IP-10 Is Elevated in Virus-Induced Acute Exacerbations in Childhood Asthma

Kazuo SUZUKI\(^1\), Masahiko KATO\(^{1,2}\), Shinichi MATSUDA\(^3\), Mariko NUKAGA\(^1\), Mayumi ENSEKI\(^1\), Hideyuki TABATA\(^1\), Kota HIRAI\(^3\), Yoshiyuki YAMADA\(^2\), Kenichi MARUYAMA\(^3\), Yasuhide HAYASHI\(^1\) and Hiroyuki MOCHIZUKI\(^1\)

\(^{1}\)Department of Pediatrics, Tokai University School of Medicine
\(^{2}\)Departments of \(^{2}\)Allergy and Immunology, \(^{3}\)Nephrology, Gunma Children's Medical Center
\(^{4}\)Gunma Red Cross Blood Center

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Objective: Viral infections and sensitization to aeroallergens are major factors in the exacerbation of asthma and its development during early childhood. However, the cytokine profiles and eosinophil activation status linked to the association between viral infections and sensitization to aeroallergens are incompletely understood. Here we investigated respiratory viruses, serum eosinophil cationic protein (ECP), and various cytokines/chemokines in acute exacerbation of childhood asthma.

Methods: We analyzed peripheral eosinophil counts, serum ECP, and 27 cytokines/chemokines in 76 virus-induced acute asthma cases with or without aeroallergen sensitization. Asthma due to sensitization was defined by a positive reaction to at least one aeroallergen in serum specific IgE antibody tests. Virus detection was performed using antigen detection kits and/or RT-PCR, followed by direct DNA sequencing analysis. Serum cytokines/chemokines were measured using a multi-cytokine detection system.

Results: Peripheral eosinophil counts and serum ECP and IL-5 levels were significantly elevated in sensitized cases compared with nonsensitized cases. Conversely, IP-10 values were significantly higher in nonsensitized cases. An inverse correlation between IP-10 and IL-5 production was identified in virus-induced acute exacerbations of asthma but not in controls.

Conclusions: Cytokine profiles and eosinophil activation status might be different between sensitized and nonsensitized cases of virus-induced acute exacerbations of asthma.

Key words: Aeroallergen sensitization, Asthma, Children, IP-10, Virus

INTRODUCTION

Risk factors for subsequent development of asthma at school age and for exacerbations of asthma symptoms include aeroallergen sensitization and virus-induced wheezing episodes during infancy and early childhood [1, 2]. Furthermore, viral respiratory illnesses are more severe after early allergic sensitization [3]. A prospective, birth cohort demonstrated that allergic sensitization precedes rhinovirus infection-induced wheezing but the infection does not induce allergic sensitization. This sequential relationship and the plausible mechanisms by which allergic sensitization can lead to more severe rhinovirus infection-induced lower respiratory illnesses lend support to the causal role of allergic sensitization in this developmental pathway, and indicate that therapeutics for preventing allergic sensitization may modify virus-induced wheezing and the development of asthma in later life [4].

From these findings, it is important to explore the different pathophysiological routes between atopic and non-atopic asthma induced by viral infection. Therefore, the purpose of this study was to investigate differences among the viruses detected, peripheral eosinophil counts, and serum levels of eosinophil cationic protein (ECP) and several cytokines and chemokines in cases of virus-induced acute exacerbations of childhood asthma with or without aeroallergen sensitization.

