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Respiratory Syncytial Virus Infection Reduces Kynurenic Acid Production and Reverses Th17/Treg Balance by Modulating Indoleamine 2,3-Dioxygenase (IDO) Molecules in Plasmacytoid Dendritic Cells

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Respiratory syncytial virus (RSV) infection causes a world-wide medical and economic burden. This study analyzed the effects of RSV infection on plasmacytoid dendritic cells (pDCs) and evaluated the immunopathogenesis of RSV infection by measuring relative numbers of FoxP3+ Treg cells and Th17 cells.

Material/Methods: pDCs were isolated from human blood samples, purified using magnetic microbeads, and treated with RSV, IFN-γ, or vehicle. These cells were mixed with purified CD4+ T cells to yield preparations of pDCs+T cells+vehicle, pDCs+T cells+RSV, and pDCs+T cells+IFN-γ. Preparations of pDCs+T cells+RSV were also incubated with an inducer or an inhibitor of indoleamine 2,3-dioxygenase (IDO). Kynurenic acid concentration was measured by high-pressure liquid chromatography (HPLC). The differentiation of Foxp3+ Treg and Th17 cells from CD4+ T cells was determined by flow cytometry.

Results: pDCs were successfully isolated and purified using the magnetic microbeads. Compared with preparations of pDCs+T cells+vehicle, RSV infection (pDCs+T cells+RSV) significantly reduced and IFN-γ treatment (pDC+T cells+IFN-γ) increased kynurenic acid concentrations and the proportions of $Foxp3^+$ Tregs ($p<0.05$ each). Conversely, RSV infection increased and IFN-γ treatment decreased the proportions of Th17 cells ($p<0.05$ each). RSV infection reduced kynurenic acid concentrations and inhibited the transformation from Th17 to $Foxp3^+$ Tregs by modulating IDO molecules.

Conclusions: RSV infection reduced the production of kynurenic acid and inhibited transformation from Th17 to $Foxp3^+$ Tregs (Th17/Treg balance) by modulating IDO molecules in pDCs.

MeSH Keywords: Dendritic Cells • Indoleamine-Pyrrole 2,3,-Dioxygenase • Kynurenic Acid • Respiratory Syncytial Virus Infections • T-Lymphocytes, Regulatory

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Background

Respiratory syncytial virus (RSV) infection causes a major worldwide medical and economic burden [1]. RSV, a pneumovirus in the family *Paramyxoviridae*, is a negative-sense, enveloped, single-stranded RNA virus [2]. Approximately two-thirds of infants are infected with RSV during the first year of life and 95% within 2 years, making RSV the leading cause of childhood hospitalization for illnesses of the respiratory tract [3–5]. Many children who experience severe disorders from RSV infection develop asthma, which can persist to adulthood [6]. The annual financial burden of RSV infection and associated diseases in young children in the USA has been estimated at over 600 million dollars [7].

Natural RSV infection does not induce immunity that blocks RSV re-infection [8]. The pathogenesis of RSV has been associated with the inefficient functions of memory T cells and B cells and their compartments [9,10]. Exposure of immune system cells to RSV antigens induces ineffective or inappropriate RSV-specific immune responses [11]. In addition, RSV can infect cord blood-derived dendritic cells (DCs) by triggering the surface expression of cytokines and biomarkers [12]. Although RSV has been found to infiltrate both myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) [13], the mechanism by which RSV affects the differentiation of FoxP3+ Treg cells and Th17 cells has not been determined.

Interferon (IFN)-γ has been shown to play a critical role in pathogenic pathways induced by RSV infection [14]. Reduction of IFN-γ after RSV infection can attenuate the inflammatory responses of immune cells [15], exacerbating airway diseases. These reductions in IFN-γ, induced by specific antibodies or other drugs, can significantly alleviate RSV-related airway inflammation [16]. Therefore, this study utilized IFN-γ-treated pDCs as positive RSV-infected cells.

This study assessed the effects of RSV infection on pDCs and evaluated the immunopathogenesis of RSV infection by measuring relative numbers of FoxP3+ Treg cells and Th17 cells.

