Wood, T. Chernova, D. Chaudhary, M. Borde, I. Chernova, Y. Iwai, A.J. Long, J.A. Brown, R. Nunes, E.A. Greenfield, K. Bourque, V.A. Boussiotis, L.L. Carter, B.M. Carreno, N. Malenkovich, H. Nishimura, T. Okazaki, T. Honjo, A.H. Sharpe, G.J. Freeman, PD-L2 is a second ligand for PD-1 and inhibits T cell activation, Nat. Immunol. 2 (2001) 261–268.

[6] S.Y. Tseng, M. Otsuji, K. Gorski, X. Huang, J.E. Slansky, S.I. Pai, A. Shalabi, T. Shin, D.M. Pardoll, H. Tsuchiya, B7-DC, a new dendritic cell molecule with potent costimulatory properties for T cells, J. Exp. Med. 193 (2001) 839–846.

[7] Y. Agata, A. Kawasaki, H. Nishimura, Y. Ishida, T. Tsubata, H. Yagita, T. Honjo, Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes, Int. Immunol. 8 (1996) 765–772.

[8] J. Kim, A.C. Myers, L. Chen, D.M. Pardoll, Q.A. Truong-Tran, A.P. Lane, J.F. McDyer, L. Fortuno, R.P. Schleimer, Constitutive and inducible expression of b7 family of ligands by human airway epithelial cells, Am. J. Respir. Cell Mol. Biol. 33 (2005) 280–289.

[9] L.A. Stanciu, C.M. Bellettato, V. Laza-Stanca, A.J. Coyle, A. Papi, S.L. Johnston, Expression of programmed death-1 ligand (PD-L) 1, PD-L2, B7-H3, and inducible costimulator ligand on human respiratory tract epithelial cells and regulation by respiratory syncytial virus and type 1 and 2 cytokines, J. Infect. Dis. 193 (2006) 404–412.

[10] M. Tsuda, K. Matsumoto, H. Inoue, M. Matsumura, T. Nakano, A. Mori, M. Azuma, Y. Nakanishi, Expression of B7-H1 and B7-DC on the airway epithelium is enhanced by double-stranded RNA, Biochem. Biophys. Res. Commun. 330 (2005) 263–270.

[11] H. Dong, S.E. Strome, D.R. Salomao, H. Tamura, F. Hirano, D.B. Flies, P.C. Roche, J. Lu, G. Zhu, K. Tamada, V.A. Lennon, E. Celis, L. Chen, Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion, Nat. Med. 8 (2002) 793–800.

[12] Y. Iwai, M. Ishida, Y. Tanaka, T. Okazaki, T. Honjo, N. Minato, Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade, Proc. Natl. Acad. Sci. USA 99 (2002) 12293–12297.

[13] N. Rodig, T. Ryan, J.A. Allen, H. Pang, N. Grabie, T. Chernova, E.A. Greenfield, S.C. Liang, A.H. Sharpe, A.H. Lichtman, G.J. Freeman, Endothelial expression of PD-L1 and PD-L2 down-regulates CD8+ T cell activation and cytolysis, Eur. J. Immunol. 33 (2003) 3117–3126.

[14] F. Tsushima, H. Iwai, N. Otsuki, M. Abe, S. Hirose, T. Yamazaki, H. Akiba, H. Yagita, Y. Takahashi, K. Omura, K. Okumura, M. Azuma, Preferential contribution of B7-H1 to programmed death-1-mediated regulation of hapten-specific allergic inflammatory responses, Eur. J. Immunol. 33 (2003) 2773–2782.

[15] M.J. Ansari, A.D. Salama, T. Chitnis, R.N. Smith, H. Yagita, H. Akiba, T. Yamazaki, M. Azuma, H. Iwai, S.J. Khoury, H. Auchincloss Jr., M.H. Sayegh, The programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese diabetic (NOD) mice, J. Exp. Med. 198 (2003) 63–69.

[16] A.D. Salama, T. Chitnis, J. Imitola, H. Akiba, F. Tushima, M. Azuma, H. Yagita, M.H. Sayegh, S.J. Khoury, Critical role of the programmed death-1 (PD-1) pathway in regulation of experimental autoimmune encephalomyelitis, J. Exp. Med. 198 (2003) 71–78.

[17] B. Zhu, I. Guleria, A. Khosroshahi, T. Chitnis, J. Imitola, M. Azuma, H. Yagita, M.H. Sayegh, S.J. Khoury, Differential role of programmed death-ligand 1 [corrected] and programmed death-ligand 2 [corrected] in regulating the susceptibility and chronic progression of experimental autoimmune encephalomyelitis, J. Immunol. 176 (2006) 3480–3489.

