

## Respiratory viral infections drive chemokine expression and exacerbate the asthmatic response

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A number of investigations have linked respiratory viral infections and the intensity and subsequent exacerbation of asthma through host response mechanisms. For example, it is likely that the immune-inflammatory response to respiratory syncytial virus can cause a predisposition toward an intense inflammatory reaction associated with asthma, and adenovirus might cause exacerbation of the immune response associated with chronic obstructive pulmonary disease. In each of these situations, the host's immune response plays a critical mechanistic role through the production of certain cytokines and chemokines. Specific aspects of these augmented immune responses are determined by the biology of the virus, the genetic variability of the host, and the cytokine-chemokine phenotype of the involved tissue. For instance, the type 1/type 2 cytokine ratio in the airways during infection with rhinovirus determines how long the viral infection endures. By this same theory, it has been demonstrated that chemokine levels produced during respiratory syncytial virus infection determine host responses to later immune stimuli in the lung, with the potential to augment the asthmatic response. Further research in this area will clarify cytokines, chemokines, or cell targets, which will provide the basis for next-generation therapies. (*J Allergy Clin Immunol* 2006;118:295-302.)

**Key words:** Asthma, chemokine, exacerbation, pulmonary, respiratory virus, rhinovirus, influenza, respiratory syncytial virus, rhinovirus

Increasing clinical evidence supports the concept that certain respiratory viral infections play an important

### Abbreviations used

BAL: Bronchoalveolar lavage  
COPD: Chronic obstructive pulmonary disease  
NLF: Nasal lavage fluid  
OVA: Ovalbumin  
RSV: Respiratory syncytial virus

mechanistic role in the initiation of acute lung pathology, as well as set the foundation for longer-term chronic effects that were initiated during the original virus-host interaction. A number of clinical epidemiology studies have identified that the exposure to respiratory syncytial virus (RSV) during early childhood can provide the underpinnings for the development of chronic asthma in later childhood. Furthermore, respiratory viruses, such as RSV and rhinovirus, appear to be intimately linked to exacerbations in the physiologic and immunologic intensity of an asthmatic response in many individuals. These exacerbations are associated with increased airway hyperresponsiveness and a significant influx of leukocytes into the lungs. The intensity of the inflammatory response has been directly correlated to the expression of chemokines by virally infected pulmonary structural cells, resident immune cells, and infiltrating leukocytes. In the clinical arena investigations have incriminated a number of chemokines, including CXCL8 (IL-8), CCL3 (macrophage inflammatory protein 1 $\alpha$ ), and CCL5 (RANTES), as major mediators released during respiratory viral infection, and the level of these chemokines correlates with the severity of disease. These studies collectively indicate an intimate connection between chemokine expression and respiratory viral infections. They support the growing notion that exposure to infectious agents in early life profoundly influences subsequent immune events that might facilitate the development of severe chronic obstructive airway disease.

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## DISPARATE HOST RESPONSE TO RESPIRATORY VIRAL INFECTIONS

It is becoming clear that not all respiratory viruses induce the same lung pathology; instead, they are responsible for disparate immune responses. Clinical studies examining patients infected with respiratory viruses have found that RSV, rhinovirus, and adenovirus cause airway obstruction and in some cases cause decreased forced expiratory volume readings.<sup>1</sup> Interestingly, this correlation is not present in patients infected with the influenza virus. Additionally, studies in mouse models have shown that although RSV infection causes the production of (T<sub>H</sub>2) cytokines, as measured on the basis of mRNA, this is not the case for influenza.<sup>2</sup> One experimental mouse model examining the role between influenza and allergy has determined that influenza infection can decrease the allergic response, although the mechanism is not clear.<sup>3</sup> These studies are supported by clinical investigations that demonstrate that a relatively low number of influenza cases, versus RSV or rhinovirus infections, actually cause exacerbation of asthma and acute bronchiolitis in adults.<sup>4-6</sup>

Some of the differences in the end physiologic response to viral infection likely come from the differences in the profile of inflammatory mediators that are produced in response to each virus. One particular difference in the host response to infection with RSV or rhinovirus is the chemokine profile that each infection elicits. Although there are often cellular similarities in the response to infection, there are clear differences in the chemokines that are present, the levels of those chemokines expressed, and the presence of the predominant chemokine-generating cell types.