Material and Methods

Isolation of human plasmacytoid dendritic cells (pDCs)

Blood samples were collected from healthy blood donors aged >18 years at our hospital. Peripheral blood mononuclear cells (PBMCs) were separated from the blood samples by Ficoll-Paque plus gradient centrifugation, as described previously [17]. pDCs were isolated from PBMCs by positive selection and purification with the CliniMACS CD304 (BDCA-4/Neuropilin-1) Microbead kit (Cat. No. 130-029-101, Mitenyi Biotech., Bergisch Gladbach, Germany), according to the manufacturer's instructions. The pDCs were cultured in RPMI-1640 medium (Gibco BRL. Co. Ltd., Grand Island, NY, USA) containing 10% fetal bovine serum (FBS; Gibco BRL. Co. Ltd.), L-glutamine (2 mM final concentration, Sigma-Aldrich, St. Louis, MO, USA), and 100 µg/ml streptomycin/100 U/ml penicillin (Sigma-Aldrich).

RSV infection of pDCs

Human RSV (type 2) was purchased from the American Type Culture Collection (ATCC; Manassas, VA, USA). The multiplicity of infection (MOI) of RSV stock was evaluated by quantitative plaque-forming assays, as described previously [18], and adjusted to 1×10^7 plaque-forming units (pfu)/ml [18]. The pDCs were re-suspended at a density of 1×10^5 cells/ml in culture medium, and 1 ml was added to each well of a 24-well plate. The pDCs were pulsed with ovalbumin (OVA) containing <20 pg/mg lipopolysaccharide (LPS) and stimulated with 10 MOI RSV for 24 h.

Isolation of CD4+ T cells

CD4+ T cells were isolated from PBMC preparations as described previously [19], with a few modifications. Briefly, $CD4+CD45RA^+$ T cells were isolated from PBMCs by negative selection with MACS native $CD4^+$ T cell Isolation Kits (Cat. No. 130-096-533, Mitenyi Biotech) according to the manufacturer's instructions, and evaluated by flow cytometry on a FACSCalibur (Beckman Coulter, Brea, CA, USA) cell sorter with Flow-Jo software (version: 9.6.2, Flow-Jo LLC, Ashland, OR, USA).

Trial grouping

Preparations of 10^6 pDCs were infected with 10 MOI RSV for 24 h, treated with IFN-γ, or mixed with PBS. Each of these cell preparations was mixed with 10^6 CD4+ T cells to yield preparations of pDCs+T cells+vehicle, pDCs+T cells+RSV, and pDCs+T cells+IFN-γ. Where indicated, preparations of pDCs+T cells+RSV were treated with 5 µM of the indoleamine 2,3-dioxygenase (IDO) inhibitor 1-methyl-tryptophan (1-MT) [20] or 10 µM of the ISO inducer immunostimulatory sequence oligodeoxynucleotides (ISS-ODN) [21].

Kynurenic acid concentrations

Kynurenic acid concentrations were measured by high-pressure liquid chromatography (HPLC; Waters Co. Ltd., Milford, MA, USA), as described elsewhere [22]. In brief, 20 µl of each pDC supernatant was applied directly to a C18 reverse-phase column (3 µm), and kynurenic acid was eluted isocratically by the mobile phase, consisting of 50 mM sodium acetate, 250 mM zinc acetate, 3% acetonitrile, pH 6.2, at a flow-rate of 1 ml/min. Kynurenic acid in the eluate was measured

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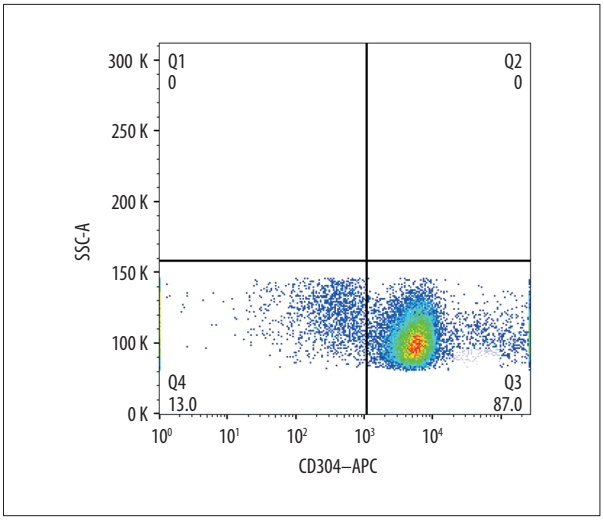

