Effects of budesonide on HRV16-induced antiviral responses and coronavirus-related receptor expression in human lung microvascular endothelial cells

WPŁYW BUDEZONIDU NA REAKCJE PRZECIWWIRUSOWE WYWOŁANE PRZEZ HRV16 I EKSPRESJĘ RECEPTORÓW KORONAWIRUSOWYCH W LUDZKICH KOMÓRKACH ŚRÓDBŁONKA NACZYNIOWEGO PŁUC

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Streszczenie

Wprowadzenie: Ludzki rinowirus 16 (HRV16) jest głównym czynnikiem wywołującym zaostrzenia astmy i indukuje reakcje przeciwwirusowe i zapalne nie tylko w komórkach nabłonka dróg oddechowych, ale także w komórkach śródbłonka naczyniowego płuc. Budezonid jest szeroko stosowany w leczeniu astmy, jednak jego bezpośredni wpływ na odpowiedź przeciwwirusową śródbłonka pozostaje słabo poznany.
Materiały i metody: Ludzkie komórki śródbłonka naczyniowego płuc (HMVEC-L) poddano wstępnej ekspozycji na budezonid (1 ng/ml), a następnie zakażono HRV16 (MOI 3,0) lub stymulowano kwasem poliinozyno-policytydylowym [poli(I:C)] jako mechanistycznym modelem wrodzonej aktywacji przeciwwirusowej. Ekspresję AP-N, DPP4, ACE2, ICAM-1, IFN-β, RANTES i IL-8 oceniano za pomocą RT-PCR, ELISA i cytometrii przepływowej.
Wyniki: Budezonid przed osłabił ekspresję AP-N, DPP4 i ACE2 indukowaną przez HRV16, zarówno na poziomie mRNA, jak i białka. Ekspresja RANTES i IL-8 indukowana przez HRV16 również uległa zmniejszeniu, podczas gdy ekspresja IFN-β nie była konsekwentnie tłumiona. Budezonid zmniejszył wczesną ekspresję mRNA ICAM-1, ale zwiększył ekspresję powierzchniową ICAM-1 po 72 godzinach. Podobne efekty modulacyjne obserwowano w komórkach stymulowanych poli(I:C), co sugeruje, że część obserwowanej odpowiedzi odzwierciedla szerszą modulację wrodzonej sygnalizacji przeciwwirusowej.
Wnioski: Budezonid może selektywnie modulować odpowiedź przeciwwirusową i zapalną ludzkich komórek śródbłonka mikronaczyniowego płuc, zamiast jednorodnie hamować odporność przeciwwirusową. Badanie sugeruje, że komórki śródbłonka mikronaczyniowego płuc mogą stanowić dodatkowy cel immunomodulacji zależnej od kortykosteroidów podczas wirusowego zapalenia dróg oddechowych.

Słowa kluczowe: budezonid, ludzki rinowirus 16, receptory wejścia koronawirusa, komórki śródbłonka naczyniowego płuc, odpowiedź immunologiczna przeciwwirusowa

Summary

Introduction: Human rhinovirus 16 (HRV16) is a major trigger of asthma exacerbations and induces antiviral and inflammatory responses not only in airway epithelial cells but also in human lung microvascular endothelial cells. Budesonide is widely used in asthma treatment, however, its direct effects on endothelial antiviral responses remain poorly understood.
Materials and Methods: Human lung microvascular endothelial cells (HMVEC-L) were pre-exposed to budesonide (1 ng/mL) and subsequently infected with HRV16 (MOI 3.0) or stimulated with polyinosinic:polycytidylic acid [poly(I:C)] as a mechanistic model of innate antiviral activation. Expression of AP-N, DPP4, ACE2, ICAM-1, IFN-β, RANTES, and IL-8 was assessed by RT-PCR, ELISA, and flow cytometry.
Results: Budesonide pre-exposure attenuated HRV16-induced expression of AP-N, DPP4, and ACE2 at both mRNA and protein levels. HRV16-induced RANTES and IL-8 expression was also reduced, whereas IFN-β expression was not consistently suppressed. Budesonide reduced early ICAM-1 mRNA expression but increased ICAM-1 surface expression at 72 h. Similar modulatory effects were observed in poly(I:C)-stimulated cells, suggesting that part of the observed response reflects broader modulation of innate antiviral signaling.
Conclusions: Budesonide may selectively modulate antiviral and inflammatory responses of human lung microvascular endothelial cells rather than uniformly suppress antiviral immunity. This study suggests that pulmonary microvascular endothelial cells may represent an additional target of corticosteroid-mediated immunomodulation during respiratory viral inflammation.