MATERIALS AND METHODS

Patients and study setting

We investigated 93 outpatients and hospitalized subjects with acute respiratory symptoms (60 boys, 33 girls, mean/median ages 3.7/2.8 years) at the Tokai University Hospital and Gunma Children's Medical Center between January 1, 2008 and December 31, 2015. All patients had a history of three or more different episodes of recurrent wheezing and documented evidence of wheezing by auscultation. Subjects with asthma were diagnosed according to the criteria of the guideline of the Japanese Society of Pediatric Allergy and Clinical Immunology [5]. Briefly, a diagnosis of asthma was confirmed on the basis of a history of recurrent wheezing and dyspnea on at least three independent occasions, and reversible bronchodilatation. Patients were prescribed short-acting \( \beta \) agonists and/or long-term controller medications and these patients were not using systemic corticosteroids at the time of further examination. We excluded children with obvious bacterial infections, congenital heart diseases, and chronic lung diseases as well as those who showed the presence of a foreign body, had signs of severe infection, or were immunosuppressed, as these complications can interfere with the assessment.
of asthma-related outcome measures. The criteria of 'sensitized asthma' patients was defined as being positive for at least one aeroallergen by serum specific IgE antibody. The severity in subjects with acute exacerbation of asthma such as mild attack, moderate attack, and severe attack was defined according to the Japanese guideline [5]. The symptom severity score was also defined as mild attack = 1, moderate attack = 2, severe attack = 3. Exclusion criteria for the controls included immunosuppression, the presence of other respiratory tract symptoms, or a history of previous wheezing and asthma. Controls and patient cases were age- and sex-matched. This study was approved by the Ethics Committees of Tokai University Hospital and Gunma Children’s Medical Center. Informed consent was obtained from parents of patients and assent was obtained from the children if they were considered old enough (generally > 9 years old).

**Virus detection**

Nasal aspirates were obtained from 93 patients during acute exacerbations of asthma and analyzed using antigen detection kits for respiratory syncytial virus (Becton Dickinson, Fukushima, Japan), influenza virus types A and B (Denka-Seiken, Gosen, Japan), and adenosivirus (Taunz, Iznokuni, Japan). The remaining secretions were frozen at −80 °C until examination by reverse transcription-polymerase chain reaction (RT-PCR), followed by direct DNA sequencing analysis as previously reported [6, 7]. Some samples were tested by multiplex PCR (Seeplex RV15 OneStep ACE Detection kit, Seegene, Inc., Seoul, Korea) for the presence of 15 human viral respiratory pathogens (adenovirus A/B/C/D/E, human metapneumovirus, enterovirus, human bocavirus 1/2/3/4, human coronavirus in 17 samples (18.3%), respectively. Although enteroviruses were dominant in exacerbations of asthma, rhinovirus was detected in 29 (31.2%), RS virus in 22 (23.7%), enterovirus in 9 (9.7%), human coronavirus in 2 (2.2%), human bocavirus in 1 (1.1%), influenza virus B in 1 (1.1%), human parainfluenza virus type 3 in 1 (1.1%), adenovirus in 1 (1.1%), and ≥ 2 viruses in 10 (10.8%); no viruses were detected in 17 samples (18.3%), respectively.

**RESULTS**

**Virus detection**

Of the 93 samples from patients with acute exacerbations of asthma, rhinovirus was detected in 29 (31.2%), RS virus in 22 (23.7%), enterovirus in 9 (9.7%), human coronavirus in 2 (2.2%), human bocavirus in 1 (1.1%), influenza virus B in 1 (1.1%), human parainfluenza virus type 3 in 1 (1.1%), adenovirus in 1 (1.1%), and ≥ 2 viruses in 10 (10.8%); no viruses were detected in 17 samples (18.3%), respectively.

In this study, we further investigated 76 cases showing the presence of viruses with or without aeroallergen sensitization; patient characteristics are shown in Table 1. Although enteroviruses were dominant in sensitized asthma cases, there was no significant difference among nonsensitized and sensitized cases (Fig. 1). In addition, we evaluated the severity of acute exacerbations of asthma attacks. Among the 76 cases with viral infection, 6 were rated as mild attacks, 66 were moderate attacks, and 4 were severe attacks. There was no significant difference in severity in acute exacerbations of asthma between nonsensitized and sensitized cases; however, 3 of 4 severe attacks were sensitized: 2 were infected by rhinoviruses, and 1 by an enterovirus. One nonsensitized case was infected by coronavirus.

Abbreviations: ECP, eosinophil cationic protein; FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; IF, interferon-c-induced protein; MCP, monocyte chemotaxant protein; MIP, macrophage inflammatory protein; PDGF, platelet-derived growth factor; RANTES, regulated on activation normal T expressed and secreted chemokine; RS, respiratory syncytial; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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Serum total IgE, cytokines/chemokines and ECP

