CD83-stimulated monocytes suppress T-cell immune responses through production of prostaglandin E2

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Edited* by Richard A. Flavell, Yale School of Medicine Howard Hughes Medical Institute, New Haven, CT, and approved October 17, 2011 (received for review January 6, 2011)

CD83 is commonly known as a specific marker for mature dendritic cells. It has been shown to be important for $CD4^+$ T-cell development in the thymus. However, its function in the peripheral immune system remains enigmatic. Here, we show that CD83 inhibits proliferation and production of IL-2 and IFN-γ by T cells, and the inhibitory effect of CD83 is mediated by monocytes. Prostaglandin E2 (PGE_2), but not IL-10 or TGF-β, was up-regulated specifically by CD83 in monocytes. Consistent with high levels of PGE_2, expression of COX-2 also was increased upon CD83 treatment. NF-κB activation also is required for induction of PGE_2 by CD83. Finally, application of the COX-2–selective inhibitor NS-398 fully prevented CD83-triggered inhibition of T-cell responses. Our study establishes an immune-regulatory mechanism by CD83 via stimulation of PGE_2 production in monocytes.

immune regulation | fusion protein | cytokine | transcription factor

CD83, a type I Ig superfamily glycoprotein, is a well-known surface marker for mature dendritic cells (DCs) (1, 2). However, high levels of surface expression of CD83 also are found on activated T and B lymphocytes, forkhead box 3P $(Fox3P)^+CD4^+CD25^+$ natural regulatory T cells, activated macrophages, activated neutrophils, and thymic epithelial cells (3). Besides the membrane form (mCD83), CD83 also has been found in a soluble form in human sera, likely as a result of shedding from cell membranes (4). The receptor for CD83 has not been identified, although experiments using recombinant CD83 protein have demonstrated the presence of a putative CD83 receptor on monocytes and DCs (5, 6).

The role of CD83 in T-cell–mediated immune responses has been elusive. Some studies suggest a costimulatory function for mCD83 during T-cell activation (7, 8). However, peripheral $CD4^+$ T cells from $CD83^{-/-}$ mice proliferated normally in response to phytohemagglutinin or DC stimulation, and $CD83^{-/-}$ and wild-type DCs stimulated comparable levels of T-cell proliferation in mixed lymphocyte reactions (9, 10). In addition, many studies suggest soluble CD83 has an immune-regulatory role. Soluble CD83 was shown to inhibit antigen-specific T-cell proliferation and IL-2 secretion potently (11). Soluble CD83 also was shown to inhibit DC-dependent in vitro allogeneic T-cell proliferation and development of experimental autoimmune encephalomyelitis substantially (5, 12). In addition, soluble CD83 released from human cytomegalovirus-infected mature DCs inhibited T-cell proliferation (13). Nevertheless, the molecular mechanism underlying CD83-stimulated immune suppression is not known.

In the present study, we demonstrate that soluble CD83 inhibits anti-CD3–induced proliferation and production of IL-2 and IFN-γ by peripheral blood mononuclear cells (PBMCs) but has no direct inhibitory effect on T cells. Strikingly, the supernatants collected from CD83-stimulated monocytes also suppress T-cell proliferation and cytokine production. We further demonstrate that prostaglandin E2 (PGE_2), produced by monocytes upon CD83 stimulation, is a key mediator of T-cell suppression. In addition, CD83-induced NF-κB activation is required for the production of PGE_2. Taken together, our results reveal a regulatory mechanism by which CD83 suppresses T-cell functions.

Results

CD83 Inhibits Proliferation and Production of IL-2 and IFN-γ by PBMCs Cultured with Anti-CD3 mAb. The recombinant CD83-Ig fusion protein was made and characterized by dot-blot and competition assays (Fig. S1). We first used PBMCs to study the function of CD83 in T-cell proliferation. PBMCs were stimulated by plate-bound agonistic anti-CD3 mAb for 72 h in the presence of various amounts of soluble or coimmobilized CD83-Ig. As shown in Fig. 1*A*, either coimmobilized or soluble CD83-Ig inhibited anti-CD3 mAb–triggered proliferation of PBMCs in a dose-dependent manner, whereas human IgG (hIgG) had no effect. The inhibition of proliferation at 0.5, 1, 2, 5, and 10 μg/mL coimmobilized CD83 was 84.7%, 72.6%, 53.7%, 47.8%, and 43.3% respectively. Similarly, analysis of PBMC supernatants showed a dose-dependent decline of IL-2 and INF-γ secretion (Fig. 1 *B* and *C*). PBMCs stimulated with coimmobilized CD83 produced five- to sixfold lower IL-2 levels and about threefold lower IFN-γ levels than controls. PBMCs cultured with soluble CD83-Ig resulted in similarly decreased IL-2 and IFN-γ production. Additional kinetic studies revealed that the difference in PBMC proliferation occurred 3–4 d after the start of the culture (Fig. 1*D*).