[18] K. Matsumoto, H. Inoue, T. Nakano, M. Tsuda, Y. Yoshiura, S. Fukuyama, F. Tsushima, T. Hoshino, H. Aizawa, H. Akiba, D. Pardoll, N. Hara, H. Yagita, M. Azuma, Y. Nakanishi, B7-DC regulates asthmatic response by an IFN-gamma-dependent mechanism, J. Immunol. 172 (2004) 2530–2541.

[19] A. Fukushima, T. Yamaguchi, M. Azuma, H. Yagita, H. Ueno, Involvement of programmed death-ligand 2 (PD-L2) in the development of experimental allergic conjunctivitis in mice, Br. J. Ophthalmol. 90 (2006) 1040–1045.

[20] T. Shin, K. Yoshimura, E.B. Crafton, H. Tsuchiya, F. Housseau, H. Koseki, R.D. Schulick, L. Chen, D.M. Pardoll, In vivo costimulatory role of B7-DC in tuning T helper cell 1 and cytotoxic T lymphocyte responses, J. Exp. Med. 201 (2005) 1531–1541.

[21] D.D. Donaldson, M.J. Whitters, L.J. Fitz, T.Y. Neben, H. Finnerty, S.L. Henderson, R.M. O'Hara Jr., D.R. Beier, K.J. Turner, C.R. Wood, M. Collins, The murine IL-13 receptor alpha 2: molecular cloning, characterization, and comparison with murine IL-13 receptor alpha 1, J. Immunol. 161 (1998) 2317–2324.

[22] G. Grunig, M. Warnock, A.E. Wakil, R. Venkayya, F. Brombacher, D.M. Rennick, D. Sheppard, M. Mohrs, D.D. Donaldson, R.M. Locksley, D.B. Corry, Requirement for IL-13 independently of IL-4 in experimental asthma, Science 282 (1998) 2261–2263.

[23] M. Wills-Karp, J. Luyimbazi, X. Xu, B. Schofield, T.Y. Neben, C.L. Karp, D.D. Donaldson, Interleukin-13: central mediator of allergic asthma, Science 282 (1998) 2258–2261.

[24] T. Yamazaki, H. Akiba, H. Iwai, H. Matsuda, M. Aoki, Y. Tanno, T. Shin, H. Tsuchiya, D.M. Pardoll, K. Okumura, M. Azuma, H. Yagita, Expression of programmed death 1 ligands by murine T cells and APC, J. Immunol. 169 (2002) 5538–5545.

[25] T. Nakano, H. Inoue, S. Fukuyama, K. Matsumoto, M. Matsumura, M. Tsuda, T. Matsumoto, H. Aizawa, Y. Nakanishi, Niflumic acid suppresses interleukin-13-induced asthma phenotypes, Am. J. Respir. Crit. Care Med. 173 (2006) 1216–1221.

[26] A. Kibe, H. Inoue, S. Fukuyama, K. Machida, K. Matsumoto, H. Koto, T. Ikegami, H. Aizawa, N. Hara, Differential regulation by glucocorticoid of interleukin-13-induced eosinophilia, hyperresponsiveness, and goblet cell hyperplasia in mouse airways, Am. J. Respir. Crit. Care Med. 167 (2003) 50–56.

[27] I. Iwamoto, H. Nakajima, H. Endo, S. Yoshida, Interferon gamma regulates antigen-induced eosinophil recruitment into the mouse airways by inhibiting the infiltration of CD4+ T cells, J. Exp. Med. 177 (1993) 573–576.

[28] C. Tang, M.D. Inman, N. van Rooijen, P. Yang, H. Shen, K. Matsumoto, P.M. O'Byrne, Th type 1-stimulating activity of lung macrophages inhibits Th2- mediated allergic airway inflammation by an IFN-gamma-dependent mechanism, J. Immunol. 166 (2001) 1471–1481.

[29] M. Yoshida, R. Leigh, K. Matsumoto, J. Wattie, R. Ellis, P.M. O'Byrne, M.D. Inman, Effect of interferon-gamma on allergic airway responses in interferon-gamma-deficient mice, Am. J. Respir. Crit. Care Med. 166 (2002) 451–456.

[30] T. Shin, G. Kennedy, K. Gorski, H. Tsuchiya, H. Koseki, M. Azuma, H. Yagita, L. Chen, J. Powell, D. Pardoll, F. Housseau, Cooperative B7-1/2 (CD80/CD86) and B7-DC costimulation of CD4+ T cells independent of the PD-1 receptor, J. Exp. Med. 198 (2003) 31–38.

[31] S. Wang, J. Bajorath, D.B. Flies, H. Dong, T. Honjo, L. Chen, Molecular modeling and functional mapping of B7-H1 and B7-DC uncouple costimulatory function from PD-1 interaction, J. Exp. Med. 197 (2003) 1083–1091.