Figure 1. Magnetic microbead method of purifying pDCs. pDCs were assessed in cell preparations by flow cytometry analysis of expression of the biomarker CD304.

fluorimetrically, with an excitation wavelength of 344 nm and an emission wavelength of 398 nm, using a fluorescence detector (Model: S200, Perkin-Elmer Co. Ltd., Waltham, MA, USA). In pilot tests, newly produced kynurenic acid was measured with the mobile phase containing 4% acetonitrile. Concentrations of kynurenic acid were calculated from standard curves, as described previously [23].

Differentiation of Foxp3+ Treg and Th17 cells

Preparations of 10^6 human pDCs were incubated with 10 µl of APC-labeled mouse anti-human IL-17A antibody (Cat. No. 17-7179-41, eBioscience, Santiago, CA, USA) and 10 µl of PerCP-cyanine 5-labeled mouse anti-human Foxp3 antibody (Cat. No. 45-5773-80, eBioscience) at room temperature for 15 min. The cells were washed and re-suspended in PBS supplemented with 1% FBS (Gibco BRL. Co. Ltd.) and 0.1% NaN3 (Sigma-Aldrich). Cells were evaluated by flow cytometry (FACSCalibur, Beckman Coulter) and analyzed using Flow-Jo software (version: 9.6.2, Flow-Jo LLC). The percentages of total pDCs positive for IL-17 and Foxp3 were determined.

Statistical analysis

Results are reported as mean±standard deviation (SD) and compared by Bonferroni post hoc-validated ANOVA tests. All statistical analyses were performed using SPSS software (version: 20.0, SPSS Inc., Chicago, IL, USA), with $p<0.05$ defined as statistically significant.

Results

Successful isolation and purification of pDCs

Flow cytometry showed that incubation of PBMCs with magnetic microbeads markedly increased the percentage of cells positive for the pDC biomarker CD304 to 87% (Figure 1). These findings indicate that this method was successful in the isolation and purification of pDCs.

RSV infection reduced kynurenic acid concentration in pDCs

Based on a standard curve for calculating the concentration of kynurenic acid (Figure 2A), treatment of pDCs with RSV markedly reduced the production of kynurenic acid. HPLC showed that the concentration of kynurenic acid was significantly lower in the pDCs+T cells+RSV supernatants than in the pDCs+T cells+vehicle supernatants (Figure 2B, $P<0.05$). In