To confirm further the specific inhibition of CD83 on PBMCs, we used another recombinant, CD83-His, in our assay and showed that CD83-His inhibition of PBMC proliferation is comparable with that of CD83-Ig (Fig. S2). In addition, depletion of CD83-Ig using a specific antibody could neutralize the inhibition of PBMC proliferation (Fig. S2). Taken together, these findings indicate that CD83 specifically suppresses anti-CD3–elicitated T-cell responses in PBMCs.

CD83 Does Not Suppress T-Cell Proliferation Directly. We next investigated whether CD83 has a direct inhibitory effect on pure T cells. Purified T cells were stimulated by plate-bound anti-CD3 mAb in combination with soluble agonistic anti-CD28 mAb (5 μg/mL) for 72 h in the presence or absence of coimmobilized (2 μg/mL) or soluble CD83-Ig (10 μg/mL). Surprisingly, neither coimmobilized nor soluble CD83-Ig had any significant effect on the proliferation of purified T cells (Fig. S3*A*). These results suggest an indirect pathway is involved in suppression of T-cell responses by CD83.

To analyze further the kinetics of CD83-Ig–mediated inhibition, PBMCs were pretreated with plate-bound CD83-Ig for 12, 18, or 24 h and then were transferred to a different plate that had been precoated with anti-CD3 mAb. These cells subsequently

Author contributions: L.C. and X.Z. designed research; L.C., Y.Z., G.Z., C.G., and W.Z. performed research; L.C. and X.Z. analyzed data; and L.C. and X.Z. wrote the paper.

The authors declare no conflict of interest.

*This Direct Submission article had a prearranged editor.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1018994108/-/DCSupplemental.

