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Mechanisms of rhinovirus-induced asthma

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Summary Several epidemiological studies using sensitive detection methodologies have confirmed that the majority of acute asthma exacerbations follow upper respiratory tract infections – common colds. Most of these colds are due to human rhinoviruses (RVs). RVs are able to reach and replicate in epithelial cells of the lower airways and can activate these cells to produce pro-inflammatory mediators. Under some circumstances, RVs can also become cytotoxic to the epithelium. Atopic asthmatic individuals produce less interferon-γ and more interleukin-10 than normal subjects in response to RV infection. Symptom severity as well as viral shedding after experimental RV infection, is inversely correlated with 'atopic' status, expressed as the interferon-γ to interleukin-5 ratio. Expression of co-stimulatory molecules on immune cells is also affected in atopic asthmatics, suggesting an aberrant immune response to RV that may lead to suboptimal viral clearance and viral persistence. Some of the above effects can be reversed in vitro by corticosteroids, second-generation antihistamines or anti-oxidants; however, the optimal strategy for treating acute asthma exacerbations requires further research at both mechanistic and clinical levels.

INTRODUCTION

There has been a remarkable increase in the prevalence of asthma and other allergic diseases in affluent societies during the last decades, particularly affecting children.[1] Asthma now affects over 150 million people worldwide and costs more than tuberculosis and AIDS combined![2] While there is no doubt that both genetic and environmental factors influence the development of asthma,[3] acute exacerbations of the disease, which account for most of the morbidity, patient discomfort and costs, are triggered by environmental stimuli including allergens, pollutants and viral infections. The association of common colds with asthma episodes is certainly an old one.[4] However, until recently, we lacked sensitive methodologies for the detection of the most prevalent respiratory viruses, such as rhinoviruses (RVs) or coronaviruses,[5] making it difficult to evaluate their importance. With the advent of polymerase chain reaction (PCR), it was shown that the majority of asthma exacerbations follow virologically confirmed upper respiratory tract infections, 60% of which are due to RVs.[6,7] This implies that the understanding of RV-induced asthma mechanisms could offer important evidence on the pathogenesis of the disease, as well as novel therapeutic targets. The initial epidemiological studies have now been confirmed in several instances; the percentage of virus-related wheeze in children is usually over 80%,[8] while in adults, this proportion is more varied (between 45% and 80% of cases).[9,10] The conclusion of the epidemiological studies was that RVs are not only responsible for the majority of common colds, but also for at least half of the acute asthma exacerbations in the community.

Crucial to our understanding of RV-associated asthma exacerbations has been the debate over whether such exacerbations are a result of direct infection of the lower airway epithelium by RVs, or of indirect mechanisms due to

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infection of the upper airway alone.[11] Resolution of this problem could reveal the initial event in the pathway that leads from upper respiratory viral infections to asthma exacerbations and suggest whether there is an opportunity to act therapeutically on asthma with antiviral therapy.

Since an immunological defect, expressed as an imbalance between type 1 (interferon-γ, interleukin (IL)-12) and type 2 (IL-4, IL-5 etc.) cytokines, is a central characteristic of atopy and asthma,[12] it would be of considerable importance to evaluate the immune response to RV infection in atopic asthmatic populations, especially in relation to the ongoing debate over the potential of another respiratory virus, respiratory syncytial virus (RSV), to deviate immunity at an early age and thus initiate asthma.[13] Such an immune deviation, if present, could help explain the apparently paradoxical induction of asthma, a paradigmally type-2-cytokine-related disease, by a type-1-cytokine-inducing stimulus, such as a viral infection.

During the last few years, an increasing number of both in-vitro and in-vivo studies have been performed in order to address the above questions. This review presents the current evidence and attempts to identify the pieces of the puzzle that are still to be discovered.