Key words: budesonide, human rhinovirus 16, coronavirus entry receptors, microvascular endothelial cells, antiviral immune response

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1. Introduction

Human rhinoviruses (HRVs) are the most common viral triggers of exacerbations in chronic inflammatory airway diseases, particularly asthma, where they contribute substantially to disease morbidity through induction of antiviral and inflammatory immune responses [1]. Although the airway epithelium is considered the primary target of HRV infection, increasing evidence indicates that the pulmonary microvascular endothelium also actively participates in virus-induced immune responses rather than functioning solely as a structural vascular barrier [2,3].

Human lung microvascular endothelial cells (HMVEC-L) respond to HRV16 infection by activating antiviral signaling pathways, producing inflammatory mediators, and upregulating intercellular adhesion molecule 1 (ICAM-1), the principal receptor mediating HRV16 cellular entry [3]. These findings support the concept that the pulmonary endothelium contributes to the broader immunopathology of respiratory viral infections and may represent an additional target for immunomodulatory therapies.

Beyond HRV-specific responses, pulmonary endothelial cells express molecules associated with the entry of distinct human coronaviruses, including aminopeptidase N (AP-N), dipeptidyl peptidase-4 (DPP4), and angiotensin-converting enzyme 2 (ACE2), which serve as entry receptors for human coronavirus 229E, MERS-CoV, and SARS-related coronaviruses, respectively [4,5]. The expression of these receptors is dynamically regulated by inflammatory and antiviral signaling, including interferon-dependent pathways [6]. Our previous work demonstrated that HRV16 infection alters the endothelial expression of AP-N, DPP4, and ACE2, suggesting that rhinovirus-driven immune activation substantially reshapes the endothelial receptor phenotype [7].

Inhaled corticosteroids remain the cornerstone of anti-inflammatory treatment in asthma and are widely used to control chronic airway inflammation and prevent virus-associated exacerbations [8]. In addition to their established anti-inflammatory effects, corticosteroids are known to modulate antiviral immune signaling, including type I interferon responses, which may influence both host antiviral defense and virus-associated receptor expression [6,12]. Most available evidence regarding corticosteroid-mediated antiviral immunomodulation originates from airway epithelial models, whereas their direct effects on pulmonary endothelial responses during rhinovirus infection remain poorly characterized.

Therefore, this study investigated whether budesonide modulates HRV16-induced antiviral and inflammatory responses in human lung microvascular endothelial cells and alters the expression of AP-N, DPP4, and ACE2. Additionally, a mechanistic model using synthetic double-stranded RNA [poly(I:C)] was included to assess the effects of budesonide on innate antiviral signaling independently of virus-specific cellular responses.

2. Materials and Methods

2.1. Cells

Human lung microvascular endothelial cells (HMVEC-L) from two different donors (CC-2527, Lonza, Walkersville, MD, USA) were cultured in Endothelial Cell Basal Medium 2 (C-2221, PromoCell, Heidelberg, Germany), supplemented with Endothelial Growth Medium-2 MV (C-39221, PromoCell, Heidelberg, Germany). The cells were cultured in an incubator at 37°C with 5% CO_2. Upon reaching 80-90% confluence, the cells were trypsinized with 0.25% trypsin and 0.02% ethylenediaminetetraacetic acid (EDTA) (59417C, Sigma Aldrich, St. Louis, MO, USA) and neutralized using Trypsin Neutralizing Solution (CC-5002, Lonza, Walkersville, MD, USA). The cells were seeded at 2.0 × 10^5/well on a 24-well plate. After 24 hours of incubation under standard conditions, the cells were ready for experimentation.

2.2. HRV16 infection and poly(I:C) stimulation

Microvascular endothelial cells were incubated with HRV16 (viral stocks were used at 3.83 × 10^7 Median Tissue Culture Infectious Dose [$TCID_{50}$]), obtained in cooperation with the Department of Respiratory Medicine, Imperial College London, UK, courtesy of Professor Sebastian Johnston. HMVEC-L monolayers were pre-exposed to budesonide (Sigma-Aldrich, St. Louis, MO, USA) at a final concentration of 1 ng/mL for 24 h and subsequently treated with HRV16 at a multiplicity of infection (MOI) of 3.0 or exposed to medium alone as a negative control. The virus-exposed cells were incubated for 3 h at 37°C with 5% CO_2. After incubation, the viral suspension was removed, and the cells were washed three times with phosphate-buffered saline (PBS; L0615-500; Biowest, Nuaille, France), followed by the addition of fresh medium. The material was collected at 5, 24, and 72 h. Stimulation of HMVEC-L with polyinosinic:polycytidylic acid [poly(I:C)] (10 µg/mL; InvivoGen, San Diego, CA, USA) was performed analogously to HRV16 infection.