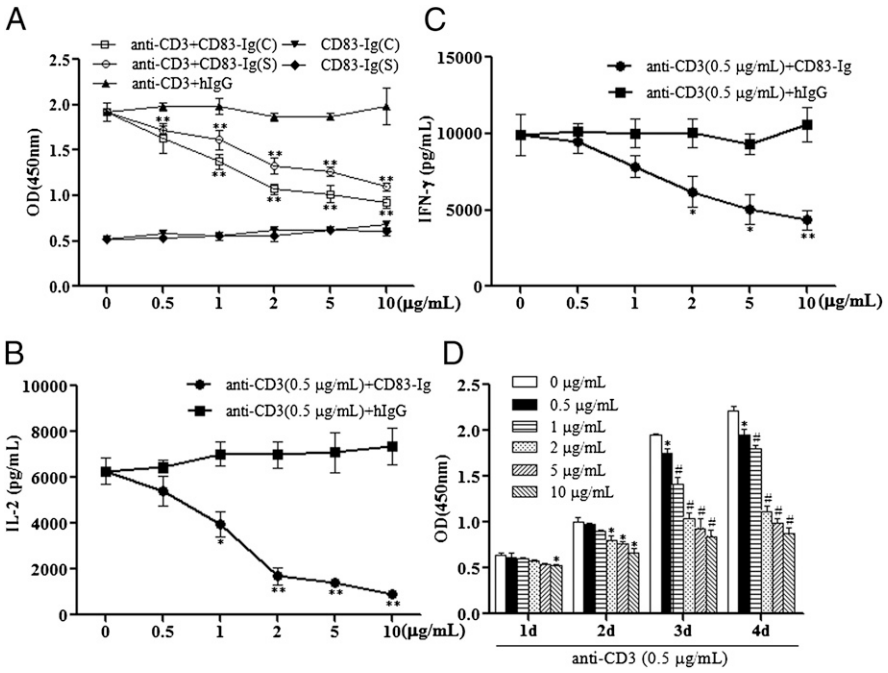

Fig. 1. CD83 inhibits anti-CD3–stimulated proliferation and production of IL-2 and IFN-γ by PBMCs. (*A–C*) PBMCs were stimulated with plate-bound anti-CD3 mAb (0.5 μg/mL) for 72 h in the presence of various amounts of soluble (S) or coimmobilized (C) CD83-Ig. Cell proliferation (*A*) and production of IL-2 (*B*) and IFN-γ (*C*) in supernatants were analyzed. (*D*) Kinetic analysis of proliferation of PBMCs stimulated with anti-CD3 in the presence of various amounts of coimmobilized CD83-Ig. Data shown are representative of at least five independent experiments. *A, B,* and *C*: $*P < 0.05$, $**P < 0.01$ compared with anti-CD3+ hIgG. *D*: $*P < 0.05$, $^{\#}P < 0.01$ compared with anti-CD3.

were stimulated for another 72 h. Compared with the hIgG control, pretreatment with CD83-Ig led to 20–50% inhibition of PBMC proliferation, depending on the length of pretreatment (Fig. S3*B*).

Putative CD83 Counter Receptor Is Expressed Predominantly on Monocytes. To explore further whether monocytes are involved in CD83-induced T-cell inhibition, expression of the putative CD83 receptor on $CD14^+$ monocytes and $CD3^+$ T cells was examined by flow cytometry. To avoid any artifact by fragment crystallizable γ (Fcγ) binding, all cell subtypes were blocked with Fc receptor blocker before any antibody incubation. In fresh PBMCs, CD83 was found to bind to ∼65% of $CD14^+$ monocytes, but the percentage decreased to ∼38% after 24-h culture of PBMCs at 37 °C (Fig. S4*A*). However, almost no binding of CD83 protein was observed in freshly isolated $CD3^+$ cells (Fig. S4*B*). After stimulation with anti-CD3 and anti-CD28 mAb for 3 d, the expression of the counter receptor on T cells increased insignificantly to about 2% (Fig. S4*B*). Thus, the putative CD83 receptor is expressed mainly on monocytes.

Soluble Factors Produced by Monocytes Are Involved in CD83-Stimulated Inhibition of T-Cell Responses. Next, we examined whether monocytes are responsible for CD83-induced suppression of T-cell proliferation and production of IL-2 and IFN-γ and, if so, whether cell contact is critical. Purified monocytes were left untreated or were cultured with immobilized or soluble CD83-Ig for 24 h. Cell-free supernatants then were collected and added to T cells, which subsequently were stimulated with anti-CD3 and anti-CD28 mAbs for 72 h. As expected, adding CD83-conditioned medium to the culture resulted in 51% and 48% suppression, respectively, of T-cell proliferation, as compared with the negative control (Fig. 2*A*). The extent of inhibition is comparable with that observed in PBMCs (Fig. 1*A*). Likewise, secretion of IL-2 and IFN-γ was inhibited by ∼78% and ∼45%, respectively (Fig. 2*B*). In contrast, addition of purified hIgG-conditioned medium did not show significant reduction in either T-cell proliferation or cytokine production. These data further support the notion that soluble mediators secreted by CD83-pretreated monocytes exert the inhibitory effects on T cells.

PGE_2 Is Specifically Up-Regulated by CD83. Because soluble factors were responsible for mediating T-cell suppression, we decided to determine the nature of these factors. The candidate factors include IL-10, TGF-β, and PGE_2 because they are known to suppress T-cell responses (14–16). We first quantified these factors in supernatants collected from monocytes cultured with CD83-Ig. As shown in Fig. 3 *A–C*, addition of CD83 to culture did not up-regulate the levels of IL-10 and TGF-β. Monocytes cultured in vitro produced PGE_2 at 3,421 ± 346 pg/mL at 12 h, 6,392 ± 1,075 pg/mL at 18 h, and 7,365 ± 1,175 pg/mL at 24 h. Incubating monocytes with CD83 for 12, 18, and 24 h further increased levels of PGE_2 to 8,540 ± 1,139, 15,504 ± 3,528, and 19,251 ± 2,404 pg/mL, respectively. We also noted that LPS increased the level of PGE_2 in monocyte cultures (Fig. 3*B*). Unlike CD83 stimulation, LPS-treated monocytes also produced 1,195 ± 234, 1,920 ± 528, and 2,375 ± 563 pg/mL IL-10 at 12, 18, and 24 h, respectively (Fig. 3*A*), although the TGF-β level was unchanged (Fig. 3*C*).