RVs ARE ABLE TO REPLICATE AT LOWER AIRWAY TEMPERATURES

The ability of RVs to infect the human bronchi has long been disputed. One of the most frequently quoted arguments against such a possibility has been the temperature restriction for replication of these viruses at an optimum of 33 °C, the temperature of the nasal cavities.[14] Nevertheless, this dogma was based on a small number of studies that only used one RV serotype.[15] Therefore, we cultured different RV serotypes at both 33 °C and 37 °C and compared their replicative capacity using titration assays.[16] Although 33 °C was preferable for several but not all serotypes, differences were small and virus titres achieved at 37 °C were high. Furthermore, when wild-type RV isolates were compared; less than half replicated better at 33 °C than 37 °C, while one isolate preferred 37 °C.[16] Consequently, it was concluded that there are no temperature restrictions for RV replication in the lower airways.

RVs INFECT BRONCHIAL EPITHELIAL CELLS

The ability of RVs to infect human bronchial epithelial cells was initially demonstrated using a transformed continuous cell line (BEAS-2B).[17] In a subsequent study, bronchial epithelium was modelled with the use of primary cells derived from surgical resection material.[18] When monolayers of these cells were exposed to different RVs, a time-dependent increase in viral RNA, assessed by RV-specific PCR, was observed, as well as an increase in viral titres. The peak of viral replication was between 24 h and 48 h, followed by a slow, gradual decline. Live virus remained in the bronchial epithelial cells for as long as 8 days after exposure. Using immunoprecipitation of radiolabelled newly synthesised proteins with specific antibodies, it was shown that newly synthesised RV proteins VP1 and VP3 were present at 48 h after exposure. Infection kinetics were very similar to those reported for nasal and tracheal epithelium,[19,20] suggesting that the whole respiratory tree is equally susceptible to RV. These results are almost identical to findings from another group[21] and have also been reproduced in murine epithelial cells using either a minor subtype RV whose receptor is present on these cells, or a major subtype in cells transfected with intercellular adhesion molecule-1 (ICAM-1), the receptor for the major subgroup RVs.[22]

RV INFECTION CAN BECOME CYTOTOXIC TO THE BRONCHIAL EPITHELIUM

An unexpected finding was that exposure of sparsely seeded monolayers of primary bronchial cells to higher concentrations of virus (10 infectious units/cell) resulted in a considerable RV-specific cytopathic effect.[18] This was also the case in the study of Schroth *et al.*;[21] however, these authors observed variations in the cytotoxic ability of different RV serotypes and proposed that serotype may be the important determinant of RV-induced cytotoxicity. These observations are in contrast to previous data showing a lack of RV cytopathic effect in several epithelial cell models,[19] suggesting that specific conditions should apply for RV to become cytotoxic. Previous studies have shown that in-vivo RV infection produces little or no histological alterations, with a patchy distribution in the respiratory epithelium.[23] This was also the case in a recent study by Mosser *et al.*[24] that investigated RV infection of adenoidal tissue; this study found that a small proportion of cells were infected with negligible epithelial cytotoxicity. However, it can be speculated that an already disrupted epithelium, as in the case of asthma,[25] may be more susceptible to RV-induced cytotoxicity. For this reason, we assessed RV-associated cytotoxicity in BEAS-2B cells seeded at varying densities and using a panel of different RVs. Cytotoxicity varied with serotype but was also dependent upon cell density in an almost linear way up to confluence.[26] Studies to characterise this phenomenon further are underway.

RVs INFECT THE BRONCHI AFTER AN EXPERIMENTALLY INDUCED COMMON COLD

Conclusive evidence of RV replication in the lungs was obtained in bronchial biopsies of human volunteers who were experimentally exposed to RV and who developed