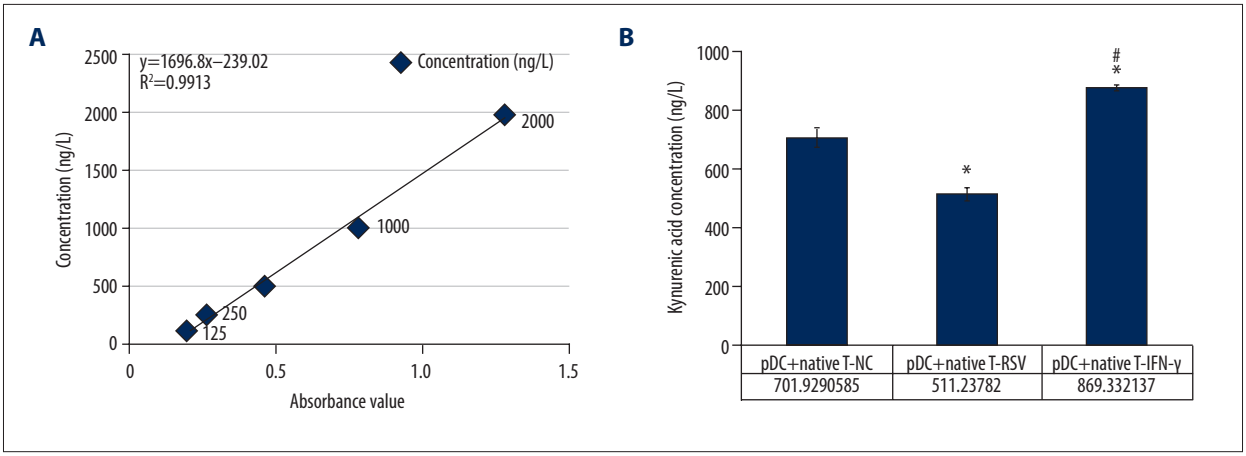

Figure 2. Determination of kynurenic acid concentrations in pDCs infected with RSV. (**A**) Standard curve for calculating kynurenic acid concentration. (**B**) Kynurenic acid concentrations in mixtures of pDCs and T cells. * $P<0.05$ compared with pDCs+T cells+vehicle. # $p<0.05$ compared with pDCs+T cells+RSV.

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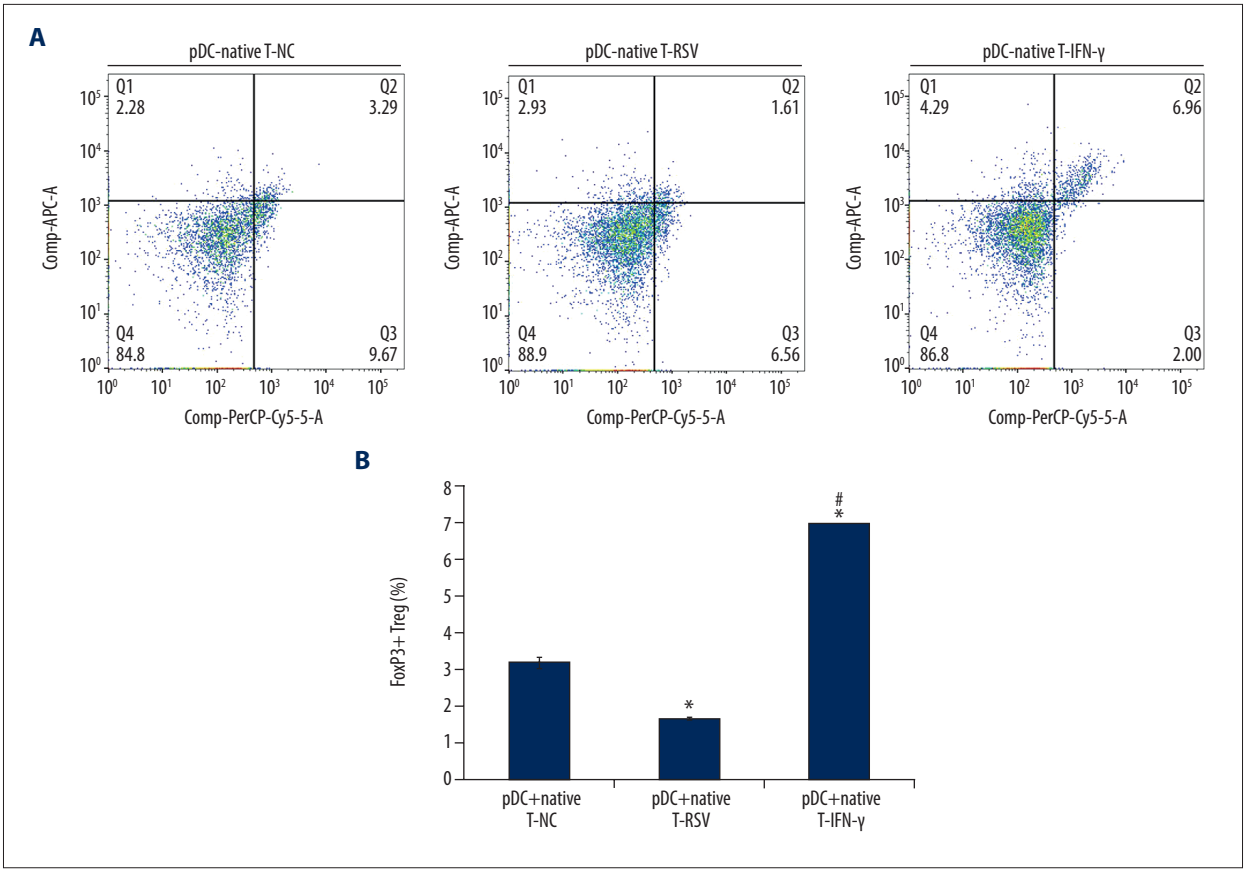