Besides immune-suppressive factors, we assessed levels of IL-1β, TNF-α, and IL-6 in monocyte cultures because these inflammatory cytokines also are strongly correlated with the production of PGE_2 (17, 18). As shown in Fig. 3 *D–F*, CD83 did not affect the levels of these cytokines. In contrast, LPS stimulated greater IL1-β, IL-6, and TNF-α production by monocytes. PGE_2 is made from arachidonic acid, and the reaction is catalyzed by COX-2, which is expressed at low levels in most tissues but can be highly induced during inflammation (19). In contrast, COX-1 is considered a constitutive enzyme and is thought to play a role in basal physiological functions. COX-1 was shown not to be responsible for PGE_2 production in monocytes (20). We then examined COX-2 expression by Western blotting in monocytes

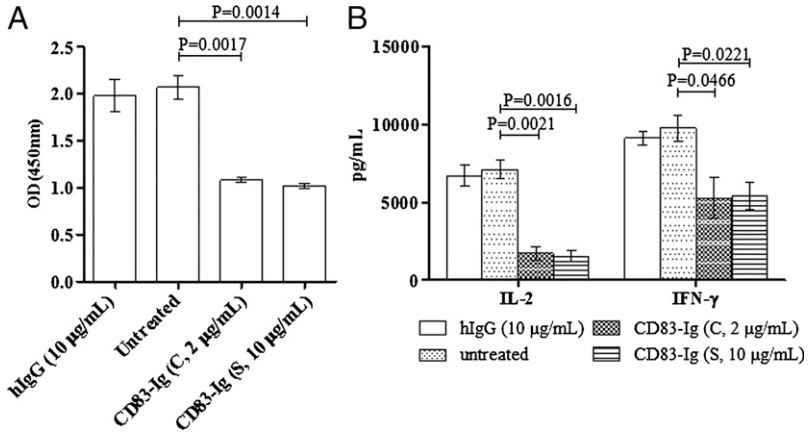

Fig. 2. Cell-free supernatants from CD83-Ig–pretreated monocytes inhibit T-cell proliferation and IL-2 and IFN-γ production. Purified monocytes were pretreated with plate-coated (C) or soluble (S) CD83-Ig for 24 h; then cell-free supernatants were transferred to culture-purified T cells stimulated with anti-CD3/CD28 mAb. Seventy-two hours later, cell proliferation (*A*) and IL-2 and IFN-γ production (*B*) of T cells were measured.

cultured with CD83-Ig or LPS for various time points. As shown in Fig. 3*G*, COX-2 was not present in resting monocytes, but a time-dependent increase in its expression was observed in CD83 or LPS-treated $CD14^+$ monocytes. The similarity in the kinetics of COX-2 expression and PGE_2 production further supports the notion that the COX-2–PGE_2 pathway is activated in monocytes cultured with CD83.

Involvement of NF-κB in PGE_2 Up-Regulation by CD83. To gain mechanistic insights into the induction of PGE_2 by CD83, we performed an oligonucleotide array-based transcription factor assay (OATFA) to profile genome-wide active transcription factor (TF) in CD83-stimulated monocytes. As shown in Fig. 4*A* and Fig. S5, the DNA-binding activities of NF-κB were significantly different (ratio >1.5) in unstimulated and stimulated cells. It has been reported that COX-2 has two putative NF-κB–binding sites in its 5′-promoter region (21); therefore we decided to validate the activation of NF-κB further by an ELISA-based assay. Using this assay, we showed that CD83 induced an approximately threefold increase in NF-κB–binding activities (Fig. 4*B*). Next, the specific NF-κB inhibitor pyrrolidine dithiocarbamate (PDTC) was used to assess the regulation of PGE_2 by NF-κB. As shown in Fig. 4*C*,

