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15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 inhibits IL-13 production in T cells via an NF-κB-dependent mechanism

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ABSTRACT

Interleukin (IL)-13 is a cytokine produced by activated $CD4^+$ T cells that plays a critical role in promoting allergic responses and tumor cell growth. The 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) is a natural ligand for the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ), a known regulator of anti-inflammatory activities. We determined the effects of 15d-PGJ_2 on IL-13 expression in the Jurkat E6.1 T-cell line and in peripheral blood mononuclear cells. Semi-quantitative reverse transcription-polymerase chain reaction and enzyme-linked immunosorbent assay revealed that treatment of activated T cells with 15d-PGJ_2 significantly decreased IL-13 mRNA transcription and secretion, respectively. This inhibition by 15d-PGJ_2 was independent of PPAR-γ since treatment with GW9662, an irreversible antagonist of the nuclear receptor, produced no effect. Our data also revealed the involvement of nuclear factor-κB in mediating 15d-PGJ_2-dependent down regulation of *IL-13* expression. Collectively, these results demonstrate the potential of 15d-PGJ_2 in attenuating expression and production of IL-13 in activated T cells.

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1. Introduction

The 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), a downstream metabolite of prostaglandin D_2 (PGD_2), is an emerging key immunoinflammatory mediator [1,2]. The 15d-PGJ_2 is a natural ligand for the peroxisome proliferator-activated receptor gamma (PPAR-γ). However, 15d-PGJ_2 also exhibits PPAR-γ-independent effects, such as regulation of the nuclear factor (NF)-κB pathway by direct inhibition and covalent modification of the IKKβ subunit of IKK [3,4].

Interleukin (IL)-13 is an immunoregulatory cytokine secreted predominantly by activated T-helper type 2 (Th-2) cells [5]. IL-13 was originally described as a cytokine involved in regulating inflammation and immune responses in monocytes and B cells [6]. More recently, however, this cytokine has been associated with many biological processes, including regulation of gastrointestinal parasite expulsion [7], airway hyper-responsiveness, allergic inflammation [8–10], IgE production in B cells [11], ulcerative colitis [12], fibrosis [13], and tumor cell growth [14].

IL-13 shares some functions with IL-4 but its regulation is poorly understood in T cells. Both cytokines play pivotal roles in regulating Th-2 cytokine-mediated immune responses and acting as a counter-regulatory system for Th-1 immune responses [15]. IL-4 and IL-13 share a 25–30% amino acid homology and their similar biological roles have been attributed to common receptor components [15].

In this study, we investigated the ability of 15d-PGJ_2 to regulate IL-13 gene expression and production. We demonstrate that 15d-PGJ_2 strongly attenuated *IL-13* expression from activated T cells through transcriptional repression involving the NF-κB transcription factor. Our data suggests a potential role for 15d-PGJ_2 in regulating *IL-13* expression in activated T cells.

2. Materials and methods

2.1. Reagents

Phorbol 12-myristate 13-acetate (PMA), phytohemagglutinin-L (PHA-L), ionomycin, IL-2, and GW9662 were purchased from Sigma (Oakville, ON, Canada). 15d-PGJ_2 was purchased from EMD Chemicals (Mississauga, ON, Canada). α-CD3 antibody was purchased from eBioscience (San Diego, CA, USA) and α-CD28 antibody was obtained from BD Biosciences (Mississauga, ON, Canada).

2.2. Cell culture

The human acute $CD4^+$ T-cell line Jurkat E6.1 (ATCC, Manassas, VA, USA) was grown in 5% CO_2 in RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum (FBS), 0.5 mM sodium pyruvate, 100 U/ml penicillin–streptomycin, and non-essential

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amino acids (all from Wisent, St.-Bruno, QC, Canada). Peripheral blood mononuclear cells (PBMCs) were isolated from healthy donors by lymphocyte separation medium (Wisent) according to the manufacturer's instructions and stimulated for 3 days with PHA-L (1 μg/ml) and IL-2 (30 U/ml) in RPMI 1640 containing10% FBS.