colds.[18] Previous attempts to investigate the hypothesis of bronchial RV infection were hampered by the possibility of contamination from the upper airways during sampling; however, it has been shown that RV genetic material is present at higher quantities in cells of broncho-alveolar lavage rather than the supernatant, suggesting intracellular presence.[27] We used in-situ hybridisation, which precludes the possibility of contamination, with probes against either the genomic or the replicative strand of the virus. It was shown that 50% of bronchial biopsies from infected volunteers contained RV RNA after an experimentally induced cold, mostly in the epithelial layer. These samples were positive with both genomic and replicative strand probes and hybridisation signals co-localised, indicating that RVs not only reach and enter the bronchial epithelium after upper airway infection but also replicate in it. The percentage of positivity was identical to that reported in studies using the same technique in nasal epithelium where RV presence is not disputed,[28,29] indicating that RV bronchial infection may be the norm rather than the exception after common colds. Similarity between RV infection rates in upper and lower epithelium was recently confirmed ex vivo.[24] It remains to be confirmed whether bronchial RV infection also takes place after natural colds; the actual proportion of upper airway infections that are followed by bronchial spread of the virus also needs to be assessed.

RV INFECTION INDUCES AN INFLAMMATORY RESPONSE IN BRONCHIAL EPITHELIUM

The above evidence strongly supports the hypothesis that RV infection of the bronchial epithelium is the initial pathogenic event in RV-induced asthma exacerbations. To determine whether RV bronchial infection can result in local inflammation, pro-inflammatory cytokines and chemokines resulting from natural infection, experimental infection or in vitro have been measured in different settings.[30,31] Primary cells infected with RV express mRNA for and produce IL-6, IL-8, RANTES and IL-16.[18,32] In BEAS-2B cells, the eosinophil-specific chemo-attractants eotaxin and eotaxin-2 are also inducible.[33] In the upper airways, eotaxin has been found to be elevated during experimental colds in subjects with allergic rhinitis.[34] This is in agreement with results from subjects with naturally acquired colds that show a prolonged eosinophilic influx in the nasal mucosa, persisting into convalescence in allergic subjects.[35] IL-6 and IL-8, which are central mediators of inflammation and neutrophil recruitment, respectively, have also been found after RV infection of the upper respiratory epithelium and/or nasal secretions. Interestingly, high IL-8 levels in nasal fluids and increased allergen-induced plasma exudation responses observed in allergic subjects before RV16 inoculation protected against the development of cold symptoms.[34] The pro-inflammatory cytokine IL-1β is produced in increased levels in the nasal secretions of experimentally infected volunteers,[36] whereas elevated nasal granulocyte-colony stimulating factor and IL-8 levels correlate with neutrophilia in blood and nasal secretions following RV16 challenge of subjects with allergic rhinitis or asthma[37] or children with viral-precipitated asthma.[30] RANTES, a potent eosinophil and neutrophil chemo-attractant, seems to be a key component of RV-mediated inflammation in in-vitro and in-vivo studies.[21] RVs can also stimulate production of angiogenic growth factors such as fibroblast growth factor-2 from bronchial epithelial cells,[38] which may act on underlying stromal cells to induce tissue remodelling.

ICAM-1 is an important component of allergic inflammation.[39] Notably, ICAM-1 is also the receptor for 90% of RVs.[40] RVs are able to upregulate ICAM-1, their own receptor, through an nuclear factor-kappa B (NF-κB)-dependent mechanism, suggesting that this might be a strategy enhancing the infectivity of these viruses.[41] The transcription of most of the above-mentioned mediators is also promoted by NF-κB,[42] indicating a common molecular pathway that may regulate RV-induced inflammation as well as represent an important therapeutic target. Furthermore, ICAM-1 upregulation can be inhibited by corticosteroids,[43] second-generation antihistamines[44] and reducing agents,[45] all of which have potential in the treatment of virus-associated wheeze.