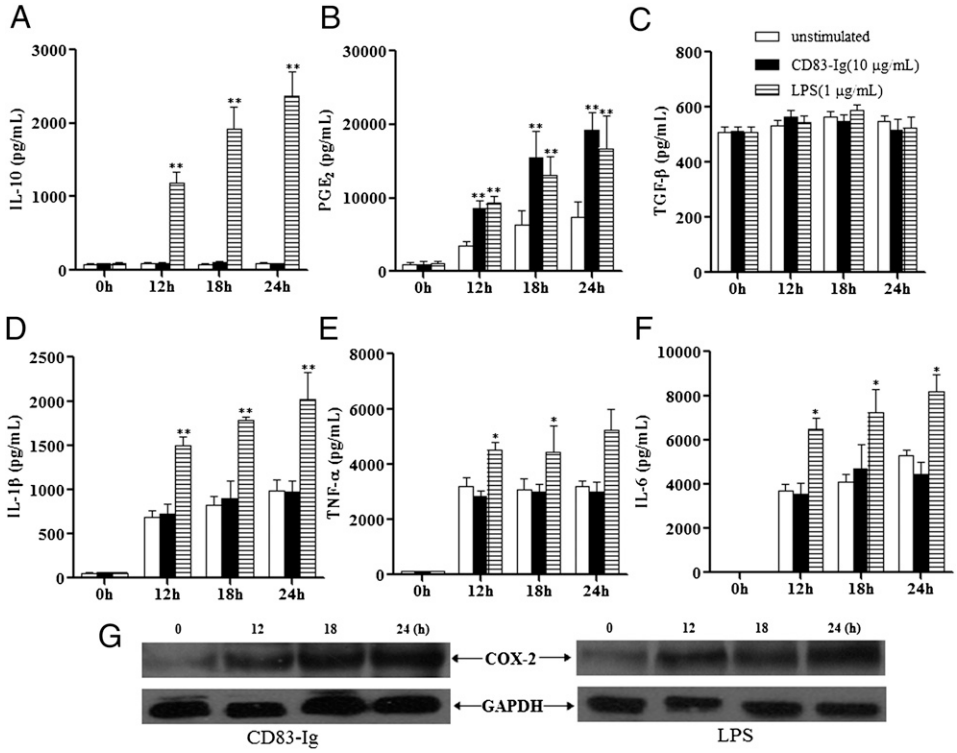

Fig. 3. COX-2 and PGE_2 are specifically up-regulated by CD83 in monocytes. Purified monocytes were left unstimulated or were pretreated with LPS or plate-bound CD83-Ig for 12–24 h. Then supernatants were collected and subjected to ELISA of secreted IL-10 (*A*), PGE_2 (*B*), TGF-β (*C*), IL-1β (*D*), TNF-α (*E*), and IL-6 (*F*). The pelleted monocytes were subjected to Western blotting analysis of COX-2 expression by immunoblotting with anti–COX-2 mAb (*G*). *A*–*F*: $*P < 0.05$, $**P < 0.01$ compared with untreated control. Data shown are representative of two independent experiments.