2.3. Transient transfections and luciferase assays

The plasmid pIL-13-luc (courtesy of Dr. Jana Stankova, Université de Sherbrooke) expresses the luciferase reporter gene under control of the *IL-13* promoter (−940 to +48). Jurkat E6.1 cells were transfected using the DEAE-Dextran method [19] with 15 μg of pIL-13-luc vector. Cells were stimulated with PMA (20 ng/ml) and PHA (1 μg/ml) for 30 min, and treated with 15d-PGJ_2 (10 μM) for 24 h at 37 °C. Cell lysis buffer (50 μl) was added to each well before addition of 100 μl luciferase assay buffer [16]. Cell lysates were evaluated for luciferase activity using the LUMIstar Galaxy software (BMG Labtechnologies, Ortenburg, Germany).

2.4. Cell stimulations for mRNA analysis

Jurkat E6.1 cells (5×10^6 cells) or PBMCs (3×10^6 cells) were left untreated or stimulated in RPMI containing 10% FBS with PMA/ionomycin (20 ng/ml per 1 μM) or α-CD3 (5 μg/ml) and α-CD28 (2.5 μg/ml) for 0, 4, 6, 8, or 24 h. Alternatively, cells were cultured in the presence of 15d-PGJ_2 (10 μM) for 30 min before (pre-treatment) or after (post-treatment) T-cell activation with PMA/ionomycin or α-CD3/α-CD28.

2.5. Semi-quantitative reverse transcription-polymerase chain reaction (RT-PCR)

Total RNA was prepared from 2×10^6 stimulated cells using the QIAzol Lysis Reagent (QIAGEN, Valencia, CA, USA). Two micrograms were reverse-transcribed into cDNA in the presence of 200 U Moloney murine leukemia virus RT (Promega, Madison, WI, USA), 0.5 μg oligonucleotide $d(T)_{15}$, and 500 μM dNTP at 42 °C for 1 h. One microliter of cDNA was amplified with 0.25 μM each of forward (5′-GACCTTGTGCGGGCAGAAT-3′) and reverse (5′-TGCAGTGCCATCGAGAACAC-3′) primer, GAPDH primers [17]), 0.4 mM dNTP, 2 mM $MgCl_2$, and 1.25 units of Taq DNA polymerase (Roche, Indianapolis, IN, USA). PCR cycling conditions consisted of initial denaturation at 95 °C for 5 min and 30 cycles of 95 °C for 15 s, 60 °C for 1 min, 72 °C for 45 s, and an additional 7-min extension using the Power SYBR® Green PCR Master Mix (Applied Biosystems, Carlsbad, CA, USA) and the 7500 Real Time PCR System