## COMPARATIVE STUDIES OF SPECIFIC CHEMOKINES DURING RESPIRATORY VIRAL INFECTIONS

Chemokines, or chemotactic cytokines, were first described for their ability to attract leukocytes to sites of inflammation, a phenomenon known as chemotaxis. However, data now support a varied and eclectic role for these cytokines during immune-inflammatory processes. Chemokines are produced by a variety of cells, including stromal cells, epithelial cells, and all immune cells. These molecules are known to have functions other than chemotaxis, including regulation of inflammation, cellular proliferation, mucus production, tumorigenesis, and angiogenesis. In addition, various chemokines have been found to be important in the initiation and maintenance of the host's response to pathogens.

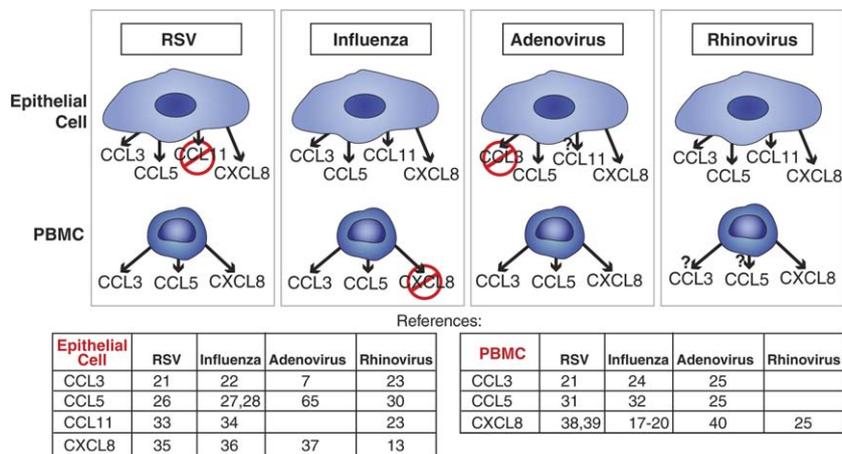
Several studies have examined the differences in the host response to respiratory viral infection in human subjects. Although none of these studies have come up with a single cytokine or chemokine that can account for the differences in physiologic and immunologic responses that occur on infection, several interesting findings have been published. Although many studies have looked at the production of CCL3 and CCL5 *in vitro* and *in vivo*, there

is no difference in the level of these ligands found in the airways of patients infected with influenza or RSV.<sup>7,8</sup> However, one report demonstrated that in patients infected with either RSV or influenza, higher levels of CCL3 protein levels in the bronchoalveolar lavage (BAL) fluid correlated with hypoxic bronchiolitis, which was not the case for CCL5.<sup>8</sup> Another study found that patients infected with RSV have higher serum levels of CCL5, soluble intercellular adhesion molecule, IL-4, IL-5, and IgE than patients infected with influenza.<sup>9</sup> This latter study suggests the importance of examining additional compartments for cytokine and chemokine levels and not only the lung when studying respiratory viral infections.

CXCL8 (IL-8) is the most studied chemokine and appears to correlate with the severity of respiratory disease. Some differences have been found in CXCL8 production in patients infected with respiratory viruses. A comparative study examining the effects of respiratory viruses on CXCL8 production found that although levels of CXCL8 protein in the nasal lavage fluid (NLF) of influenza virus- and rhinovirus-infected patients correlated with a higher symptom score, this was not the case for RSV-infected patients. Interestingly, in this same study the RSV-infected group had the greatest incidence of wheezing,<sup>1</sup> an indicative correlate for the development of asthma. Another group found that influenza infection was associated with higher CXCL8 levels in nasal washes than RSV.<sup>10</sup> Additionally, the peak production of CXCL8 is different when comparing infections. In experimental RSV infection of human subjects, there is an initial spike of CXCL8 protein levels in NLF on day 1, with a more significant peak production occurring between days 6 and 14 of infection.<sup>11</sup> However, during influenza infection, CXCL8 protein in NLF peaks between days 4 and 6 and is back to baseline by day 7.<sup>12</sup> Rhinovirus infection mimics the CXCL8 secretion pattern seen in influenza infection, with the peak production occurring between days 2 and 3 and dropping off by day 5.<sup>13</sup> These data clearly demonstrate that the biology between the viruses is different, which might account for some of the differences in inflammation and pathophysiology of the different pathogens.