2.3. Isolation of mRNA and real-time polymerase chain reaction (RT-PCR)

mRNA was extracted from HMVEC-L using the RNA ReliaPrep™ RNA Cell Miniprep System (Z6012, Promega, Madison, WI, USA) according to the manufacturer's instructions. Subsequently, cDNA was synthesized using the RevertAid H Minus First Strand cDNA Synthesis Kit (K1632, Thermo Fisher Scientific, Waltham, MA, USA). The following TaqMan probes were used to assess gene expression: *ANPEP* (aminopeptidase N)*, DPP4, ACE2, ICAM1, IFNB1, CCL5* (RANTES), and *CXCL8* (IL-8) (Thermo Fisher Scientific, Waltham, MA, USA). mRNA expression was analyzed using the StepOnePlus™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA), with results normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (Thermo Fisher Scientific, Waltham, MA, USA) as the housekeeping gene. Quantitative reverse transcriptase real-time PCR (qRT-PCR) was performed using the Genesig Kit (PrimerDesign, Chandler's Ford, UK).

2.4. Cytokine concentration

Cytokine concentrations were measured using enzyme-linked immunosorbent assays (ELISA) specific for each protein, following the manufacturer's instructions. IFN-β (Human IFN-beta DuoSet ELISA, DY814, assay range: 7.8–1000 pg/mL) and IL-8/CXCL8 (Human IL-8/CXCL8 DuoSet ELISA, Cat. no. DY208, assay range: 31.3–2000 pg/mL) assays were used. All assays were purchased from R&D Systems, Minneapolis, MN, USA.

2.5. Analysis of ACE2, DPP4, AP-N and ICAM-1 surface expression on HMVEC-L by flow cytometry

Protein surface expression in HMVEC-L was assessed by flow cytometry (BD LSRFortessa flow cytometer) at 72 h after HRV16 infection and poly(I:C) stimulation. HMVEC-L cells were incubated with specific antibodies and isotype control antibodies for 30 min on ice, as described in the Supplementary Table 1. After incubation, the cells were washed with HEPES-buffered saline. Next, the cells were blocked with 1% bovine serum albumin (BSA; A790650G, Sigma Aldrich, St. Louis, MO, USA) in PBS. Data were analyzed using BD FACSDiva software.

2.6. Statistical analysis

Results are presented as the mean ± standard error of the mean (SEM) from independent experiments. Statistical comparisons between two groups were performed using the Mann–Whitney U test. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism software (GraphPad Software, La Jolla, CA, USA).

3. Results

3.1. Budesonide pre-exposure modulates HRV16-induced expression of AP-N, DPP4, ACE2, and ICAM-1 in lung endothelial cells

In HRV16-infected cells, AP-N mRNA expression increased at 24 and 72 h compared to that in mock cells. When compared directly with HRV16-infected cells, budesonide pre-exposure did not significantly affect AP-N mRNA expression at 24 h. At 72 h, AP-N mRNA expression was reduced in budesonide pre-exposed and subsequently HRV16-infected cells by approximately 1.7-fold compared to HRV16-infected cells alone ($p < 0.05$) (Fig. 1A). At the protein level, HRV16 induced a marked increase in AP-N surface expression assessed at 72 h after infection. This HRV16-induced increase was strongly attenuated in cells pre-exposed to budesonide prior to HRV16 infection, resulting in an approximately 75% reduction in AP-N surface expression compared to HRV16-infected cells alone ($p < 0.01$) (Fig. 1B).

HRV16 infection had a limited effect on DPP4 mRNA expression. Budesonide pre-exposure was associated with reduced DPP4 mRNA expression at 24 and 72 h when compared directly with HRV16-infected cells (Fig. 1C). In contrast, HRV16 increased DPP4 surface expression at 72 h, and this increase was attenuated in budesonide pre-exposed and subsequently HRV16-infected cells, resulting in an approximately 10% reduction compared to HRV16-infected cells ($p < 0.05$) (Fig. 1D).

For ACE2, HRV16 induced a significant early increase in mRNA expression at 5 h compared to mock cells. When compared directly with HRV16-infected cells, budesonide pre-exposure significantly reduced ACE2 mRNA expression at this early time point by approximately 1.6-fold ($p < 0.05$) (Fig. 1E). ACE2 surface expression assessed at 72 h was reduced in budesonide pre-exposed and subsequently HRV16-infected cells compared to HRV16-infected cells alone (Fig. 1F).