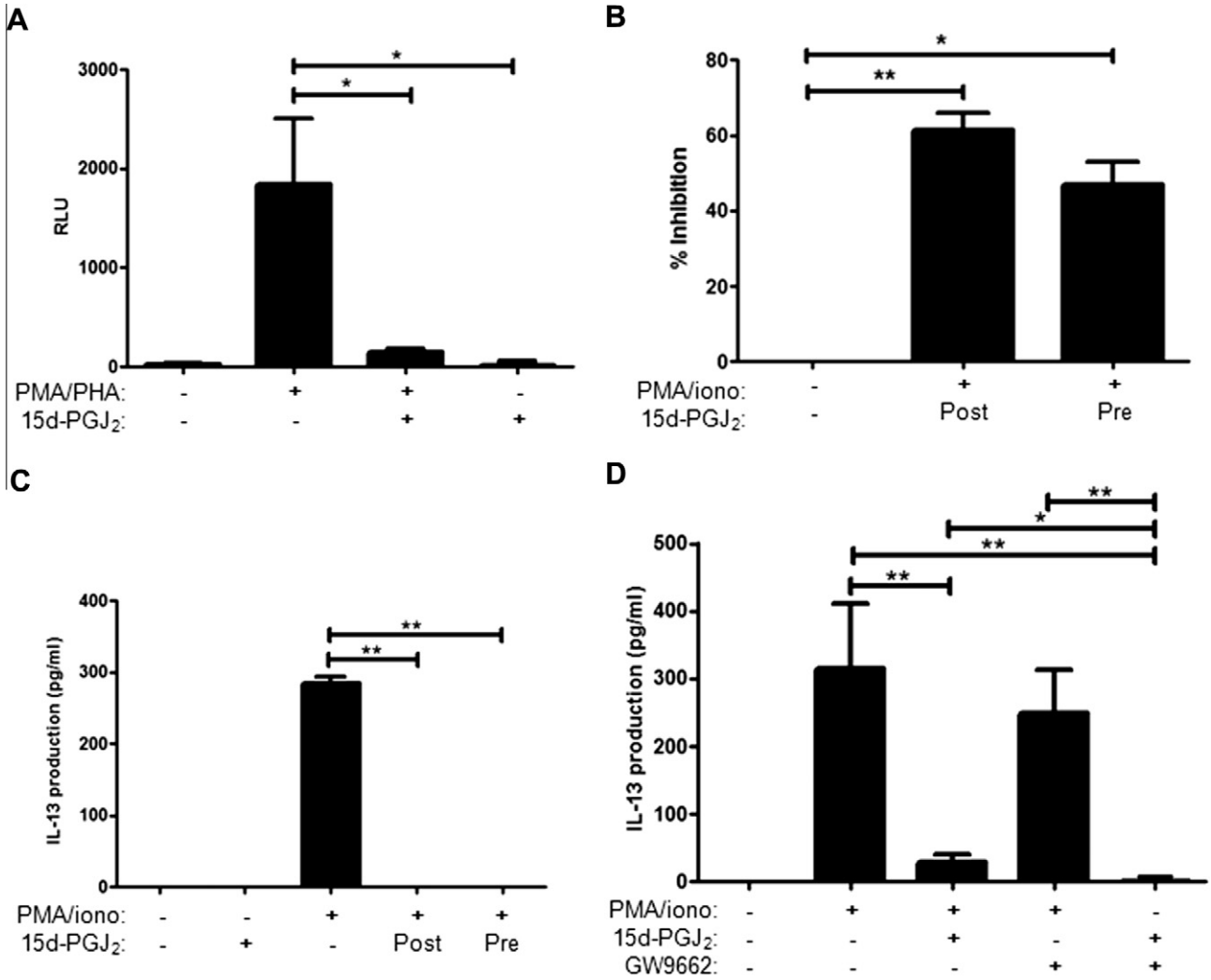

Fig. 1. 15d-PGJ_2 inhibits IL-13 expression in Jurkat E6.1 T cells via a PPAR-γ-independent mechanism. (A) Jurkat E6.1 cells were transiently transfected with pIL-13-luc, stimulated with PMA/PHA, and treated with 15d-PGJ_2. Cells were then lysed and luciferase activity was monitored. Data are graphed as the mean (± standard deviation) of four replicates and are expressed in relative luciferase units (RLUs). These results are representative of four independent experiments. PMA/ionomycin-activated Jurkat E6.1 cells were pre- or post-treated with 15d-PGJ_2 before measurement of (B) IL-13 mRNA by real-time RT-PCR ($n = 4$) and (C) secreted IL-13 protein by ELISA ($n = 3$). (D) Cells were pre-treated with the PPAR-γ inhibitor GW9662 before stimulation with PMA/ionomycin or 15d-PGJ_2. Secreted IL-13 was measured by ($n = 4$). $^*p < 0.05$ and $^{**}p < 0.01$.

(Applied Biosystems). Preliminary experiments were performed to ensure the linearity of the PCR products. The inhibition of IL-13 mRNA production by 15d-PGJ_2 was calculated as the % of inhibition based on the PCR values ($\Delta\Delta$Ct) obtained: ($\Delta\Delta$Ct of PMA/iono − $\Delta\Delta$Ct of 15d-PGJ_2 treatment)/$\Delta\Delta$Ct of PMA/iono × 100%.

2.6. IL-13 measurements by enzyme-linked immunosorbent assay (ELISA)

Cells (1×10^6) were left untreated or were stimulated as described above in combination with pre- or post-treatment with 15d-PGJ_2. In some experiments, the irreversible PPAR-γ antagonist GW9662 (10 μM) was used as described elsewhere [18]. After incubation, cells were centrifuged and supernatants were analyzed using the Human IL-13 ELISA Kit (eBioscience).