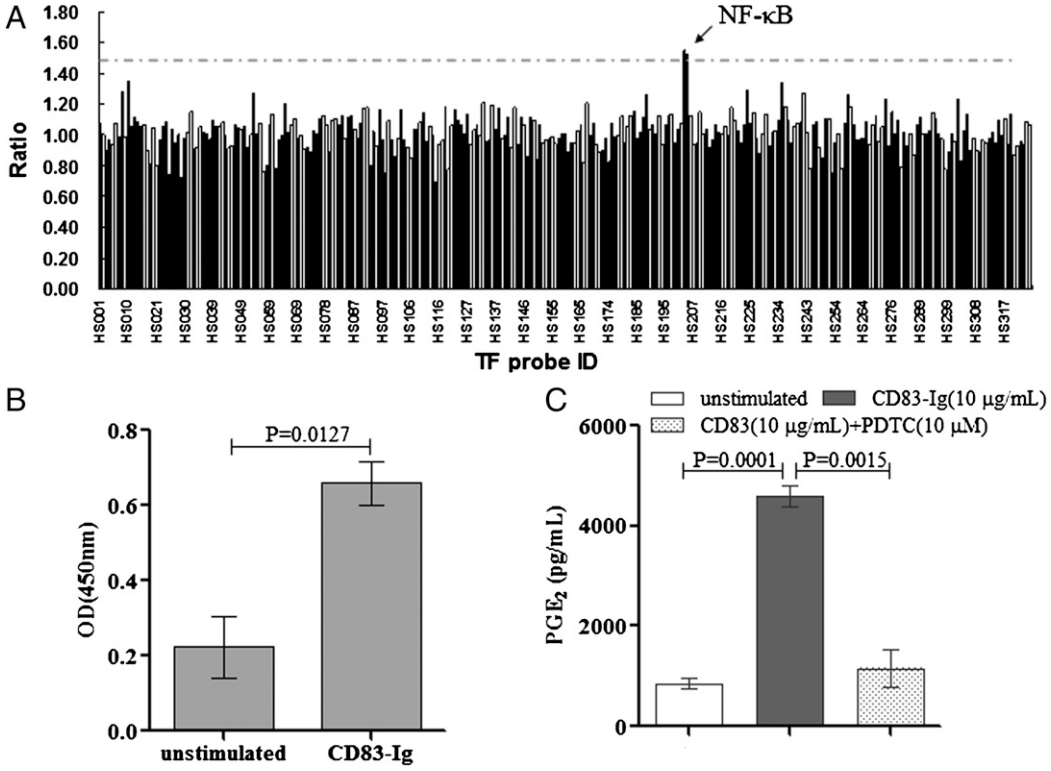

Fig. 4. NF-κB activation is required for CD83-mediated PGE_2 production. (*A* and *B*) Purified monocytes were left unstimulated or were stimulated with plate-bound CD83-Ig (10 μg/mL) for 12 h. Then nuclear extracts were used for an oligonucleotide array-based TF assay (positive signals are identified if the median of ratio is >1.5) (*A*) or for an ELISA-based assay of NF-κB (*B*). (*C*) Purified monocytes were stimulated with plate-bound CD83-Ig (10 μg/mL) in the presence or absence of PDTC (10 μM) for 24 h. Then supernatants were collected for the PGE_2 assay. Data shown are representative of three independent experiments.

10 μM PDTC resulted in fourfold reduction of PGE_2 level as compared with CD83 stimulation alone. These results indicate that NF-κB is required for PGE_2 induction by CD83 in monocytes.

NS-398 Reverses CD83-Triggered Inhibition of T-Cell Responses. To investigate further whether up-regulated PGE_2 is responsible for the observed inhibition of T-cell activation, we performed COX-2–blocking experiments. First, PBMCs were stimulated by plate-bound anti-CD3 mAb in the presence of CD83-Ig. The selective COX-2 inhibitor NS-398 was added, and exogenous PGE_2 was used as positive control. As expected, the incorporation of NS-398 to the coculture almost fully reversed the CD83-stimulated suppression on PBMCs proliferation (Fig. 5*A*). Second, purified $CD14^+$ monocytes were pretreated with CD83 in the presence or absence of NS-398 for 24 h. The cell-free supernatants were added to pure T cells, which then were activated by anti-CD3 and anti-CD28 mAbs for 72 h. Similarly, supernatants collected from cultures with CD83 plus NS-398 exerted little or no inhibitory effects, in contrast to cultures with CD83 alone (Fig. 5*B*). Collectively, these results support the idea that CD83 suppresses T-cell proliferation by stimulating PGE_2 production by monocytes.

Discussion

CD83 plays an important role in both the central and peripheral immune system. However, the underlying mechanisms by which CD83 regulates immune responses remain poorly understood. Here, we provide evidence that CD83 is able to up-regulate PGE_2 expression in monocytes, which in turn suppress T-cell proliferation and IL-2 and IFN-γ production by T cells. We further demonstrate that NF-κB is required for PGE_2 induction by CD83. Thus, our study establishes a mechanism by which CD83 regulates T-cell immune responses.