We compared several parameters between nonsensitized and sensitized patients with aeroallergen-specific IgE antibodies. The peripheral eosinophil counts, and concentrations of ECP and IL-5 were significantly elevated in sensitized virus-induced asthma cases compared with nonsensitized cases (Fig. 2). In contrast, among 27 cytokines/chemokines, only IP-10 was significantly higher in nonsensitized asthma cases compared with sensitized cases (Fig. 2). Although the age in nonsensitized cases was significantly smaller than in sensitized cases (Table 1), there was no correlation between the age and values of IP-10 in nonsensitized asthma cases compared with sensitized cases (Fig. 2). Although the age in nonsensitized cases was significantly smaller than in sensitized cases (Table 1), there was no correlation between the age and values of IP-10 in nonsensitized asthma cases compared with sensitized cases (Fig. 2). Although the age in nonsensitized cases was significantly smaller than in sensitized cases (Table 1), there was no correlation between the age and values of IP-10 in nonsensitized asthma cases compared with sensitized cases (Fig. 2). Although the age in nonsensitized cases was significantly smaller than in sensitized cases (Table 1), there was no correlation between the age and values of IP-10 in nonsensitized asthma cases compared with sensitized cases (Fig. 2).

We then evaluated the correlation between each parameter in acute exacerbations of asthma. Total serum IgE showed significant correlation with peripheral eosinophils counts, serum ECP, and IL-5 (Fig. 3). As expected, IL-5 correlated significantly with peripheral eosinophil counts. However, IL-5 showed an inverse correlation with IP-10 (Fig. 4). In contrast, these parameters did not correlate among the control subjects (data not shown).

DISCUSSION

The sequences of events that lead to sensitization and virus-induced wheezing during early life are important for the identification of potential causal relationships in the development of atopic asthma [1, 2]. A recent birth cohort study suggested that aeroallergen sensitization is a fundamental risk factor for the development of human rhinovirus wheezing illnesses [4]. Furthermore, rhinoviruses are the most common cause of exacerbations in established asthma and are causative in 30–90% of child and adult cases [9–12]. In a cohort of school-aged children with asthma, aeroallergen sensitization cases were associated with similar numbers of viral infections, but atopic asthma patients experienced more frequent and severe upper and lower virus-induced respiratory illnesses [13]. Furthermore, Heymann et al. [14] found that viral infection is the main risk factor for wheezing in children hospitalized before 3 years of age. Conversely, the majority of children aged 3 to 18 years who experience wheezing episodes show prominent atopic characteristics that may represent key risk factors for hospitalization and adverse reactions to viral infections, especially rhinovirus infections. Indeed, our study showed that 3 of 4 severe attacks were in sensitized patients and 2 of 3 cases were infected by rhinoviruses, although the two major viruses, rhinovirus and RS virus, were not significantly associated with aeroallergen sensitization.
in acute exacerbations of asthma.

However, the role of aeroallergen sensitization on immunological responses during virus-induced asthma are not well clarified. Previous studies suggested that the interferon (IFN)-α, -β, and -λ to rhinovirus or RS virus infection are deficient in both adult and child atopic asthmatic patients [15-17] and that this deficiency correlates with the severity of virus-induced asthma exacerbations [16] and asthma symptoms [18]. Furthermore, anti-IgE antibody, omalizumab improved IFN-α response to rhinovirus, and in the omalizumab group, increases in IFN-α were associated with fewer exacerbations [19]. These results collectively suggest that antigens sensitization is closely related to IFN productions to viral infection and exacerbations of virus-induced asthma. On the other hand, a recent report suggest that rhinovirus type 16-induced IFN-β and -λ productions were significantly reduced in not only atopic asthmatic children but nonatopic asthmatic, and atopic nonasthmatic children compared with nonatopic nonasthmatic children. In addition, IFN-β and IFN-λ induction correlated inversely with the airway Th2 immunopathologic profile such as eosinophilia and IL-4 production and with epithelial damage. Furthermore, total serum IgE levels correlated negatively with rhinovirus-induced IFN-λ mRNA levels and positively with rhinovirus viral RNA levels. These findings suggest that deficient immune responses to viral infections are not limited to patients with atopic asthma but are present in those with other Th2-oriented conditions.

We also found that peripheral eosinophil counts and serum concentrations of ECP and IL-5 as the Th2 conditions were significantly elevated in sensitized acute exacerbations of asthma cases compared with nonsensitized cases. The results of eosinophil counts, and ECP and IL-5 concentration measurements were similar to those in previous reports. Zimmerman et al. [20] showed that atopic asthmatic children have higher eosinophil counts and greater levels of serum ECP than non-atopic patients. Amin et al. [21] compared biopsy samples of patients with atopic and non-atopic asthma and showed that the levels of IL-5-positive cells were higher in atopic cases. Furthermore, IL-5 levels and eosinophilia in induced sputum samples were significantly higher in pediatric patients with atopic asthma compared with non-atopic and control cases [22].