HRV16 infection strongly induced ICAM-1 expression. At 5 h, ICAM-1 mRNA expression was markedly increased in HRV16-infected cells compared to mock cells. Budesonide pre-exposure was associated with reduced ICAM-1 mRNA expression at 5 and 24 h compared with HRV16-infected cells (Fig. 1G). At the protein level, HRV16 significantly increased ICAM-1 surface expression at 72 h, and this HRV16-induced increase was further enhanced in cells pre-exposed to budesonide, resulting in an approximately 10% increase compared to HRV16-infected cells alone ($p < 0.05$) (Fig. 1H)..

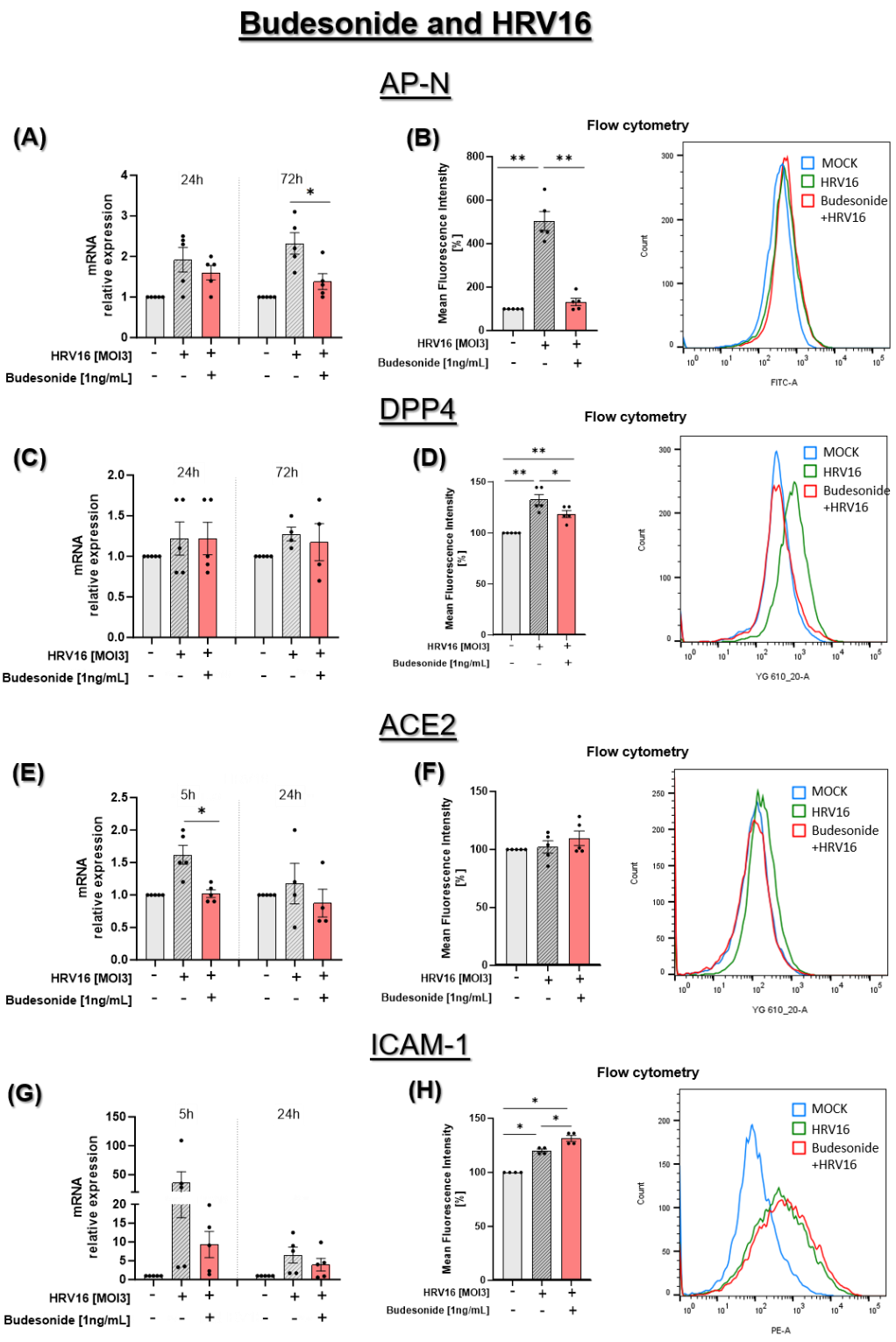

Figure 1. Budesonide modulates HRV16-induced expression of AP-N, DPP4, ACE2, and ICAM-1 in HMVEC-L.