We have shown that cell-free supernatants collected from purified monocytes treated with CD83 substantially inhibit T-cell proliferation as well as the production of IL-2 and IFN-γ in T cells. This result strongly supports the hypothesis that monocytes are involved in mediating CD83-induced inhibition of T-cell responses. Furthermore, direct cell contact is not required for

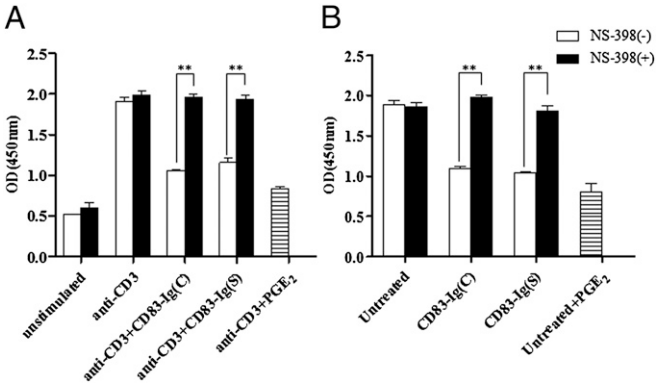

Fig. 5. The COX-2–specific inhibitor NS-398 reverses CD83-induced inhibition of T-cell proliferation. (*A*) PBMCs were stimulated with anti-CD3 mAb (0.5 μg/mL) for 72 h in the presence of soluble (S, 10 μg/mL) or coimmobilized (C, 2 μg/mL) CD83-Ig with or without NS-398 (10 μM). Anti-CD3 stimulation with exogenous PGE_2 (50 ng/mL) was used as a positive control. (*B*) Purified monocytes were pretreated with soluble (S, 10 μg/mL) or plate-coated (C, 2 μg/mL) CD83-Ig in the presence or absence of NS-398 (10 μM) for 24 h. Then cell-free supernatants were transferred to culture-purified T cells stimulated by anti-CD3/CD28 mAb. T cells cultured with supernatants from untreated monocytes in the presence of exogenous PGE_2 (50 ng/mL) were used as positive control. $^{**}P < 0.01$.

monocytes to exert their effects, and cell-free supernatants are able to suppress T cells. Among common inhibitory factors, PGE_2, but not IL-10 and TGF-β, is up-regulated potently in monocytes cultured with CD83. CD83 treatment did not result in elevated levels of inflammatory cytokines such as IL-1β, IL-6, and TNF-α. This result is in contrast with LPS, which induced a significant increase of these inflammatory cytokines in addition to IL-10 and PGE_2. Of note, Zhang et al. (22) showed that immune complex/Ig stimulated PGE_2 production from macrophages through Fcγ receptor IIb (FcγRIIb), an inhibitory Fc receptor with low affinity. Here, PGE_2 stimulated by our CD83-Ig fusion protein is unlikely to occur via FcγRIIb, because CD83-Ig is a monomer, and previous observations have shown that monomeric IgG is incapable of crosslinking low-affinity Fc receptors (23). Furthermore, the monomer could act as functional antagonist for FcγIIR, because it interferes with the binding of aggregated IgG to FcγIIR, although it itself did not elicit any responses (24). Importantly, we show that human IgG does not inhibit T-cell proliferation or cytokine production, and depletion of anti-CD83 reversed the effect of CD83-Ig. Last, we show that recombinant CD83-His has an inhibitory effect similar to that of CD83-Ig. Collectively, these data support the immune regulatory function of CD83.

We show that NS-398 reverses CD83-Ig–stimulated suppression of T-cell functions (Fig. 5). These results support the idea that PGE_2, an important immunomodulator, is responsible for CD83-stimulated inhibition of T cells as well as inhibition of IL-2 and IFN-γ production by T cells. PGE_2 has long been known as a key mediator in regulating the intensity and quality of cellular immune responses. Passwell et al (25) observed in Hodgkin's lymphoma that activated monocytes secreted markedly elevated levels of PGE_2 that might be responsible for declined cellular immunity in these patients. In addition, PGE_2 serves as mediator of $FoxP3^+CD4^+CD25^+$ adaptive regulatory T cells and suppresses effector T-cell functions (26). In recent years, the underlying mechanisms of PGE_2 inhibition on T cells have become increasingly clear with the discovery of its four specific receptors (27). PGE_2 is thought to inhibit T-cell responses by enhancing cAMP intracellular concentration (28).