In contrast, this is the first report to show that serum IP-10 values were significantly higher in nonsensitized patients compared with sensitized patients in acute exacerbations of asthma. Furthermore, serum IP-10 and IL-5 production showed an inverse correlation in virus-induced acute exacerbations of childhood asthma but not in controls.

T-helper 2 (Th2)-mediated immune responses are a well-recognized feature of bronchial asthma [23].

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Fig. 2 Peripheral eosinophil counts, serum ECP, and cytokines/chemokines in virus-induced acute exacerbation of asthma in patients who are nonsensitized or sensitized to aeroallergens. Peripheral eosinophil counts and serum ECP and IL-5 concentrations were significantly elevated in sensitized virus-induced asthma cases compared with nonsensitized cases. In contrast, only IP-10 was significantly lower in sensitized compared with nonsensitized cases. A horizontal bar represents the median. Data were analyzed using the Mann-Whitney U test. *p < 0.05; **p < 0.01; ***p < 0.001.
<table>
<thead>
<tr>
<th></th>
<th>Asthma, All (n = 76)</th>
<th>Asthma, Nonsensitized (n = 29)</th>
<th>Asthma, Sensitized (n = 47)</th>
<th>Control (n = 13)</th>
</tr>
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<tbody>
<tr>
<td><strong>IgE (RIST)</strong></td>
<td>474.2 (1.9–3150.0)</td>
<td>173.6 (1.9–3150.0)</td>
<td>674.6 (40.2–3018.0)</td>
<td>55.0 (4.0–96.2)</td>
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<tr>
<td><strong>Eosinophils</strong></td>
<td>174 (0–2646)</td>
<td>79 (0–1520)</td>
<td>278 (0–2646)</td>
<td>152 (0–936)</td>
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<tr>
<td><strong>ECP</strong></td>
<td>22.9 (3.0–107.0)</td>
<td>10.1 (4.5–51.4)</td>
<td>32.4 (3.0–107.0)</td>
<td>7.3 (3.2–80.6)</td>
</tr>
<tr>
<td><strong>IL-1β</strong></td>
<td>5.6 (0.0–52.7)</td>
<td>4.8 (0.0–19.0)</td>
<td>6.3 (0.1–52.7)</td>
<td>8.5 (2.2–31.0)</td>
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<tr>
<td><strong>IL-1ra</strong></td>
<td>393.0 (137.0–4556.2)</td>
<td>337.0 (137.0–1373.7)</td>
<td>413.1 (145.5–4556.2)</td>
<td>196.0 (100.6–1253.9)</td>
</tr>
<tr>
<td><strong>IL-2</strong></td>
<td>6.8 (0.4–248.8)</td>
<td>9.8 (3.7–57.5)</td>
<td>6.0 (0.4–248.8)</td>
<td>8.2 (3.6–11.9)</td>
</tr>
<tr>
<td><strong>IL-4</strong></td>
<td>13.8 (3.5–151.5)</td>
<td>13.2 (3.5–151.5)</td>
<td>13.9 (4.3–151.5)</td>
<td>18.5 (2.04–73.31)</td>
</tr>
<tr>
<td><strong>IL-5</strong></td>
<td>5.3 (0.1–52.8)</td>
<td>3.4 (0.1–37.0)</td>
<td>9.1 (0.2–52.8)</td>
<td>3.0 (0.0–4.6)</td>
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<tr>
<td><strong>IL-6</strong></td>
<td>79.8 (6.8–893.8)</td>
<td>97.3 (6.8–893.8)</td>
<td>75.4 (12.5–550.3)</td>
<td>52.7 (14.1–238.5)</td>
</tr>
<tr>
<td><strong>IL-7</strong></td>
<td>14.8 (1.5–42.8)</td>
<td>13.3 (1.5–42.8)</td>
<td>15.3 (2.6–38.1)</td>
<td>17.6 (0.8–27.1)</td>
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<tr>
<td><strong>IL-8</strong></td>
<td>13.3 (0.2–236.1)</td>
<td>14.2 (1.3–236.1)</td>
<td>12.2 (0.2–108.7)</td>
<td>9.1 (0.4–17.6)</td>
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<tr>