Relative mRNA expression of AP-N (A), DPP4 (C), ACE2 (E), and ICAM-1 (G) was assessed in HMVEC-L infected with HRV16 in the presence or absence of budesonide pre-exposure. Surface expression of AP-N (B), DPP4 (D), ACE2 (F), and ICAM-1 (H) was analyzed by flow cytometry. The Mann–Whitney U-test was used to analyze differences between the two groups. Data are representative of at least four independent experiments and are presented as means ± SEM; n = 4–8; *p < 0.05; **p < 0.01; ***p <0.001.

3.2. Modulatory effects of budesonide on Poly(I:C)-induced expression of coronavirus entry receptors and ICAM-1 in HMVEC-L

In Poly(I:C)-stimulated cells, AP-N mRNA expression increased at 24 and 72 h compared to that in mock cells. When compared directly with Poly(I:C)-stimulated cells, budesonide pre-exposure was associated with reduced AP-N mRNA expression at both time points (Fig. 2A). At the protein level, Poly(I:C) induced an increase in AP-N surface expression assessed at 72 h. This Poly(I:C)-induced increase was reduced in cells pre-exposed to budesonide compared to Poly(I:C)-stimulated cells alone (Fig. 2B).

Poly(I:C) stimulation increased DPP4 mRNA expression. Budesonide pre-exposure was associated with reduced DPP4 mRNA expression at 24 and 72 h when compared directly with Poly(I:C)-stimulated cells (Fig. 2C). At the protein level, DPP4 surface expression assessed at 72 h was significantly reduced in budesonide pre-exposed cells compared to Poly(I:C)-stimulated cells, by approximately 10% ($p < 0.01$) (Fig. 2D).

Poly(I:C) stimulation resulted in reduced ACE2 mRNA expression at both 5 and 24 h. When compared directly with Poly(I:C)-stimulated cells, budesonide pre-exposure was associated with further reductions in ACE2 mRNA expression at both time points (Fig. 2E). ACE2 surface expression assessed at 72 h was modestly reduced in budesonide pre-exposed cells compared to Poly(I:C)-stimulated cells, without reaching statistical significance (Fig. 2F).

Poly(I:C) stimulation strongly induced ICAM-1 expression. At 5 h, ICAM-1 mRNA expression was markedly increased following Poly(I:C) stimulation. Budesonide pre-exposure was associated with reduced ICAM-1 mRNA expression at both 5 and 24 h compared to Poly(I:C)-stimulated cells (Fig. 2G). At the protein level, Poly(I:C) increased ICAM-1 surface expression at 72 h, and budesonide pre-exposure did not significantly modify this Poly(I:C)-induced increase (Fig. 2H).