The CD83 receptor and signaling cascade leading to production of PGE_2 remain elusive. We detected high-level expression of the putative CD83 receptor on monocytes but not on T cells (Fig. S4). This result is in agreement with previous observations (5, 6). The low level of CD83 receptor expression on T cells is in line with the lack of a direct effect of CD83 on T cells. In contrast, pretreatment of PBMCs and monocytes with CD83 was sufficient to induce their suppressive effects on T-cell proliferation (Fig. 2 and Fig. S3*B*), consistent with active signaling of the CD83 receptor on monocytes. We also show that NF-κB is activated in response to CD83 stimulation of monocytes. In addition, NF-κB inhibition greatly decreases PGE_2 production (Fig. 4). Undoubtedly, identification of putative CD83 receptor remains crucial for understanding CD83 function and its clinical application.

Materials and Methods

Production, Purification, and Characterization of Monomeric CD83-Ig. The extracellular domain of human CD83 cDNA (amino acids 1–128) and the Fcγ portion of human IgG1 were fused by using overlap extension PCR techniques. After purification on the protein G column (Pharmacia Biotech), CD83-Ig was subjected to dot-blot assay as previously described (29) and to Coomassie blue staining after SDS/PAGE. (See *SI Materials and Methods* and Fig. S1 for details.)

Isolation, Purification, and Activation of PBMCs, T Cells, and Monocytes. PBMCs collected from healthy donors (who provided informed consent) were isolated by Ficoll-Hypaque density-gradient centrifugation. Total $CD14^+$ monocytes and $CD3^+$ T cells were purified from PBMCs using a positive and negative enrichment kit (StemCell), respectively. All cells were stimulated in the presence or absence of CD83-Ig or CD83-His (Sino Biological). (See *SI Materials and Methods* for details.

Cell Proliferation Assay and Cytokine Measurements. Cell proliferation was performed by using the Cell Counting Kit-8 (Dojindo). The levels of IL-2 and IFN-γ in PBMC or T-cell culture supernatants and of TNF-α, IL-1β, IL-6, PGE_2, IL-10, and TGF-β in monocyte culture supernatants were measured in duplicate for each of the serial aliquots by ELISA kit (R&D Systems) in accordance with the manufacturer's instructions.

Specific Immunodepletion of CD83-Ig. CD83-Ig (4 μg/mL) was incubated with 2 μg/mL of anti-CD83 (clone HB15e) or mouse IgG1 for 30 min at 4 °C with gentle rotation. An equal volume of protein A polystyrene particles (4.0–4.9 μm; Spherotech) was added and incubated overnight (4 °C with gentle rotation). The beads were pelleted by centrifugation (20,000 × *g*, 15 min, 4 °C), and supernatants were harvested and used directly to coimmobilize with anti-CD3.

High-Throughput Profiling of Human Active TFs and ELISA-Based TF Activity Assay. Purified monocytes were left unstimulated or were stimulated with 10 μg/mL CD83-Ig for 12 h. After preparation of nuclear extracts, an OATFA and an ELISA-based NF-κB–activity assay were performed as previously reported (30, 31). Rabbit anti–NF-κB p65 (SC-372) and anti–NF-κB p50 (SC-114) polyclonal antibodies were from Santa Cruz Biotechnology.

Flow Cytometry Analysis. To detect the CD83 counterpart, PBMCs or T cells were incubated with Fc Receptor Blocker (Innovex Biosciences) for 0.5 h and then with CD83-Ig (20 μg/mL) for 1 h. Cells then were labeled with phycoerythrin-conjugated goat anti-human IgG Fc fragments (Sigma). Meanwhile, FITC-labeled mAbs against CD3 or CD14 were added, and a two-color acquisition protocol was used for flow cytometry analysis.

Statistical Analysis, All data are shown as mean values ± SEM. The one-sided student's *t* test was used to assess the effects of CD83-Ig or CD83-His on PBMC, monocyte, or T-cell proliferation and/and on cytokine secretion. The comparison between groups with or without NS-398 was analyzed by two-way ANOVA. *P* values <0.05 were considered statistically significant for all analyses.

ACKNOWLEDGMENTS. We thank Dr. Yimin Sun (CapitalBio) for assistance in the OATFA and ELISA-based TF assay. This work was supported by Grant 2007CB512402 from the National Program on Key Basic Research Project (973 Program), Grant IRT0849 from the Program for Changjiang Scholars and Innovative Research Team, Grants 30930085, 30330540, 30700728, and 30901789 from the National Natural Science Foundation of China, and by A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

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