2.7. Nuclear extracts and electromobility shift assay (EMSA)

Cells were stimulated as described above and nuclear extracts were prepared according to the microscale preparation of nuclear proteins [22]. EMSA was performed using either an NF-κB consensus probe (Santa Cruz Biotechnology, Santa Cruz, CA, USA) or an IL-13 p element-like probe [17,20]. Antibodies (0.2 μg/ml) against p65, p50, and nuclear factor of activated T cells (NFAT) were used (Santa Cruz Biotechnology).

2.8. Statistical analysis

Data are expressed as the mean obtained from triplicate or quadruplicate wells within the same experiment. Each experiment was performed at least three to five times to obtain the standard error of the mean. All data were analyzed using GraphPad Prism 5 Software (Graph Pad, San Diego, CA, USA) using the paired two-tailed Student's *t*-test. Depending on the experiment, a *p*-value less than 0.05 or 0.01 was considered statistically significant.

3. Results

3.1. 15d-PGJ_2 inhibits PMA-induced IL-13 expression in T cells

We initially examined the effects of 15d-PGJ_2 on *IL-13* promoter activity. Jurkat E6.1 T cells were transiently transfected with a vector encoding the luciferase gene driven by the *IL-13* promoter. Cells were left untreated or stimulated with PMA/PHA and then treated with 15d-PGJ_2. As shown in Fig. 1A, we observed that PMA/PHA activation increased *IL-13* promoter-mediated luciferase activity approximately 36-fold. Addition of 15d-PGJ_2 to PMA/PHA-activated cells significantly inhibited this promoter activity by 96%, whereas treatment with 15d-PGJ_2 alone had no effect on luciferase activity. The trypan blue exclusion assay was conducted to verify that the suppressive effect of 15d-PGJ_2 was not due to a decrease in cell viability (data not shown).

Next, we assessed whether 15d-PGJ_2 inhibited IL-13 gene expression or cytokine production. Using semi-quantitative RT-PCR, we determined whether 15d-PGJ_2 can modulate IL-13 mRNA transcription in activated Jurkat E6.1 T cells. Kinetic experiments showed that stimulation of Jurkat E6.1 cells with PMA/ionomycin for 0, 4, 6, 8, and 24 h increased IL-13 mRNA transcription in a time-dependent manner (data not shown). Treatment with PMA/ionomycin for 8 h increased mRNA expression approximately 131-fold. Not surprisingly, pre-treatment of Jurkat E6.1 cells with 15d-PGJ_2 significantly inhibited PMA/PHA-induced IL-13 mRNA expression up to 61% (Fig. 1B). Addition of 15d-PGJ_2 after an 8 h PMA/PHA stimulation (post-treatment) also resulted in a similar inhibitory effect. Consistent with these results, IL-13 cytokine production in PMA/ionomycin-treated Jurkat E6.1 cells was inhibited completely by 15d-PGJ_2 (Fig. 1C).