Differences have also been found in the levels of some nonchemotactic cytokines when comparing respiratory viruses, specifically influenza and RSV. One study found that IL-6 levels were higher in the NLF of RSV-infected patients than in uninfected control subjects, which was not the case for influenza-infected patients. An additional difference between the groups was that although levels of IL-11 were increased in asthmatic subjects infected with RSV, this was not the case for influenza-infected asthmatic patients.<sup>10</sup>

Experimental infection of human subjects with viruses has yielded additional valuable data on the duration of infection and peak of chemokine and cytokine production. Although a direct comparative study has not been conducted in experimental infection, it is clear that RSV infection lasts longer than influenza or rhinovirus infection. RSV is detected in nasal washes between days 5 and 14, whereas influenza and rhinovirus titers peak at day 2



**FIG 1.** Chemokine profiles of epithelial cells and PBMCs infected with various respiratory viruses. The production of CCL3, CCL5, CCL11, and CXCL8 is depicted with respect to infection with 4 different respiratory viruses. References to relevant research are included in the tables.

and disappear by day 8.<sup>11,12,14</sup> In contrast, adenovirus might be able to establish a latent infection that is correlated with chronic obstructive pulmonary disease (COPD).<sup>15</sup> Thus the phenotypic cytokine and chemokine production profiles and disease severity are likely affected by the ability of the virus to propagate.

Infecting cells *in vitro* and measuring chemokine production has been beneficial in understanding which chemokines are relevant during viral infection. Although several chemokines, such as CCL3, CCL5, CCL11, and CXCL8, are consistently found to be produced in cell culture systems upon viral infection, microarray data from RSV-infected epithelial cells suggests that other chemokines might also play a role in the response to viral infection.<sup>16</sup> Interestingly, there seems to be some disparity in the chemokines produced during a given viral infection. For example, PBMCs infected with influenza do not produce CXCL8,<sup>17-20</sup> and epithelial cells infected with adenovirus do not produce CCL3<sup>7</sup> (summarized in Fig 1).<sup>7,13,17-40</sup> Chemokines and their receptors might also play a more direct role in the outcome of viral infection than cell recruitment or activation. For example, *in vitro* CCL5 production has been shown to inhibit binding of RSV to cells.<sup>41</sup> Additionally, the RSV G protein was shown to mimic the ligand for CX3CR1<sup>42</sup> and might inhibit T cells from migrating to the lung during RSV infection.<sup>43</sup>

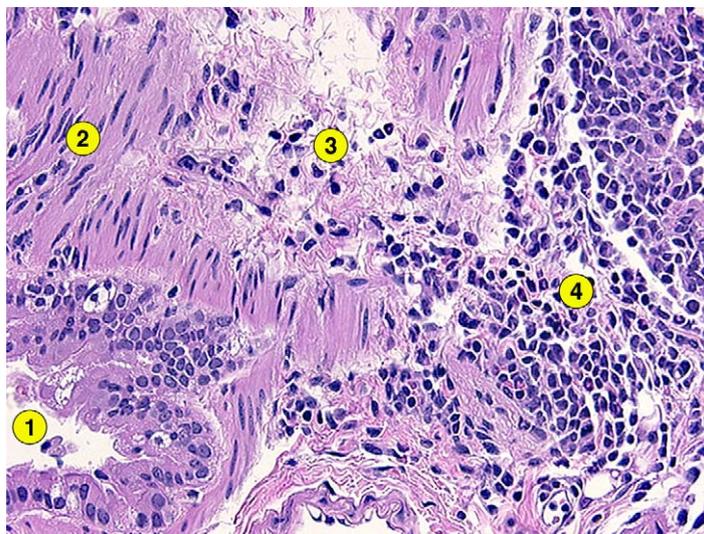
## RESPIRATORY VIRAL INFECTION AND PREDISPOSITION TO ASTHMA

Although the host response to viral infection differs depending on the infectious agent, perhaps the most interesting and clinically relevant differences occur well after the infection has taken place. For example, many have speculated that RSV infection can result in childhood asthma, and research has been published to suggest this hypothesis might be true. Other research suggests that

adenovirus infection might predispose children to chronic obstructive bronchitis.<sup>44</sup> Another report implicated that exacerbation of COPD might be the result of latent adenoviral infection.<sup>45</sup> It is clear that some viruses can have a lasting effect on the structure and function of the lung as shown in Fig 2. Interestingly, no research studies to date draw a correlation between influenza infection and the later development of respiratory disorders. One study did find that the percentage of influenza-infected children affected by bronchiolitis, which is thought to be a marker for wheezing later in life, was only 5%.<sup>46</sup>