Figure 3. Effects of RSV infection on proportions of Foxp3⁺ Tregs derived from CD4+ T cells. (**A**) Flow cytometry analyses of Foxp3⁺ Treg cells in preparations of pDCs+T cells+vehicle, pDCs+T cells+RSV and pDCs+T cells+IFN-γ. (**B**) Statistical comparison of proportions of Foxp3⁺ Treg cells in these preparations. * $P<0.05$ compared with pDCs+T cells+vehicle. # $P<0.05$ compared with pDCs+T cells+RSV.

contrast, IFN-γ treatment of pDCs enhanced the production of kynurenic acid, with its concentration being significantly higher in the pDCs+T cells+IFN-γ than in the pDCs+T cells+vehicle and pDCs+T cells+RSV supernatants (Figure 2B, $P<0.05$ each).

RSV infection down-regulated proportion of Foxp3⁺ Tregs

Flow cytometry analysis of the proportions of Foxp3⁺ Tregs in the mixed cell preparations (Figure 3A) showed that the proportion of Foxp3⁺ Tregs was significantly lower in pDCs+T cells+RSV than in pDCs+T cells+vehicle preparations (Figure 3B, $P<0.05$) and that the proportion of Foxp3⁺ Tregs was significantly higher in pDCs+T cells+IFN-γ than in pDCs+T cells+vehicle and pDCs+T cells+RSV preparations (Figure 3B, $P<0.05$ each).

RSV infection up-regulated proportion of Th17 cells

Flow cytometry analysis (Figure 4A) also showed that the proportion of Th17 cells was significantly higher in pDCs+T cells+RSV than in pDCs+T cells+vehicle preparations (Figure 4B, $p<0.05$), whereas the proportion of Th17 cells was significantly lower in pDCs+T cells+IFN-γ than in pDCs+T cells+vehicle and pDCs+T cells+RSV preparations (Figure 4B, $P<0.05$ each).

RSV infection decreased kynurenic acid concentration through modulating IDO

To determine the mechanism by which RSV infection reduced kynurenic acid concentrations, pDCs were treated with the IDO inhibitor 1-MT or the IDO inducer ISS-ODN. Kynurenic acid concentrations were significantly lower in pDCs+T cells+RSV preparations treated than in those not treated with the IDO inhibitor 1-MT, but were significantly higher in pDCs+T cells+RSV preparations treated than not treated with the IDO inducer ISS-ODN (Figure 5, $P<0.05$ each).