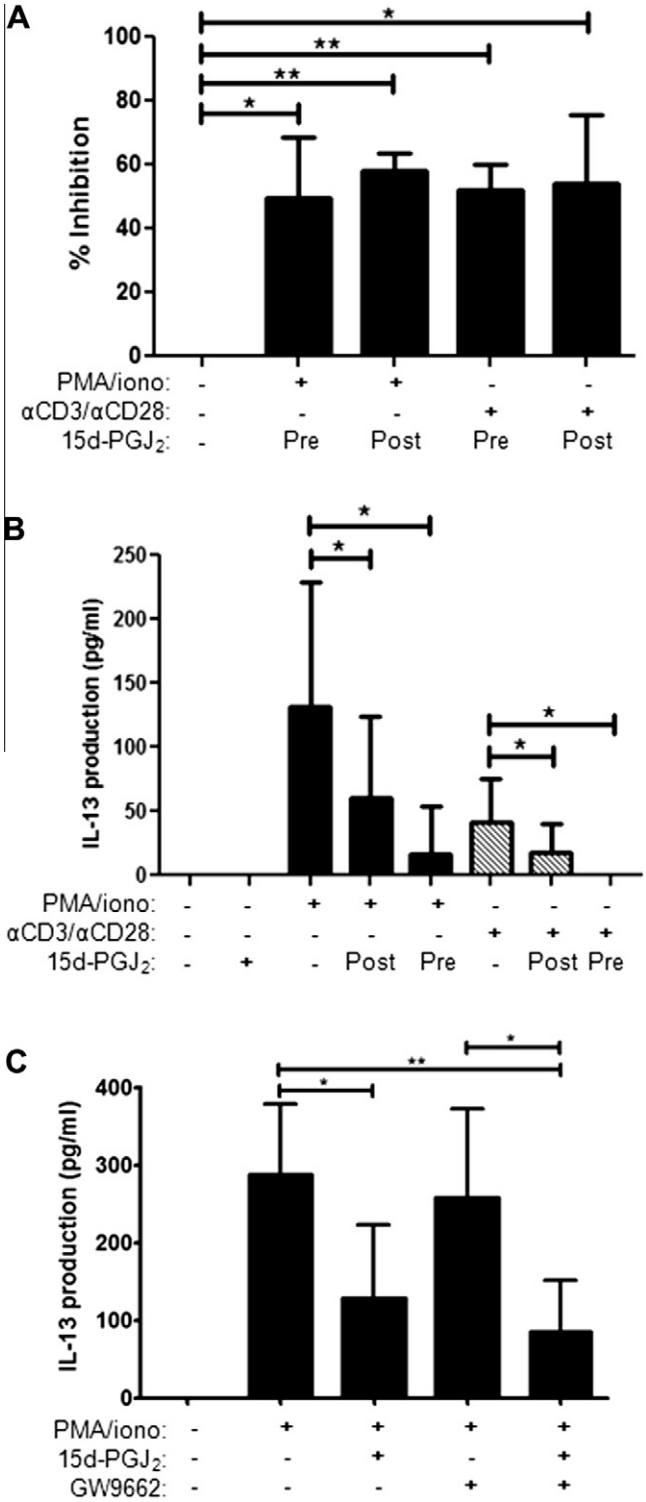

Fig. 2. 15d-PGJ_2 inhibits IL-13 expression and cytokine production in PBMCs. PBMCs pre- or post-treated for 30 min with 15d-PGJ_2 were left untreated or activated with PMA/ionomycin or α-CD3/α-CD28. (A) Cells were incubated for 8 h before measurement of IL-13 mRNA by real-time RT-PCR ($n = 3$). Results are shown as a percentage (%) of inhibition compared to PMA/ionomycin-treated cells. (B) Secreted IL-13 protein in culture supernatants was assessed by ELISA ($n = 5$ for black series, $n = 4$ for grey series). (C) Jurkat E6.1 cells were pre-treated with GW9662 for 30 min before stimulation with PMA/ionomycin or 15d-PGJ_2. Secreted IL-13 protein in culture supernatants was measured by ELISA ($n = 5$). $^{*}p < 0.05$ and $^{**}p < 0.01$.