<td><strong>IL-9</strong></td>
<td>55.8 (5.4–2036.2)</td>
<td>39.9 (8.8–2036.2)</td>
<td>58.6 (5.4–1470.0)</td>
<td>33.8 (29.4–72.9)</td>
</tr>
<tr>
<td><strong>IL-10</strong></td>
<td>15.7 (0.1–145.4)</td>
<td>12.2 (0.1–88.1)</td>
<td>18.3 (0.6–145.4)</td>
<td>16.9 (0.4–64.3)</td>
</tr>
<tr>
<td><strong>IL-12</strong></td>
<td>9.5 (0.9–110.7)</td>
<td>18.4 (2.3–110.7)</td>
<td>8.3 (0.9–83.5)</td>
<td>6.9 (0.3–52.3)</td>
</tr>
<tr>
<td><strong>IL-13</strong></td>
<td>3.4 (0.1–3.7)</td>
<td>6.9 (0.1–23.3)</td>
<td>2.9 (0.5–33.7)</td>
<td>3.6 (0.5–4.0)</td>
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<tr>
<td><strong>IL-15</strong></td>
<td>10.1 (0.0–71.3)</td>
<td>10.1 (5.3–71.3)</td>
<td>10.1 (0.0–66.0)</td>
<td>18.6 (5.9–90.1)</td>
</tr>
<tr>
<td><strong>IL-17</strong></td>
<td>11.4 (0.0–217.9)</td>
<td>21.3 (11.7–33.9)</td>
<td>6.5 (0.0–217.9)</td>
<td>0.1 (0.1–0.1)</td>
</tr>
<tr>
<td><strong>IFN-γ</strong></td>
<td>132.6 (3.5–570.1)</td>
<td>109.7 (4.5–570.1)</td>
<td>138.0 (3.5–529.6)</td>
<td>152.1 (44.8–1061.3)</td>
</tr>
<tr>
<td><strong>IP-10</strong></td>
<td>1592.6 (423.5–13882.2)</td>
<td>1930.8 (702.5–9437.7)</td>
<td>1287.4 (423.5–13882.2)</td>
<td>508.7 (330.9–824.4)</td>
</tr>
<tr>
<td><strong>TNF-α</strong></td>
<td>20.5 (0.1–682.8)</td>
<td>8.9 (0.2–91.6)</td>
<td>41.4 (0.1–682.8)</td>
<td>36.0 (0.3–392.1)</td>
</tr>
<tr>
<td><strong>GM-CSF</strong></td>
<td>33.5 (0.2–962.0)</td>
<td>61.9 (5.3–844.6)</td>
<td>27.1 (0.2–962.0)</td>
<td>22.2 (0.6–72.0)</td>
</tr>
<tr>
<td><strong>G-CSF</strong></td>
<td>45.9 (4.2–1586.7)</td>
<td>56.4 (19.2–1586.7)</td>
<td>43.5 (4.2–173.8)</td>
<td>36.0 (19.4–129.6)</td>
</tr>
<tr>
<td><strong>MCP-1</strong></td>
<td>48.2 (13.0–223.6)</td>
<td>61.1 (13.5–223.6)</td>
<td>47.8 (13.5–164.1)</td>
<td>57.3 (30.2–81.0)</td>
</tr>
<tr>
<td><strong>MIP-1α</strong></td>
<td>10.1 (1.5–46.8)</td>
<td>8.8 (2.6–46.8)</td>
<td>11.8 (1.5–36.9)</td>
<td>12.5 (10.6–14.8)</td>
</tr>
<tr>
<td><strong>MIP-1β</strong></td>
<td>80.7 (6.0–228.4)</td>
<td>85.1 (6.0–200.7)</td>
<td>79.3 (14.4–228.4)</td>
<td>112.4 (15.3–168.0)</td>
</tr>
<tr>
<td><strong>Eotaxin</strong></td>
<td>77.9 (8.2–440.8)</td>
<td>63.7 (8.2–354.9)</td>
<td>81.4 (35.5–440.8)</td>
<td>127.0 (69.8–577.4)</td>
</tr>
<tr>
<td><strong>RANTES</strong></td>
<td>7256.1 (3198.8–114340.4)</td>
<td>9455.9 (7624.3–66245.6)</td>
<td>4903.2 (3198.8–114340.4)</td>
<td>5831.7 (4632.5–7030.9)</td>
</tr>
<tr>
<td><strong>PDGF-bb</strong></td>
<td>5012.9 (433.3–14969.3)</td>
<td>4143.6 (789.0–11617.3)</td>
<td>5412.2 (433.3–14969.3)</td>
<td>6200.3 (2622.6–12493.9)</td>
</tr>
<tr>
<td><strong>FGF-basic</strong></td>
<td>73.3 (15.4–471.6)</td>
<td>65.5 (25.2–471.6)</td>
<td>74.4 (15.4–215.7)</td>
<td>71.6 (35.2–156.8)</td>
</tr>
<tr>
<td><strong>VEGF</strong></td>
<td>124.8 (5.2–729.1)</td>
<td>153.4 (21.6–319.6)</td>
<td>94.1 (5.2–729.1)</td>
<td>55.4 (18.1–171.0)</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; *p < 0.001 versus Control; #p < 0.05; *p < 0.01; 'p < 0.001 versus Asthma, Nonsensitized. IgE: IU/ml; Eosinophils: /mm<sup>3</sup>; ECP: ng/ml; cytokines/chemokines: pg/ml.