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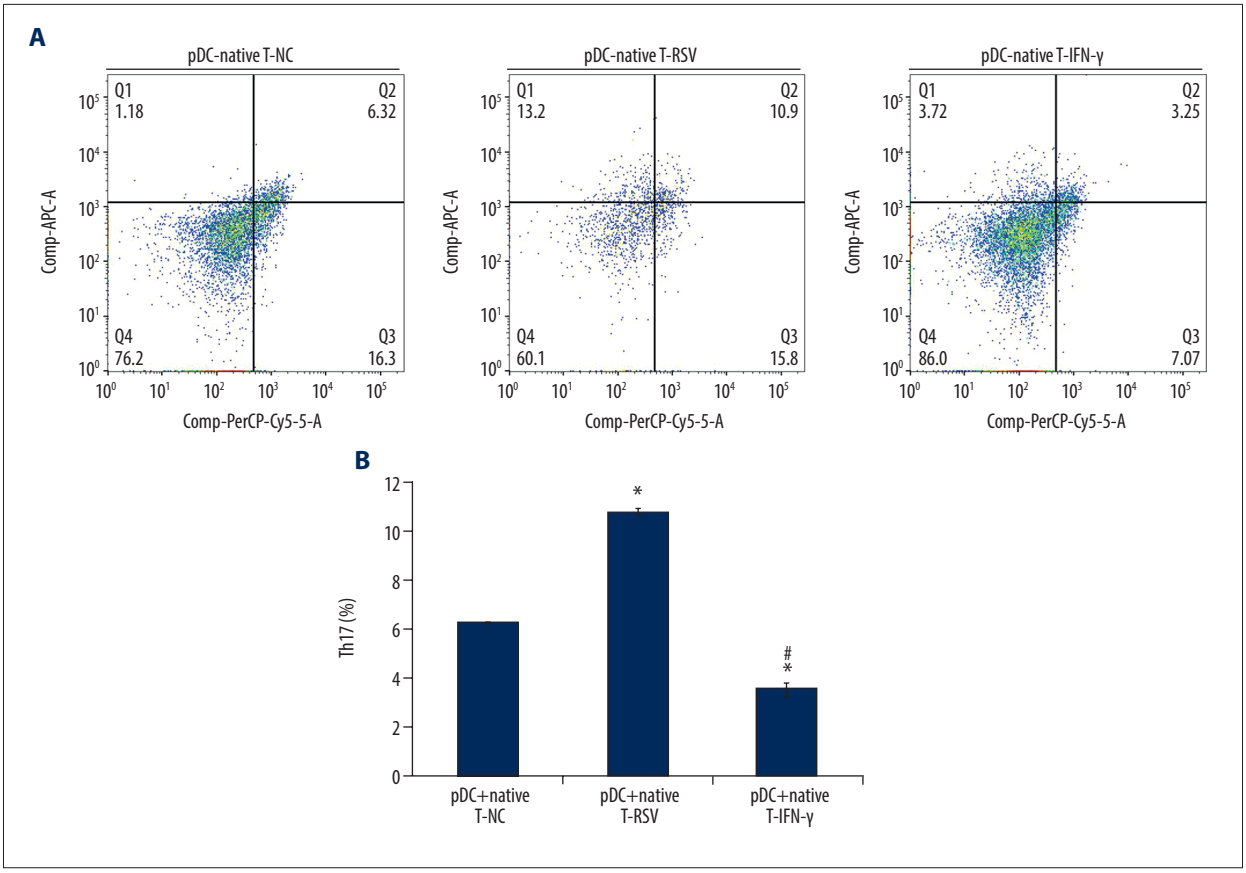

Figure 4. Effects of RSV infection on proportions of Th17 cells derived from CD4+ T cells. (**A**) Flow cytometry analyses of Th17 cells in preparations of pDCs+T cells+vehicle, pDCs+T cells+RSV and pDCs+T cells+IFN-γ. (**B**) Statistical comparison of proportions of Th17 cells in these preparations. * $P<0.05$ compared with pDCs+T cells+vehicle. # $P<0.05$ compared with pDCs+T cells+RSV.

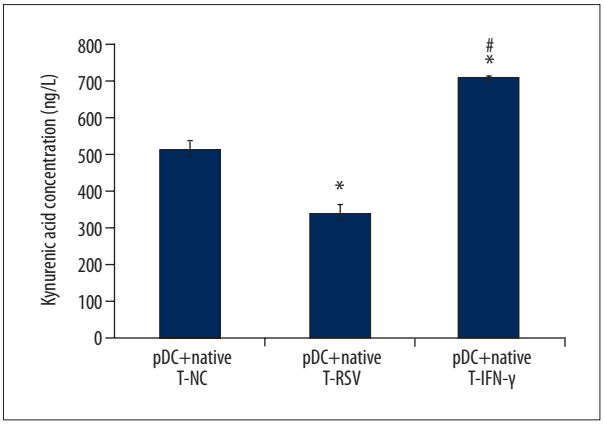

Figure 5. Effects of IDO inhibitor and IDO inducer on kynurenic acid concentrations in RSV-infected pDCs. * $P<0.05$ compared with pDCs+T cells+vehicle. # $P<0.05$ compared with pDCs+T cells+RSV.

RSV infection inhibited transformation from Th17 to Foxp3⁺ Tregs by modulating IDO

The effects of IDO inhibition and induction on RSV infection-induced changes in the proportions of Foxp3⁺ Tregs and Th17 pDCs were also evaluated by flow cytometry (Figure 6A, 6B). Treatment of pDCs+T cells+RSV preparations with IDO inhibitor significantly reduced the proportion of Th17 pDCs while significantly increasing the proportion of Foxp3⁺ Tregs (Figure 6C, $P<0.05$ each). Conversely, treatment of pDCs+T cells+RSV preparations with IDO inducer significantly increased the proportion of Foxp3⁺ Tregs while significantly reducing the proportion of proportion of Th17 pDCs (Figure 6C, $P<0.05$ each).