A DEFECTIVE TYPE 1 RESPONSE TO RV IN ATOPIC ASTHMA

A hallmark in the pathophysiology of asthma is the imbalance between two types of polarised immune responses, initially demonstrated for T-helper cells and subsequently shown to involve cytotoxic T cells and probably dendritic cells as well.[12] IFN-γ is the central cytokine in type 1 responses, while type 2 responses are characterised by IL-4 and IL-5; an increasing array of cytokines and chemokines are known to take part in or influence this balance. While asthma is paradigmally a type 2 cytokine-related disease, most evidence suggests that antiviral immune responses are usually dominated by type 1 cytokines. In order to model the possible effects of RV infection in atopic asthma, we used peripheral blood mononuclear cells (PBMC) derived from normal and atopic asthmatic subjects, exposed them to RV and assessed type 1 and type 2 cytokine production. When PBMCs were exposed to RV, time- and dose-dependent increases of IFN-γ, IL-12 and IL-10 were observed.[46] IFN-γ and IL-12 concentrations were significantly higher in cells from normal individuals, while IL-10 predominated in cultures from atopic asthmatic subjects. Furthermore, IL-4 was induced in cultures from asthmatic subjects only, while induction of IL-13 was found in both normal and atopic asthmatic subjects. These data suggest that following bronchial epithelial infection by RV and the concomitant inflammatory response described above, the systemic immune response that is known to

occur in vivo during and after a common cold[47] is probably defective in atopic asthmatic individuals. Decreased levels of type 1 cytokines and increased levels of type 2 cytokines, expressed as more than a three-fold difference in the ratio of IFN-γ/IL-4 between normal and atopic individuals in our experiments, support the notion of a suboptimal antiviral response that may be further enhanced in an already type 2 environment, as occurs in asthma. These data are in agreement with recent evidence from Parry *et al*.[48] showing an inverse correlation of IFN-γ production by PBMCs before an experimentally induced infection with RV shedding after the infection. Another study demonstrated an inverse correlation of RV persistence and symptom score after experimental infection with the ratio of IFN-γ/IL-5 levels in nasal secretions.[37] Even more interesting is further evidence from the same group showing an inverse correlation between PBMC IFN-γ responses and virus-induced airway hyper-reactivity in patients with asthma.[49]

PBMC PHENOTYPE AFTER IN-VITRO RV INFECTION

Taking the above data into consideration, we hypothesised that RVs may induce phenotypic changes in immune cells. When PBMCs were exposed to RV in vitro and phenotyped by flow cytometry, several alterations were observed.[50] Not surprisingly, cells were activated, as indicated by increased CD25 expression, in agreement with previous reports.[51] While there were no changes in the numbers of T cells (CD3, CD4 or CD8 positive) or B cells in these cultures, the number of CD14+ monocytes was reduced after RV infection. This was more pronounced in cells from normal subjects compared with asthmatic subjects. Furthermore, B7-1 (CD80) was induced on monocytes and B7-2 (CD86) on B cells; this upregulation was less marked in the asthmatic population. Finally, CTLA-4, considered a negative regulator of the CD28/B7 co-stimulatory system, was upregulated on T cells of the asthmatic patients alone. These data confirm the ability of RV to activate the antigen presentation system, as has also been shown in respiratory epithelial cells.[43] They also indicate that this process is defective in atopic asthmatic subjects. Such a defect in antigen presentation may partly explain the delayed viral clearance and increased symptomatology observed in the experimental infection studies.[37,48]

CONCLUDING REMARKS

The mechanisms of RV-induced asthma exacerbations are of great importance in the understanding of childhood asthma. RVs are the most common respiratory pathogens and are responsible for the majority of asthma exacerbations in childhood. Therapeutic strategies aimed at these viruses and/or their inflammatory consequences have the potential for greatly alleviating the morbidity and cost of asthma. Several questions are still to be answered in order to design any effective therapies. Nevertheless, the pieces of the puzzle seem to be getting closer together. We now know that bronchial infection frequently develops subsequent to a common cold. Such an infection is able to induce an epithelial inflammatory response that can, among others, lead to bronchial cellular infiltration, demonstrated after experimental RV infections. This is probably related to the development of asthma exacerbation symptomatology. In this respect, it will be necessary to determine whether a window of opportunity exists for the introduction of specific anti-rhinoviral drugs as potential therapies in the prevention of acute asthma exacerbations.