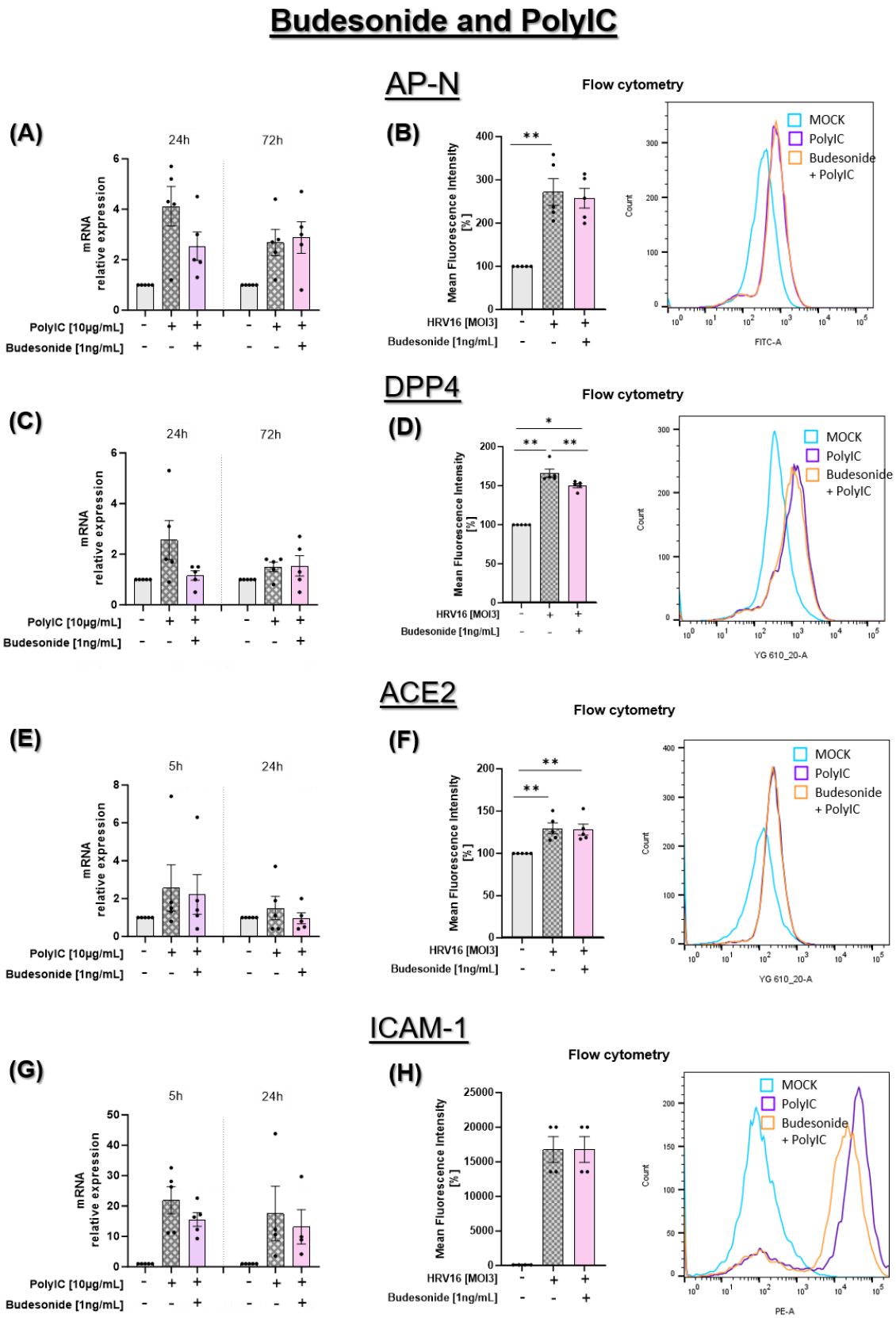

Figure 2. Budesonide modulates Poly(I:C)-induced expression of AP-N, DPP4, ACE2, and ICAM-1 in HMVEC-L.

Relative mRNA expression of AP-N (A), DPP4 (C), ACE2 (E), and ICAM-1 (G) was assessed in HMVEC-L stimulated with Poly(I:C) in the presence or absence of budesonide pre-exposure. Surface expression of AP-N (B), DPP4 (D), ACE2 (F), and ICAM-1 (H) was analyzed by flow cytometry. The Mann–Whitney U-test was used to analyze differences between the two groups. Data are representative of at least four independent experiments and are presented as means ± SEM; n = 4–8; *p < 0.05; **p < 0.01; ***p < 0.001.

3.3. Budesonide modulates HRV16- and Poly(I:C)-induced antiviral and inflammatory responses in HMVEC-L

HRV16 infection induced antiviral and inflammatory responses in HMVEC-L, which were differentially modulated by budesonide pre-exposure.

In HRV16-infected cells, IFN-β mRNA expression was increased compared to mock cells. In cells pre-exposed to budesonide and subsequently infected with HRV16, IFN-β mRNA expression was modestly higher than that observed in HRV16-infected cells alone (Fig. 3A).

Additionally, HRV16 markedly induced RANTES mRNA expression compared to mock cells ($p < 0.05$). Budesonide pre-exposure significantly attenuated HRV16-induced RANTES mRNA expression, resulting in an approximately 1.6-fold reduction compared to HRV16-infected cells ($p < 0.05$) (Fig. 3B).

HRV16 also increased IL-8 mRNA expression compared to mock cells ($p < 0.05$). Budesonide pre-exposure was associated with reduced HRV16-induced IL-8 mRNA expression (Fig. 3C).

Poly(I:C) stimulation also induced antiviral and inflammatory activation in HMVEC-L. Poly(I:C) increased IFN-β mRNA expression compared to mock cells, and this response was reduced in cells pre-exposed to budesonide (Fig. 3D).

Similarly, Poly(I:C)-induced RANTES mRNA expression was attenuated in budesonide pre-exposed cells compared to Poly(I:C)-stimulated cells alone (Fig. 3E).

Additionally, Poly(I:C) increased IL-8 mRNA expression compared to mock cells. Budesonide pre-exposure was associated with reduced Poly(I:C)-induced IL-8 mRNA expression (Fig. 3F).