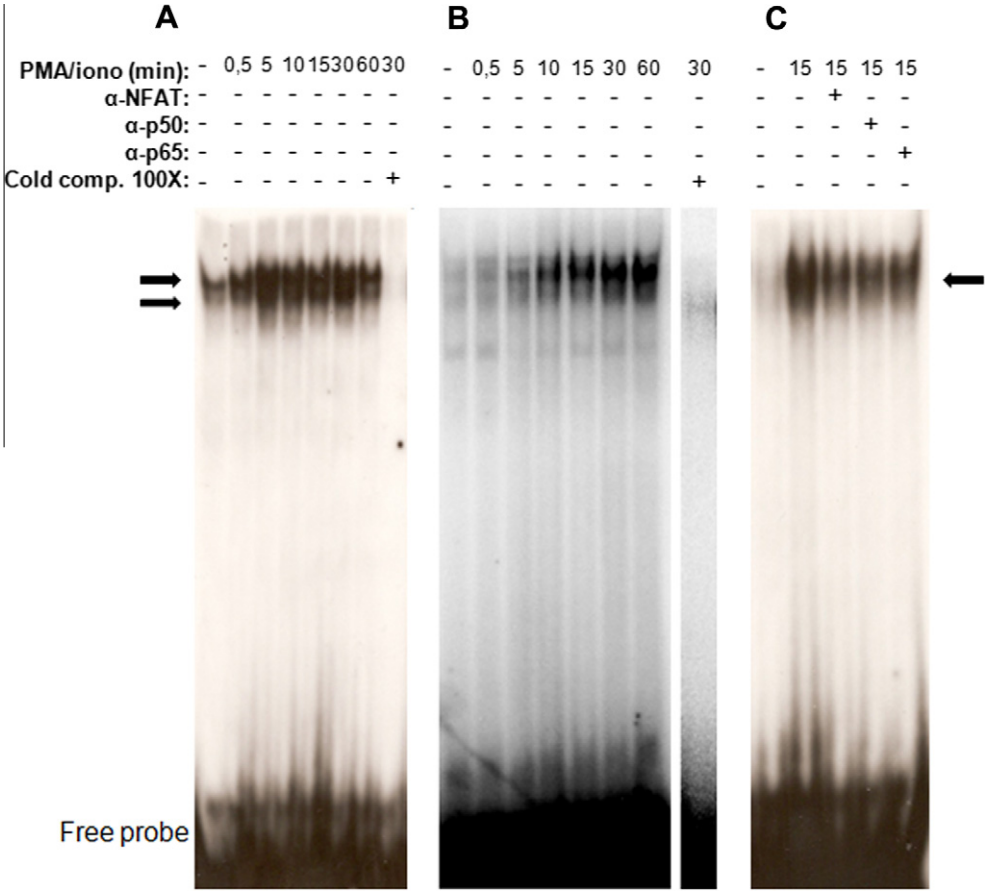

Fig. 3. PMA/ionomycin stimulation induces NFAT and NF-κB binding to the IL-13 p element-like probe. Transcription factor binding to the IL-13 p element-like probe was tested by EMSA with nuclear extracts isolated from (A) Jurkat E6.1 cells and (B) PBMCs stimulated with PMA/ionomycin for the times indicated ($n = 3$). (C) Nuclear extracts from PBMCs either left untreated or treated for 15 min with PMA/ionomycin were subjected to EMSA in the presence of antibodies against NFAT, NF-κB p50, or NF-κB p65 for 20 min before addition of the IL-13 p element-like probe ($n = 4$).

To test whether 15d-PGJ_2 regulates PMA/PHA-induced IL-13 expression through a PPAR-γ-dependent or independent mechanism, we treated cells with the PPAR-γ inhibitor GW9662 and examined IL-13 production by ELISA. This inhibitor covalently modifies the PPAR-γ ligand-binding domain and acts as an irreversible antagonist [24]. However, GW9662 did not relieve the inhibitory effect of 15d-PGJ_2 on PMA/ionomycin-induced IL-13 production (Fig. 1D). Furthermore, GW9662 alone showed little significant effect on IL-13 production. To assess whether the inhibitor blocked the activity of 15d-PGJ_2, Jurkat E6.1 cells were treated with GW9662 for 30 min before PMA/ionomycin stimulation in combination with 15d-PGJ_2. Our ELISA results show that GW9662 did not affect 15d-PGJ_2-mediated inhibition of IL-13 cytokine production (Fig. 1D). These results suggest that 15d-PGJ_2 suppresses PMA/ionomycin-mediated IL-13 production in Jurkat E6.1 cells through a PPAR-γ-independent pathway.

These experiments were repeated on PBMCs using α-CD3/α-CD28 as a physiologic stimulus and PMA/ionomycin as a mitogenic one. Stimulation with PMA/ionomycin and α-CD3/α-CD28 led to a time-dependent induction of IL-13 mRNA (data not shown). Pre- and post-treatments with 15d-PGJ_2 drastically inhibited ($p < 0.01$) IL-13 mRNA production in PBMCs (Fig. 2A). ELISA confirmed the inhibition of IL-13 protein production in these cells (Fig. 2B). The results also showed that pre- and post-treatments of PBMCs with 15d-PGJ_2 significantly blocked PMA/ionomycin- and α-CD3/α-CD28-induced IL-13 protein secretion. Pre-treating cells with 15d-PGJ_2 resulted in greater inhibition of IL-13 production than treating cells after stimulation. Like Jurkat T cells, 15d-PGJ_2 affected PMA/ionomycin-induced IL-13 production in PBMCs through a PPAR-γ-independent pathway (Fig. 2C).