Moreover, atopic asthmatic individuals demonstrate a defective in-vitro antiviral immune response that is consistent with our understanding of their aberrant immunity to ubiquitous environmental antigens (allergens). It is therefore possible that RV infection in these individuals initiates or amplifies the immune-mediated type 2 inflammation that characterises the pathophysiology of asthma. As no animal model of RV infection currently exists, additional human studies are now required to explore this observation further.

PRACTICE POINTS

- Common colds are the most frequent triggers of acute asthma exacerbations in both children and adults
- Human RVs are responsible for the majority of common colds
- RVs are able to reach and replicate in the bronchial epithelium of both healthy and asthmatic individuals
- Epithelial RV infection induces production of many pro-inflammatory mediators (including IL-6, IL-8, RANTES and eotaxin) and upregulation of ICAM-1 (receptor for most RVs)
- The immune response to RV is affected by the atopic status of the host, both in vitro and in vivo. This seems to regulate viral shedding and symptoms

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REFERENCES

1. Hartert TV, Peebles RSJ. Epidemiology of asthma: the year in review. *Curr Opin Pulm Med* 2000; **6**: 4–9.

2. World Health Organisation. Bronchial Asthma. WHO Fact Sheet. World Health Organisation, Geneva, 2000. http://www.who.int/inf-fs/en/fact206.html.
3. Holgate ST. Asthma and allergy – disorders of civilization? *QJM* 1998; **91**: 171–184.
4. Pattemore PK, Johnston SL, Bardin PG. Viruses as precipitants of asthma symptoms. I. Epidemiology. *Clin Exp Allergy* 1992; **22**: 325–336.
5. Papadopoulos NG, Hunter J, Sanderson G, Meyer J, Johnston SL. Rhinovirus identification by Bgl I digestion of picornavirus RT-PCR amplicons. *J Virol Methods* 1999; **80**: 179–185.
6. Johnston SL, Pattemore PK, Sanderson G *et al.* Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995; **310**: 1225–1228.
7. Nicholson KG, Kent J, Hammersley V, Cancio E. Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *BMJ* 1997; **315**: 1060–1064.
8. Freymuth F, Vabret A, Brouard J *et al.* Detection of viral, Chlamydia pneumoniae and Mycoplasma pneumoniae infections in exacerbations of asthma in children. *J Clin Virol* 1999; **13**: 131–139.
9. Teichtahl H, Buckmaster N, Pertnikovs E. The incidence of respiratory tract infection in adults requiring hospitalization for asthma. *Chest* 1997; **112**: 591–596.
10. Atmar RL, Guy E, Guntupalli KK *et al.* Respiratory tract viral infections in inner-city asthmatic adults. *Arch Int Med* 1998; **158**: 2453–2459.
11. Papadopoulos NG, Johnston SL. Rhinovirus – not such an innocent? *QMJ* 2001; **94**: 1–3.
12. Romagnani S. The Th1/Th2 paradigm. *Immunol Today* 1997; **18**: 263–266.
13. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000; **161**: 1501–1507.
14. Corne JM, Holgate ST. Mechanisms of virus induced exacerbations of asthma. *Thorax* 1997; **52**: 380–389.
15. Killington RA, Stott EJ, Lee D. The effect of temperature on the synthesis of rhinovirus type 2 RNA. *J Gen Virol* 1977; **36**: 403–411.
16. Papadopoulos NG, Sanderson G, Hunter J, Johnston SL. Rhinoviruses replicate effectively at lower airway temperatures. *J Med Virol* 1999; **58**: 100–104.
17. Subauste MC, Jacoby DB, Richards SM, Proud D. Infection of a human respiratory epithelial cell line with rhinovirus. Induction of cytokine release and modulation of susceptibility to infection by cytokine exposure. *J Clin Invest* 1995; **96**: 549–557.
18. Papadopoulos NG, Bates PJ, Bardin PG *et al.* Rhinoviruses infect the lower airways. *J Infect Dis* 2000; **181**: 1875–1884.
19. Winther B, Gwaltney JM, Hendley JO. Respiratory virus infection of monolayer cultures of human nasal epithelial cells. *Am Rev Respir Dis* 1990; **141**: 839–845.
20. Terajima M, Yamaya M, Sekizawa K *et al.* Rhinovirus infection of primary cultures of human tracheal epithelium: role of ICAM-1 and IL-1beta. *Am J Physiol* 1997; **273**: L749–L759.
21. Schroth MK, Grimm E, Frindt P *et al.* Rhinovirus replication causes RANTES production in primary bronchial epithelial cells. *Am J Respir Cell Mol Biol* 1999; **20**: 1220–1228.
22. Tuthill TJ, Papadopoulos NG, Jourdan P *et al.* Mouse respiratory epithelial cells support efficient replication of human rhinovirus. *J Gen Virol* 2003; **84**: 2829–2836.