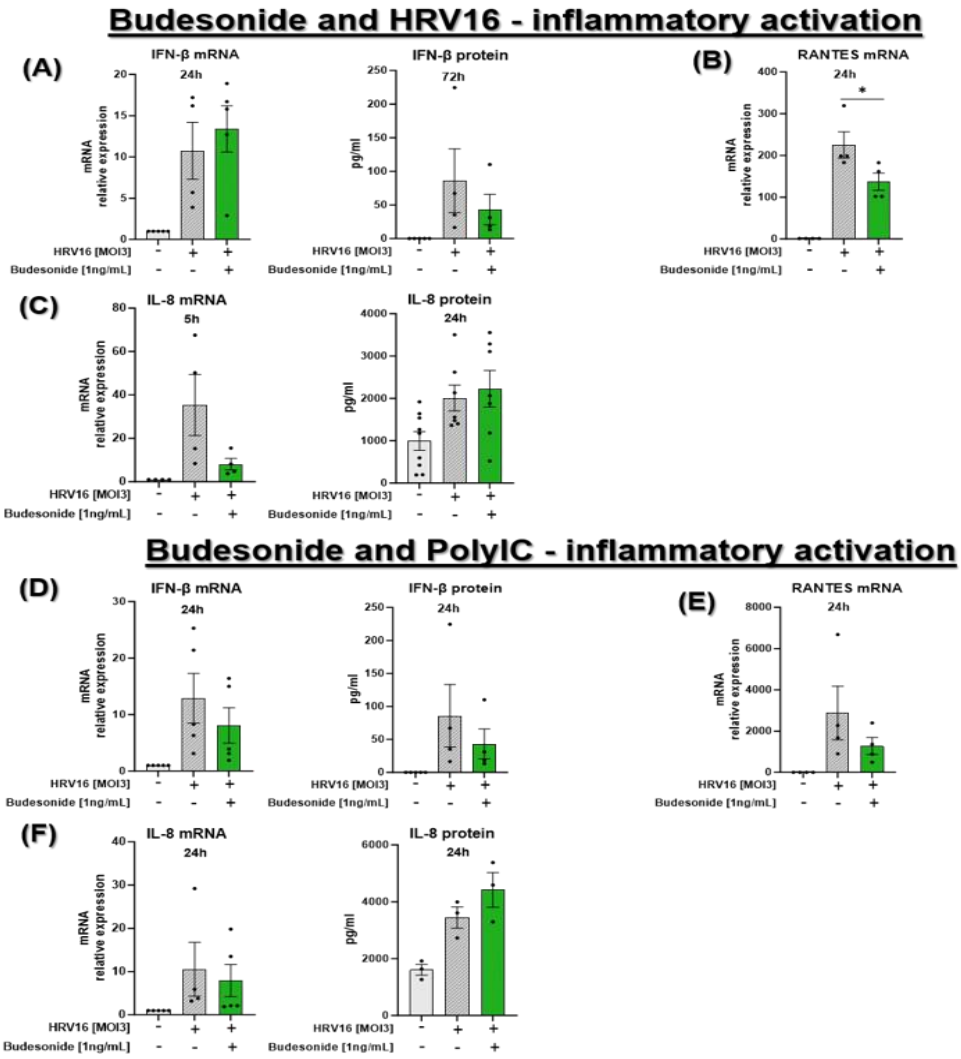

Figure 3. Budesonide modulates HRV16- and Poly(I:C)-induced antiviral and inflammatory responses in HMVEC-L.

Relative mRNA expression of IFN-β (A, D), RANTES (B, E), and IL-8 (C, F) was assessed in HMVEC-L after HRV16 infection (A–C) or Poly(I:C) stimulation (D–F), in the presence or absence of budesonide pre-exposure. The Mann–Whitney U-test was used to analyze differences between the two groups. Data are representative of at least four independent experiments and are presented as means ± SEM; n = 4–8; *p < 0.05; **p < 0.01; ***p < 0.001.

4. Discussion

The present study suggests that budesonide may modify the response of pulmonary microvascular endothelial cells to HRV16 infection. The main findings were that budesonide pre-exposure was associated with reduced HRV16-induced expression of AP-N, DPP4, and ACE2, together with lower expression of the inflammatory mediators RANTES and IL-8. Budesonide also reduced ICAM-1 mRNA expression at earlier time points, although ICAM-1 surface expression was increased at 72 h. Importantly, in contrast to its anti-inflammatory effects, budesonide did not reduce HRV16-induced IFN-β expression. These findings suggest that budesonide may not simply suppress antiviral endothelial responses, but rather selectively modify specific pathways involved in the response to viral infection.