Discussion

RSV, a member of the Paramyxoviridae family, causes respiratory morbidity in both elderly individuals and infants [24]. RSV has been shown isocratically to activate human DCs and induce the production of immunomodulatory cytokines [25], including both the Th1-type cytokine IFN-γ and Th2-type cytokines [26].

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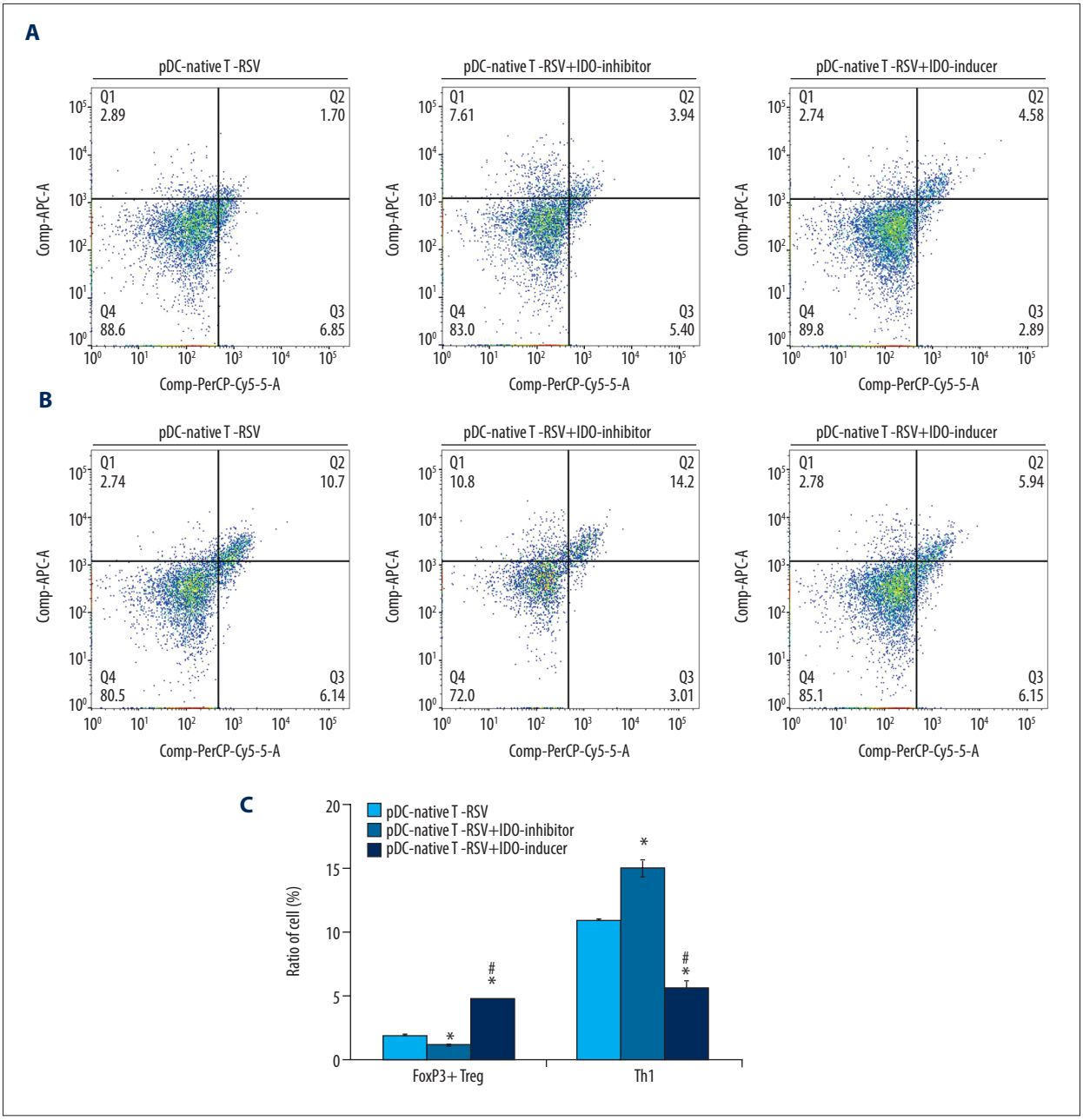