23. Winther B, Farr B, Turner RB, Hendley JO, Gwaltney JMJ, Mygind N. Histopathologic examination and enumeration of polymorphonuclear leukocytes in the nasal mucosa during experimental rhinovirus colds. *Acta Otolaryngol Suppl (Stockh)* 1984; **413**: 19–24.
24. Mosser AG, Brockman-Schneider R, Amineva S *et al.* Similar frequency of rhinovirus-infectible cells in upper and lower airway epithelium. *J Infect Dis* 2002; **185**: 734–743.
25. Campbell AM, Chanez P, Vignola AM, Bousquet J. Functional characteristics of bronchial epithelium obtained by brushing from asthmatic and normal subjects. *Am Rev Respir Dis* 1993; **147**: 529–534.
26. Papadopoulos NG, Bossios A, Xatzipsalti M, Karpathios T, Saxoni-Papageorgiou P, Gourgiotis D. Rhinovirus-induced cytotoxicity on bronchial epithelial cells is serotype and cell-density dependent. *Allergy* 2001; **56**: 36.
27. Gern JE, Galagan DM, Jarjour NN, Dick EC, Busse WW. Detection of rhinovirus RNA in lower airway cells during experimentally induced infection. *Am J Respir Crit Care Med* 1997; **155(1)**: 159–1161.
28. Arruda E, Boyle TR, Winther B, Pevear DC, Gwaltney JMJ, Hayden FG. Localization of human rhinovirus replication in the upper respiratory tract by in situ hybridization. *J Infect Dis* 1995; **171**: 1329–1333.
29. Bardin PG, Johnston SL, Sanderson G *et al.* Detection of rhinovirus infection of the nasal mucosa by oligonucleotide in situ hybridization. *Am J Respir Cell Mol Biol* 1994; **10**: 207–213.
30. Teran LM, Johnston SL, Schrφder JM, Church MK, Holgate ST. Role of nasal interleukin-8 in neutrophil recruitment and activation in children with virus-induced asthma. *Am J Respir Crit Care Med* 1997; **155**: 1362–1366.
31. Grunberg K, Sterk PJ. Rhinovirus infections: induction and modulation of airways inflammation in asthma. *Clin Exp Allergy* 1999; **29(Suppl. 2)**: 65–73.
32. Johnston SL, Papi A, Bates PJ, Mastronarde JG, Monick MM, Hunninghake GW. Low grade rhinovirus infection induces a prolonged release of IL-8 in pulmonary epithelium. *J Immunol* 1998; **160**: 6172–6181.
33. Papadopoulos N, Johnston S. The role of viruses in the induction and progression of asthma. *Curr Allergy Asthma Rep* 2001; **1**: 144–152.
34. Greiff L, Andersson M, Svensson C, Linden M, Myint S, Persson CG. Allergen challenge-induced acute exudation of IL-8, ECP and alpha2-macroglobulin in human rhinovirus-induced common colds. *Eur Respir J* 1999; **13**: 41–47.
35. van Benten IJ, KleinJan A, Neijens HJ, Osterhaus AD, Fokkens WJ. Prolonged nasal eosinophilia in allergic patients after common cold. *Allergy* 2001; **56**: 949–956.
36. Proud D, Gwaltney JMJ, Hendley J, Dinarello C, Gillis S, Schleimer R. Increased levels of interleukin-1 are detected in nasal secretions of volunteers during experimental rhinovirus colds. *J Infect Dis* 1994; **169**: 1007–1013.
37. Gern JE, Vrtis R, Grindle KA, Swenson C, Busse WW. Relationship of upper and lower airway cytokines to outcome of experimental rhinovirus infection. *Am J Respir Crit Care Med* 2000; **162**: 2226–2231.
38. Psarras S, Xatzipsalti M, Volonaki A *et al.* Rhinovirus infection stimulates production of fibroblast growth factor-2 by airway epithelial and stromal cells. *Allergy* 2002; **57**: 296.
39. Canonica G, Ciprandi G, Pesce G, Buscaglia S, Paolieri F, Bagnasco M. ICAM-1 on epithelial cells in allergic subjects: a hallmark of allergic inflammation. *Int Arch Allergy Immunol* 1995; **107**: 99–102.
40. Greve JM, Davis G, Meyer AM *et al.* The major human rhinovirus receptor is ICAM-1. *Cell* 1989; **56**: 839–847.
41. Papi A, Johnston SL. Rhinovirus infection induces expression of its own receptor intercellular adhesion molecule 1 (ICAM-1) via increased NF-kappaB-mediated transcription. *J Biol Chem* 1999; **274**: 9707–9720.
42. Zhu Z, Tang W, Gwaltney JMJ, Wu Y, Elias JA. Rhinovirus stimulation of interleukin-8 in vivo and in vitro: role of NF-kappaB. *Am J Physiol* 1997; **273**: L814–L824.
43. Papi A, Papadopoulos NG, Degitz K, Holgate ST, Johnston SL. Corticosteroids inhibit rhinovirus-induced intercellular adhesion molecule-1 up-regulation and promoter activation on respiratory epithelial cells. *J Allergy Clin Immunol* 2000; **105**: 318–326.
44. Papi A, Papadopoulos NG, Stanciu LA, Degitz K, Holgate ST, Johnston SL. Effect of desloratadine and loratadine on rhinovirus-