To better understand whether these effects were specific to HRV16 infection or reflected broader modulation of antiviral signaling, poly(I:C) was included as a mechanistic model. Poly(I:C) is a synthetic analogue of viral double-stranded RNA that is widely used to mimic innate antiviral immune activation in vitro through RNA-sensing pathways, independently of active viral replication [10,11]. The observation that budesonide also attenuated inflammatory mediator expression and HCoVs receptors modulation in the poly(I:C) model suggests that at least part of the observed effects may be explained by broader regulation of innate antiviral signaling rather than exclusively HRV16-specific mechanisms.

The reduced expression of RANTES and IL-8 in both experimental models is consistent with the established anti-inflammatory activity of corticosteroids. Glucocorticoids suppress inflammatory gene expression through glucocorticoid receptor-dependent mechanisms involving inhibition of key transcriptional pathways, including NF-κB and AP-1, which regulate chemokine production during antiviral immune responses [12]. This likely explains the consistent reduction in inflammatory mediator expression observed in our model. The reduction in AP-N, DPP4, and ACE2 expression further suggests that budesonide may influence endothelial receptor regulation during viral immune activation. This may be particularly relevant for ACE2, as interferon-associated signaling has been implicated in its regulation in respiratory cells [13].

One of the most interesting findings was the different effect of budesonide on IFN-β expression depending on the experimental model. In poly(I:C)-stimulated cells, budesonide reduced IFN-β expression, which is consistent with previous reports showing suppression of innate antiviral signaling by corticosteroids [9]. In contrast, HRV16-induced IFN-β expression was changed depending on time point. This suggests that the effect of budesonide may depend on the biological context in which antiviral signaling is activated. Poly(I:C) activates relatively defined innate immune pathways, whereas live rhinovirus infection induces a more complex cellular response involving viral replication, endogenous interferon signaling, and dynamic host regulatory mechanisms [14]. The preservation of IFN-β expression in HRV16-infected cells may therefore suggest selective modulation of inflammatory responses rather than uniform suppression of antiviral immunity. Another noteworthy finding was the discrepancy between ICAM-1 mRNA and surface protein expression. Budesonide reduced ICAM-1 mRNA expression at earlier time points, whereas surface ICAM-1 expression was increased at 72 h. This suggests that transcriptional changes do not necessarily correspond directly to later protein expression and may reflect differences in the timing and regulation of endothelial responses. Because ICAM-1 serves as the major receptor for HRV16, this observation also highlights the complexity of corticosteroid effects on virus-related endothelial biology.

These findings may be relevant in the clinical context of asthma, where HRV infections remain the most common trigger of acute exacerbations. Inhaled corticosteroids are the cornerstone of asthma treatment and substantially reduce exacerbation risk. Their beneficial effects are generally attributed to suppression of airway inflammation, but the present findings suggest that pulmonary endothelial cells may also represent a relevant target of corticosteroid action. The pulmonary endothelium is increasingly recognized as an active participant in respiratory viral inflammation through regulation of leukocyte recruitment, cytokine production, and vascular inflammatory responses [15].

Our findings are partially consistent with previous studies performed in airway epithelial models. Singanayagam et al. showed that corticosteroid exposure may suppress antiviral immunity and impair host defense during virus-associated exacerbations [9]. Dysregulated interferon responses have also been implicated in the pathogenesis of virus-induced asthma exacerbations [16]. However, most available studies have focused on airway epithelium, whereas much less is known about pulmonary endothelial responses. Our previous work demonstrated that HRV16 induces antiviral and inflammatory responses in pulmonary endothelial cells, and that HRV16 alters endothelial expression of AP-N, DPP4, and ACE2 [7]. The present study extends these observations by suggesting that these endothelial responses may also be modified by budesonide.

Several limitations of this study should be acknowledged. First, this was an in vitro study using primary endothelial cells from a limited number of donors, which may not fully reflect the biological heterogeneity of pulmonary endothelial responses in vivo. Second, only one corticosteroid and one experimental concentration were evaluated. Third, although changes in receptor expression were clearly observed, the functional consequences for viral infectivity or endothelial susceptibility were not directly assessed.

Despite these limitations, the present findings suggest that pulmonary microvascular endothelial cells may represent a relevant target of corticosteroid-mediated immunomodulation during viral inflammation. This broadens the current understanding of inhaled corticosteroid biology beyond the airway epithelium and suggests that endothelial responses may contribute to their therapeutic effects in respiratory viral disease.

Further studies are needed to clarify the molecular mechanisms underlying the observed changes in HCoVs receptors expression and antiviral signalling, and to determine whether these effects influence susceptibility to viral infection.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared with the corresponding author upon reasonable request.

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