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Th1-associated chemokines have the potential to downregulate allergic inflammation [24]. However, interferon-inducible protein 10 (IP-10)/CXCL10 also contributes to bronchial hyperreactivity and Th2-type allergic inflammation in animal models of asthma [25]. Furthermore, IP-10 is present in bronchial lavage fluid during human allergic pulmonary late-phase reactions [26]. Brightling et al. [27] found that IP-10 was expressed more frequently in bronchial biopsies of asthmatic airway smooth muscle compared with tissue from healthy control subjects. T cells recruited during viral infections are predominantly Th1 and characterized by the production of a pattern of cytokines that includes IFN-γ and IL-2 [28]. Th1 chemokine IP-10 attracts Th1 cells through interaction with CXCR3 and plays a prognostic role in viral infection [28].
man studies, serum IP-10 levels in virus-induced acute asthma subjects aged 16–74 years are higher than in non-virus-induced acute asthma cases, specifically in cases of rhinovirus infection [29]. Our recent study also suggests that serum IP-10 is elevated in rhinovirus- and RS virus-induced acute childhood asthma exacerbations [6]. Another report showed that the levels of plasma IP-10 in infants are elevated during acute RS virus infection compared with the convalescence period and controls [30]. Furthermore, serum IP-10 is elevated in viral-induced acute exacerbations of asthma compared with stable asthma [6, 29] and acute non-virus-induced asthma [29]. These observations and the present study collectively suggest that Th1 chemokine, IP-10, could be used to predict a virus-induced acute exacerbations, specifically in nonsensitized cases and that the inhibition of the CXCL10/CXCR3 axis may be a novel target for the treatment of virus-induced asthma. Although the exact reasons for the higher production of IP-10 in nonsensitized virus-induced acute exacerbations of childhood asthma remain elusive, they might be explained by Th1-dominant immune responses to, for example, virus infections, but not Th2 immune responses that include aeroallergen sensitization and eosinophil activation.

The limitation of the present study is that we used serum sample to measure 27 cytokines and chemokines. Previous report suggest that the large amounts of RANTES and MIP-1z are released from platelets during ex vivo clotting [31], suggesting that the measurement of serum sample, but not plasma sample is not appropriate for some cytokines and chemokines. Further studies are needed to investigate to correct levels of them.

Further work is required to clarify the mechanisms leading to acute exacerbations of asthma and the relationship between allergen sensitization and IP-10 production. These studies might ultimately lead to the prevention and/or treatment of non-atopic/atopic asthma exacerbations caused by both virus infections and aeroallergens.

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AUTHORSHIP
MK conducted the study design. KS and MK collected samples, performed data analysis, wrote first draft, and finalized the manuscript. SK, MN, ME, HT, KH, YY, and KM collected samples and performed measurement of serum sample, but not plasma sample is not appropriate for some cytokines and chemokines. Further studies are needed to investigate to correct levels of them.

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