3.2. 15d-PGJ_2 abrogates transcription factor binding to the human IL-13 promoter

We next proceeded to identify the transcription factors involved in regulating IL-13 production. Nuclear extracts isolated from activated Jurkat E6.1 cells (Fig. 3A) and PBMCs (Fig. 3B) were subjected to EMSA with the IL-13 p element-like probe. Fig. 3A shows two bands that have increased intensity following Jurkat E6.1 stimulation with PMA/ionomycin. Only one band was modulated in PBMCs. Specific binding was confirmed by competition with 100-fold molar excess of unlabelled oligonucleotide. The observed band was supershifted with the addition of polyclonal antibodies against NFAT, as well as the p50 and p65 subunits of NF-κB. Thus, these data suggest that a protein complex consisting of both NFAT and NF-κB bound to the IL-13 p element-like probe in stimulated Jurkat E6.1 T cells and PBMCs (Fig. 3C).

Because our results demonstrated that IL-13 mRNA and cytokine production were inhibited by 15d-PGJ_2, which has also been shown to interfere with NF-κB [21], we hypothesized that this prostaglandin affects transcription factor binding to the *IL-13* promoter. As expected, pre-treatment of Jurkat E6.1 cells with 15d-PGJ_2 considerably decreased the binding intensity of the upper complex to a probe containing the NF-κB consensus binding site (lane 4, Fig. 4A). Likewise, pre-treatment with 15d-PGJ_2 inhibited the formation of PMA/ionomycin-induced complexes onto the IL-