The most powerful research suggesting that RSV infection predisposes children to later asthma followed the same cohort of children for 13 years. One group of these children was hospitalized as infants for RSV-induced bronchiolitis, whereas the control group did not have an RSV infection during infancy. The studies show that children infected with RSV have increased wheezing and allergies when compared with control subjects.<sup>47,48</sup> Analyzing the cytokine secretion of T cells from these individuals in response to a panel of aeroallergens revealed that T cells from children hospitalized for RSV in their infancy secreted more IL-4 in response to aeroallergens than control subjects.<sup>49</sup> Another publication demonstrated that although RSV infection at a young age leads to a significant increase in wheeze up to age 11 years, the incidence of wheeze in RSV-infected individuals decreases by age 13 years.<sup>50</sup> Two other studies found that although there was no correlation between RSV infection in infancy and clinically diagnosed asthma later in life, children infected with RSV had impaired lung function when compared with control subjects.<sup>51,52</sup> These investigators argue that RSV does not cause skewing of the immune system, but rather those children affected by RSV infection have preexisting lung abnormalities. These same abnormalities cause decreased lung function later in life.

In accordance with this research, another study followed a cohort of children admitted to a hospital for acute bronchiolitis, the cause of which was not determined. Nine



**FIG 2.** The various biologic activities of chemokines can contribute to the pathology associated with respiratory virus–exacerbated asthma, including (1) effect on epithelial cells, (2) induction of cell proliferation, (3) matrix deposition, and (4) recruitment of specific leukocyte populations to the lungs.

years after admission, children in the index group had a higher incidence of asthma when compared with control subjects.<sup>53</sup> Further research will clarify whether viral infection is necessary for predisposition to asthma or whether it merely uncovers abnormalities in individuals who are already predisposed to have asthmatic responses.

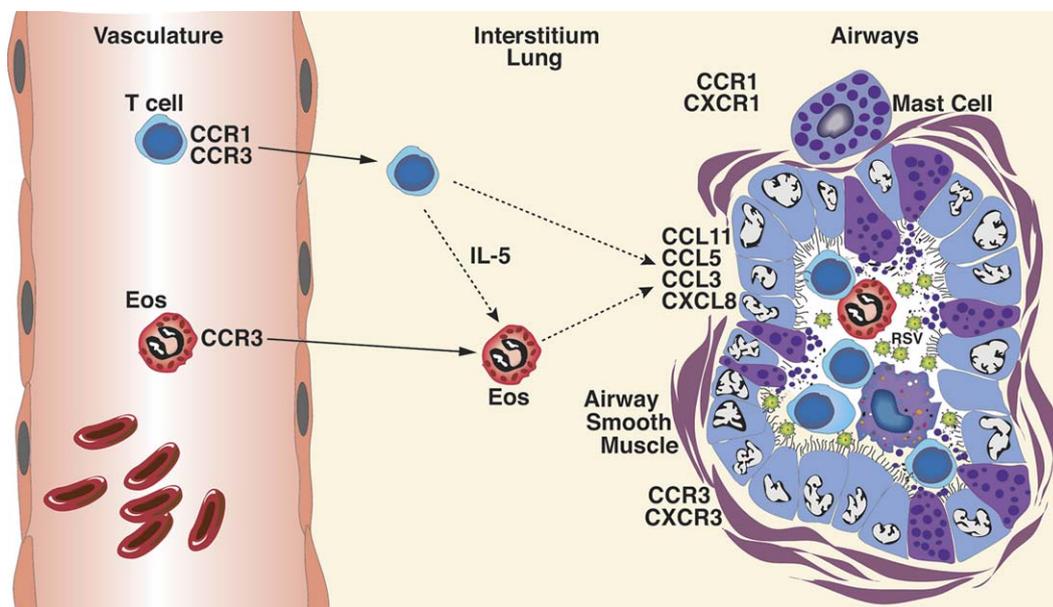
Murine studies have also yielded conflicting results in regard to the ability of viral infection to enhance subsequent allergic responses. Although some research suggests that RSV infection occurring during the allergen sensitization phase prolongs airway hyperreactivity and increases inflammation and mucus production in the lungs,<sup>54</sup> other reports suggest that RSV given before allergen sensitization reduces airway hyperreactivity, eosinophilia, and IL-13 production.<sup>55</sup> Another study with repeated RSV infections before and during allergen challenge demonstrated a decrease in mucus-producing cells and alveolitis, although infection did not alter lymphocytic infiltration into the lungs.<sup>56</sup> This research suggests that the timing of RSV infection is critical in determining how the immune system responds to subsequent stimuli. If applied clinically, these data could determine which RSV-infected patients receive treatment. Several studies in which mice were infected with RSV and then sensitized to allergen suggest CCL5 might be important in predisposing virally infected mice to more severe allergies. In these studies RSV infection was initiated 21 days before allergen sensitization. In control mice previous RSV infection increased airway hyperreactivity and the level of chemokines in the lungs. Blocking IL-13 during RSV infection reduced the levels of chemokines, as well as airway hyperreactivity, in the lungs of mice that were subsequently sensitized and challenged with allergen.<sup>57</sup> When CCL5 was blocked during the course of RSV infection, subsequent allergen sensitization and challenge was reduced to the phenotype of allergen-