Figure 6. Effects of IDO inhibitor and IDO inducer on Foxp3⁺ Treg/Th17 balance in RSV-infected pDCs. (**A, B**). Flow cytometry analyses of the proportions of (**A**) Foxp3⁺ Tregs and (**B**) Th17 in pDC preparations. (**C**) Statistical analysis of the ratios of Foxp3⁺ Treg to Th17 cells in pDCs. * *P*<0.05 compared with pDCs+T cells+vehicle. # p<0.05 compared with pDCs+T cells+RSV.

Moreover, the functions of pDCs in respiratory viral infections have not been fully clarified. Therefore, the present study assessed the pathological mechanisms of RSV infection in pDCs.

The kynurenine pathway has been shown to modulate tryptophan metabolism and the serotonergic system and to play critical roles in the secretion of pro-inflammatory cytokines [27]. In the kynurenine metabolic pathway, tryptophan is initially oxygenated by IDO to yield kynurenine, which is subsequently transformed by kynurenine aminotransferase to kynurenic acid [28]. Our findings showed that RSV infection markedly reduced kynurenic acid concentrations in pDCs, suggesting that RSV infection can modulate inflammatory responses in pDCs by regulating the production of kynurenic acid.

The anti-inflammatory effects of kynurenic acid have been found to correlate with the modulation of immune responses in DCs undergoing pro-inflammatory stimulation [29]. Similarly, the

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Th1/Th2 balance in cell immune responses, especially the balance between Tregs and Th17 cells, plays critical roles in various infectious diseases and nervous system disorders [30,31]. Thus, changes in Foxp3+ Treg cells and Th17 cells in pDCs in response to RSV infection were assessed by flow cytometry. Our findings indicated that RSV infection reduced the proportion of Foxp3$^+$ Treg cells and increased the proportion of Th17 cells. Because RSV infection is associated with a Th1-type immune response, including the secretion of IFN-γ [32], we also tested the effects of IFN-γ treatment on the balance between Tregs and Th17 cells [32]. We found that IFN-γ increased the proportion of Foxp3$^+$ Tregs while reducing the proportion of Th17 cells. These findings suggest that IFN-γ promotes the transformation from Th17 cells to Foxp3+ Treg cells, whereas RSV infection suppresses this transformation, altering the Th17/Treg balance.

IDO is a rate-limiting enzyme in the synthesis of tryptophan-related metabolites such as kynurenic acid. IDO expression can be induced by inflammatory cytokines [33]. Disorders can be treated by altering the metabolism and/or balance of immune system cells, thereby modulating immune responses [34,35]. One example may be the ability of IDO activity to modulate tryptophan metabolism. Treatment of pDCs with the IDO inhibitor 1-MT or the IDO inducer ISS-ODN affected both kynurenic acid production and the Th17/Treg balance. Kynurenic acid concentration was significantly reduced by the IDO inhibitor and significantly enhanced by the IDO inducer, suggesting that RSV infection decreased kynurenic acid concentration by modulating IDO activity. In addition, the proportion of T cell-derived Foxp3$^+$ Tregs was significantly reduced by IDO inhibitor, but was significantly increased by IDO inducer. Conversely, the proportion of Th17 cells was significantly increased by IDO inhibitor but was significantly reduced by IDO inducer, suggesting that RSV infection inhibited the transformation from Th17 to Foxp3$^+$ Tregs by modulating IDO activity.

Conclusions

To the best of our knowledge, this study is the first to clarify changes in kynurenic acid resulting from RSV infection of human pDCs. We found that RSV infection decreased kynurenic acid concentration and altered the balance between Th17 and FoxP3+ Treg cells. IDO inhibitor reduced kynurenic acid concentration, whereas IDO inducer increased its concentration in RSV-infected pDCs. In summary, RSV infection reduced production of kynurenic acid and inhibited the transformation from Th17 to Foxp3$^+$ Tregs (Th17/Treg balance) by altering IDO activity in pDCs.

Conflict of interest

None.

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