induced intercellular adhesion molecule 1 upregulation and promoter activation in respiratory epithelial cells. *J Allergy Clin Immunol* 2001; **108**: 221–228.
45. Papi A, Papadopoulos NG, Stanciu LA *et al*. Reducing agents inhibit rhinovirus-induced up-regulation of the rhinovirus receptor intercellular adhesion molecule-1 (ICAM-1) in respiratory epithelial cells. *Faseb J* 2002; **16**: 1934–1936.
46. Papadopoulos NG, Stanciu LA, Papi A, Holgate ST, Johnston SL. A defective type-1 response to rhinovirus in atopic asthma. *Thorax* 2002; **57**: 328–332.
47. Wilamasundera S, Katz DR, Chain BM. Responses to human rhinovirus in CD45 T cell subsets isolated from tonsil. *Eur J Immunol* 1998; **28**: 4374–4381.
48. Parry DE, Busse WW, Sukow KA, Dick CR, Swenson C, Gern JE. Rhinovirus-induced PBMC responses and outcome of experimental infection in allergic subjects. *J Allergy Clin Immunol* 2000; **105**: 692–698.
49. Brooks GD, Buchta KA, Swenson CA, Gern JE, Busse WW. Rhinovirus-induced interferon gamma and airway responsiveness in asthma. *Am J Respir Crit Care Med* 2003; **168**: 1091–1094.
50. Papadopoulos NG, Stanciu LA, Papi A, Holgate ST, Johnston SL. Rhinovirus-induced alterations on peripheral blood mononuclear cell phenotype and costimulatory molecule expression in normal and atopic asthmatic subjects. *Am J Respir Crit Care Med* 2000; **161**: A898.
51. Gern J, Vrtis R, Kelly E, Dick E, Busse W. Rhinovirus produces nonspecific activation of lymphocytes through a monocyte-dependent mechanism. *J Immunol* 1996; **157**: 1605–1612.