sensitized uninfected mice. This was correlated to a reduced level of leukotriene production.<sup>58</sup> Additionally, the absence of CCR1 in this model caused a reduction in airway hyperreactivity and mucus, which was accompanied by a reduced amount of IL-13 in the lungs, as well as reduced numbers of T cells and eosinophils.<sup>59</sup> These studies implicate that CCL5 and other CCR1 ligands might be important in setting up the immune system in the lung to respond inappropriately to allergens after RSV infection. Fig 3 shows some of the chemokines induced during RSV infection and the cell types on which the receptors for these chemokines are present.

## RESPIRATORY VIRAL INFECTIONS, CHEMOKINES, AND EXACERBATION OF ALLERGIC ASTHMA

Many viruses have been implicated in the exacerbation of allergic asthma, including influenza, rhinovirus, RSV, adenovirus, and coronaviruses. Experimental infection of human subjects with rhinovirus demonstrated that exacerbation was associated with increased airway hyperreactivity in response to allergen.<sup>60</sup> Interestingly, RSV appears to cause the most severe exacerbations,<sup>61</sup> whereas rhinovirus appears to be responsible for the majority of exacerbations.<sup>6,62</sup> For this reason, the bulk of human studies have examined the role of rhinovirus in exacerbation of allergic responses. The exacerbation of allergic asthma by viruses seems to be correlated with both CCL5 and CXCL8.

There is a definite link between rhinovirus infection in exacerbation of asthma and increased CXCL8 levels. One report found that CXCL8 levels correlated with severity of symptoms in asthmatic subjects who had rhinovirus infection,<sup>63</sup> which mimics what is seen in subjects infected with rhinovirus alone. Not surprisingly, there was also a



**FIG 3.** Chemokines play an important role in respiratory virus-induced asthma because they provide one of the mechanisms for the successful delivery of specific blood borne leukocytes to the airways of the lung. In particular, CCL11 (eotaxin), CCL5 (RANTES), and CCL3 (macrophage inflammatory protein 1 $\alpha$ ) and their respective receptors CCR3, CCR1, and CCR5 have been identified as important to the exacerbation of experimentally induced asthma.

correlation between CXCL8 levels and neutrophils found in the airway. This report found no differences in airway hyperreactivity of asthmatic subjects on rhinovirus infection, which is in contrast to other published studies, but did find an increased sensitivity to histamine challenge. Another investigation examining the different cell types recruited to the respiratory tract during the common cold found a difference in the number of mast cells present in allergic patients versus those seen in nonallergic patients on viral infection.<sup>64</sup> This result could account for the increased sensitivity to histamine that was observed by van Benten et al.<sup>64</sup> This report also found that the number of CCL5- and CCL11-producing cells increased on viral infection in both allergic and nonallergic individuals. The investigators also observed an increase in almost every type of inflammatory cell, including eosinophils, T cells, macrophages, and neutrophils, regardless of allergen sensitization. Other research has demonstrated a correlation between IFN- $\gamma$  levels and symptom scores in rhinovirus-infected asthmatic subjects. Those patients with a higher ratio of IFN- $\gamma$ /IL-5 mRNA in the airways had less severe symptom scores. Interestingly, these subjects also had no detectable virus 14 days after infection, whereas those patients with a lower IFN- $\gamma$ /IL-5 mRNA ratio had worse symptoms and detectable virus at 14 days after infection.<sup>65</sup> The implications of this latter study are that the virus itself might not cause the exacerbation of asthma, but rather the individual's host response to the virus could be responsible. In this case perhaps higher levels of IL-5 or lower levels of IFN- $\gamma$  are responsible for delayed viral clearance. The mechanism could be due to recruitment of inappropriate cells or unnecessary regulation