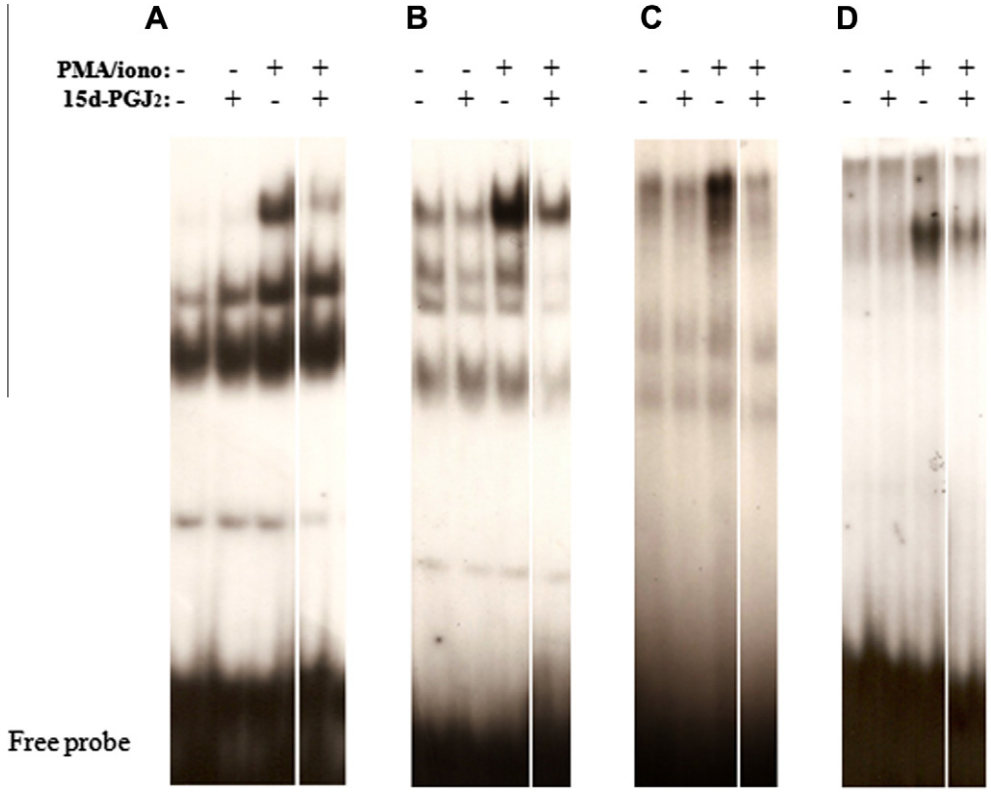

Fig. 4. 15d-PGJ_2 inhibits NF-κB binding to the IL-13 p element-like probe in both Jurkat E6.1 cells and PBMCs. Jurkat E6.1 cells were treated with 15d-PGJ_2 for 15 min before stimulation with PMA/ionomycin for 15 min. Nuclear extracts were then prepared and subjected to EMSA with the (A) NF-κB or (B) IL-13 p element-like probe. PBMCs were treated similarly and then nuclear extracts were subjected to EMSA with the (C) NF-κB or (D) IL-13 p element-like probe ($n = 3$ for all experiments).

13 p element-like probe (Fig. 4B). Similar results were also observed in PBMCs using both the NF-κB and IL-13 p element-like probes (Fig. 4C and D). These findings indicate that the effects of 15d-PGJ_2 on IL-13 gene expression and production are at least partly mediated by the inhibition of NF-κB binding to the *IL-13* promoter in Jurkat E6.1 cells and PBMCs.

4. Discussion

IL-13 plays multiple immunomodulating functions in T cells [22–25]. The importance of this cytokine is further highlighted by its link to leukemogenesis in Hodgkin's lymphoma [26] and possibly the pathogenesis of Dalton's lymphoma, a malignant T-cell lymphoma characterized by very high IL-13 serum titers [27]. Therefore, understanding the mechanisms that regulate *IL-13* gene expression in T cells is essential. Recently, 15d-PGJ_2 has gained research interest since it was found to be an important immunomodulatory molecule (reviewed in [1]). In the present study, we demonstrate for the first time that 15d-PGJ_2 inhibits *IL-13* promoter activation, mRNA expression, and protein production in T cells (Figs. 1 and 2). We also examined whether 15d-PGJ_2 exerts its inhibitory activity via a PPAR-γ-dependent manner. Blocking the PPAR-γ receptor with a specific antagonist, GW9662, failed to interfere with 15d-PGJ_2-mediated inhibition of IL-13 production (Figs. 1B and 2C), suggesting that this function of 15d-PGJ_2 occurs via a PPAR-γ-independent mechanism. Other cytokines have been shown to be regulated similarly, including IL-1β in human chondrocytes [28], IL-8 in endothelial cells [29], and IL-4 in murine $CD4^+$ T cells [30].

IL-13 gene expression is regulated by the transcription factor NFAT, which has been shown to be important for IL-13 production in TPA/ionomycin- and α-CD3/α-CD28-activated T cells [20,31]. Our EMSA data confirmed that NFAT, as well as NF-κB, translocates to the nucleus in activated T cells and binds the IL-13 p-element-like probe (Fig. 3). The IL-13 p element-like site has been described as a dual-responsive element to which NF-κB and NFAT compete for binding in HTLV-1 infected T cells [32]. NFAT consists of a highly conserved DNA-binding domain of approximately 300 amino acids that exhibits little sequence homology but significant structural homology with the DNA-binding domain of Rel/NF-κB [33]. 15d-PGJ_2 can covalently bind to IκB kinase, inhibiting its function and therefore the activation of NF-κB. Studies have also demonstrated 15d-PGJ_2-mediated inhibition of NF-κB DNA binding in a PPAR-γ-independent manner via alkylation of a conserved cysteine residue located within the NF-κB DNA-binding site [34].

In conclusion, we demonstrated that 15d-PGJ_2 interferes with NF-κB nuclear translocation to suppress IL-13 gene expression and production in activated T cells. Although our data reveal that this inhibition occurs via a PPAR-γ-independent pathway and involves the transcription factor NF-κB, further experiments are needed to determine the exact mechanism.

Acknowledgments

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