of cells already recruited. Although these results suggest that there are few differences in the types of inflammatory processes that occur in allergic individuals infected with a respiratory virus when compared with nonallergic individuals, it is likely that exacerbation of allergic asthma by viral infection still exists.

One criterion that might cause the exacerbation of asthma appears to be the presence of allergen at the time of viral infection. If both viral infection and allergen exposure do not occur at the same time, then the increase in inflammation caused by the virus has a limited ability to exacerbate an allergic response. Confirmation of this hypothesis stems from a report demonstrating that there was a higher risk of hospital admission for exacerbation of asthma in patients who were both infected with a respiratory virus and exposed to allergen at the same time.<sup>66</sup> Another study in which allergic individuals were infected 1 week after allergen exposure reported that subjects infected with rhinovirus had no differences in airway hyperreactivity when compared with infected nonallergic individuals. This provides further evidence that viral infection and allergen exposure need to be concurrent for exacerbation to occur.<sup>67</sup> However, concomitant exposure to allergen and virus is likely not the only cause of asthma exacerbation because nonallergic asthmatic subjects can also experience periods of increased wheezing.<sup>68</sup>

A number of studies have been done in murine models to examine the role of viral infection in allergen-sensitized mice. These models sensitize mice to an allergen and then infect the mice with virus before allergen challenge. Although several models have proved that influenza<sup>69</sup>

and RSV<sup>70</sup> can increase inflammation in the lungs of allergic mice on infection and augment the allergic response, other studies have actually proved the opposite. For example, one study shows that influenza infection actually inhibits the recruitment of T<sub>H</sub>2 cells to the BAL fluid of allergic mice.<sup>3</sup> A report comparing the effects of several viruses on animals previously sensitized to allergen showed that although both influenza and RSV induced similar patterns of inflammation, influenza downregulated the expression of type 2 cytokines in the lung.<sup>2</sup> It is possible that some of the changes in inflammation that take place on respiratory viral infection of allergic mice are due to differences in chemokine expression. For instance, RSV infection increased levels of CCL11,<sup>71</sup> CCL3, and CCL5 in the lungs of allergic mice (Schaller and Lukacs, unpublished data). The increase in chemokines could cause an increase in T cells to the lungs and BAL fluid of allergen-sensitized mice. This has been shown in both an influenza<sup>69</sup> and an RSV model of exacerbated asthma (Schaller and Lukacs, unpublished data). The research using the influenza model demonstrated that allergen-specific cells can be recruited to the lymph node on viral infection and secrete IL-4. This suggests a prominent role for T cells during the virally exacerbated response.

Further evidence supporting the hypothesis that increased T-cell recruitment might be responsible for asthma exacerbation comes from research using an influenza virus expressing the MHC I and MHC II epitopes of the ovalbumin (OVA) peptide. These studies have shown that OVA-specific T cells of both the CD4<sup>+</sup> and CD8<sup>+</sup> subsets can be recruited to the lung and BAL fluid nonspecifically, even in the absence of an influenza infection.<sup>72,73</sup> Viral infection with wild-type influenza increased recruitment of these T cells to the lung and lymph node; however, only the influenza virus expressing OVA peptide was able to induce activation and expansion of the OVA-specific T-cell population. These studies provide insight into the mechanism of asthma exacerbation. Although respiratory viral infection causes increased recruitment of T cells to the lung and lymph node, only some of these T cells are specific for viral antigen. In addition, some of the recruited T cells might be specific for inhaled allergens. If allergen exposure occurs at the time of viral infection, the increase in allergen-specific T cells to the lung would cause an increased allergic response. In addition to an ongoing viral infection, this could cause increased airway hyperreactivity and increased pathology in the respiratory tract.

The recruitment of allergen-responsive T cells to the lung and draining lymph nodes has been linked to CCR1 in a murine model of RSV-induced exacerbation of allergic asthma (Schaller and Lukacs, unpublished data). Studies initiated in our laboratory have demonstrated that RSV infection increases the numbers of both CD4<sup>+</sup> and CD8<sup>+</sup> T cells in the lungs and lymph nodes of allergic mice. This was correlated with increased inflammatory cytokine levels and increases in the chemokines CCL3 and CCL5. These studies also provide evidence that CCR1 might be in part responsible for exacerbation because CCR1<sup>-/-</sup> mice do not have an exacerbated phenotype.

CCR1<sup>-/-</sup> mice exhibited a reduction in recruitment of allergen-specific CD8<sup>+</sup> T cells to the lymph node. Thus it is possible that CCR1 is part of the chemokine receptor profile of allergen-specific and virus-specific T cells, and the production of CCR1 ligands during viral infection could cause the recruitment of T cells to the site of infection and enhance allergic responses.

The role of CCR1 in T cell-mediated allergen exacerbation correlates well with data from multiple laboratories indicating that CCL5 is one of the most highly expressed chemokines during virally induced disease.<sup>7,8,74</sup> A subset of memory CD8<sup>+</sup> T cells can also express the CXCR1 receptor and chemotax in response to CXCL8.<sup>75</sup> These T cells are activated, expressing high levels of perforin and granzyme, and are more cytotoxic than the larger population of memory CD8<sup>+</sup> T cells. Interestingly, in patients infected with influenza, a high percentage of CXCR1<sup>+</sup>CD8<sup>+</sup> T cells are specific for the virus.<sup>76</sup>

## CONCLUSIONS

Taken together, a variety of investigations suggest an important role for chemokines during respiratory viral infection. In cases of viral infection alone, the differences in production of chemokines, such as CCL5, CCL3, CCL11, and CXCL8, on infection might cause differences in the host response. These chemokines might also be important in setting up later immune responses in the lung.

The way the host responds to infection with different viruses might cause the association of various viral infections with chronic diseases. For example, it is possible that the host response to RSV can cause a predisposition toward asthma and that adenovirus causes exacerbation of COPD, thereby leading to do the production of certain cytokines and chemokines. Although some of this response is determined by the biology of the virus, genetic variability of the host also plays a role. For instance, the T<sub>H</sub>1/T<sub>H</sub>2 cytokine ratio in the airways during infection with rhinovirus determines how long the viral infection endures. By this same theory, it is possible that the amount of CCL5 produced during RSV infection determines host responses to later immune stimuli in the lung and that the amount of CXCL8 produced during adenoviral infection correlates with the degree of exacerbation of a patient with COPD. Further research in this area might clarify what cytokines, chemokines, or cell types need to be targeted to prevent viral infection from influencing other immune responses.

Although certain viruses might set up later immune responses in the respiratory tract, it is likely that all respiratory viruses are able to exacerbate asthmatic responses in the lung. This is because the production of excess chemokines in the lung will not only recruit virus-specific T cells but also allergen-specific T cells. These allergen-specific cells will augment any allergic response that is already ongoing in the lung. Although a previous study has shown that CCR1 is responsible for this, there are likely other chemokine receptors that are also shared between allergen-specific and virus-specific cells.

With the identification of the chemokine receptors responsible for virally induced respiratory diseases, treatments might become more likely as therapies develop that could target cells that express these receptors. Although it is clear that many different cell types are responsible for clearing viral infection, perhaps targeting ones that are responsible for much of the pathology could eliminate many of the side effects of viral infection that result in skewing of later immune responses. For example, by targeting CCR1<sup>+</sup>CD8<sup>+</sup> T cells, but not CXCR1<sup>+</sup>CD8<sup>+</sup> T cells, viral clearance would not be delayed, and the pathology of viral infection could be reduced. A better understanding of how the host responds to different respiratory viral infections will also contribute significantly to our understanding of immunology in general. For example, how virus biology affects cell signaling is key in understanding how the host later responds to an infection. Because there are clear differences in which chemokines are produced on viral infection, this might be a good beginning in our understanding of how different viral infections cause disparate responses in the host.

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