REVIEW SERIES

Asthma exacerbations · 3: Pathogenesis

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Asthma exacerbations are an exaggerated lower airway response to an environmental exposure. Respiratory virus infection is the most common environmental exposure to cause a severe asthma exacerbation. Airway inflammation is a key part of the lower airway response in asthma exacerbation, and occurs together with airflow obstruction and increased airway responsiveness. The patterns of airway inflammation differ according to the trigger factor responsible for the exacerbation. The reasons for the exaggerated response of asthmatic airways are not completely understood, but recent studies have identified a deficient epithelial type 1 interferon response as an important susceptibility mechanism for viral infection.

Asthma is characterised by episodic symptoms and variable airflow obstruction that occur either spontaneously or in response to environmental exposures. Current therapeutic approaches are based on an understanding of allergen induced airway responses and, when optimally applied, minimise the day-to-day variability of asthma and lead to significant improvements in quality of life. Despite this, however, people with asthma continue to experience exacerbations of their disease. These exacerbations are frequently triggered by viral respiratory infection and current treatment approaches are of limited value during these exacerbations.[1–3] This indicates that asthma exacerbations have a different immunopathogenesis, and emphasises the need to identify the pathways involved in order to improve their treatment.

Asthma exacerbations are an exaggerated lower airway response to an environmental exposure. The major environmental exposures are listed in table 1, with respiratory virus infection being the most common cause of severe asthma exacerbation. Airway inflammation is a key part of the lower airway response in asthma exacerbation, and occurs together with airflow obstruction and increased airway responsiveness. The patterns of airway inflammation differ according to the trigger factor responsible for the exacerbation (table 2 and fig 1). The reasons for the exaggerated response of asthmatic airways are not completely understood (table 3), but recent studies have identified an important susceptibility mechanism for viral infection (table 4 and fig 2).

BURDEN OF ASTHMA EXACERBATIONS

Asthma exacerbations can be severe and require medical intervention, either as an emergency department (ED) visit, admission to hospital, or an unscheduled visit to the doctor. Children experience the majority of ED attendances for asthma (63%). The ED attendance rates for asthma exacerbations in Australian children range between 35 and 240 visits/100 000 head of population.[4] There is a significant seasonal variation in presentation to ED with severe asthma exacerbations, with a peak occurring in early summer in school age children, coinciding with a return to school. For infants, the peak occurs in winter months. The weekly variation in ED attendance for asthma can be as great as 100%. These trends reflect variation in the exposures causing asthma exacerbations and, given the pivotal role for rhinovirus in asthma exacerbations in children, these trends imply specific viral transmission patterns within the community.

Severe asthma exacerbations may also result in death. While numerically most asthma deaths occur in the older age groups, asthma is overrepresented as a cause of death in young people. The death rates from asthma are higher in winter months, consistent with the winter rise in influenza infection which is associated with very severe asthma exacerbations. Wark *et al* found that influenza infection led to severe and refractory asthma exacerbation requiring ICU admission.[5] In contrast to rhinovirus, influenza causes a different airway response with extensive lower airway involvement and marked epithelial cell lysis. The pathogenesis of severe asthma exacerbation leading to death from asthma is multifactorial. There is frequently evidence of airway inflammation, with the pattern of granulocyte response related to the acuity of the episode. Rapid onset fatal asthma typically exhibits a neutrophil infiltrate,[6 7] whereas slower onset exacerbations have a predominant eosinophil infiltrate.

PATHOLOGY OF ACUTE ASTHMA

Studies of airway inflammation using induced sputum in acute asthma suggest a heterogeneous inflammatory infiltrate with a mixture of neutrophils and eosinophils.[8 9] The pattern of this inflammatory infiltrate differs from the allergen induced asthma model. This suggests that the pathogenesis of acute asthma is different from that seen in chronic disease, although it is not clear whether this is a feature of acute disease or

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Abbreviations: BEC, bronchial epithelial cell; ECP, eosinophil cationic protein; FEV_1, forced expiratory volume in 1 second; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; LDH, lactate dehydrogenase; PBMC, peripheral blood monocyte; RV, rhinovirus; TNF, tumour necrosis factor; URTI, upper respiratory tract infection

Table 1 Triggers of asthma exacerbation

- Virus infection
- Allergen
- Environmental pollutants
- Occupational sensitisers/irritants
- Medication: aspirin

the acute trigger. Pathological studies of the most severe acute group—those with status asthmaticus who require mechanical ventilation—have examined bronchoalveolar lavage (BAL) fluid and endobronchial biopsy tissue. Increased numbers of neutrophils are seen in the BAL fluid, with raised levels of eosinophils in the first 48 hours but appearing to fall quickly in response to corticosteroid therapy.[10] BAL fluid from a comparable group contained markedly increased levels of the pro-inflammatory mediators interleukin (IL)-1β, IL-6, and tumour necrosis factor (TNF)-α.[11] This intense airway inflammation was present despite the use of very high dose parenteral corticosteroids, implying an inherent resistance in controlling acute airway inflammation not generally seen in stable asthma. While it is possible that these findings are the effect of severe chronic asthma alone and it is this entity that is resistant to treatment with corticosteroids, it is likely that the acute triggers of asthma exacerbations may also directly modify the airway inflammatory phenotype, making it more resistant to treatment.

T cell activation is also a feature of acute severe asthma,[12] with increased T cell markers in peripheral blood and increased numbers of activated (CD25+) CD8 cells in the tissue of fatal cases of asthma.[13] Oxidant stress is an additional key component of acute asthma. The marked granulocyte influx and activation in acute asthma is accompanied by increased oxygen free radical production which overwhelms host antioxidant defences and results in oxidation of lipids and proteins (fig 3). Lipid peroxidation, assessed as isoprostane levels, is found to be markedly increased in acute asthma, and falls with resolution of the exacerbation.[14]

Mucus plugging

Pathological studies of fatal asthma exacerbations reveal marked hyperinflation due to air trapping from mucus plugging of the airways.[15] Additional findings confirm the presence of inflammation that is intense but restricted to the airways, and occurs in association with airway remodelling. Both airway mucus cell hyperplasia and mucus secretion are relevant mechanisms of mucus plugging in asthma. Mucus cell hyperplasia may be mediated by IL-13 and epidermal growth factor receptor activation.[16–18] Mediators that can trigger mucus secretion include neutrophil elastase, mast cell chymase, eosinophil cationic protein (ECP), and leukotrienes.[18] Many of these mediators are present as part of the airway inflammatory response in acute asthma. Whereas mild asthma and allergen induced asthma are characterised by eosinophilic airway inflammation, in acute severe asthma the intense neutrophilic inflammation demonstrates increased levels of neutrophil elastase, as well as eosinophil degranulation with high levels of ECP.[5 8 9] Compared with controls, cases of fatal asthma show increased mucous gland area, increased percentage of degranulated mast cells, and increased numbers of neutrophils in the submucosal glands.[15] The mucus plugs in fatal asthma are found to contain mucins, plasma proteins, and inflammatory cells.[19]

VIRUS INDUCED ACUTE ASTHMA

An association between acute respiratory virus infection and asthma exacerbations has been observed for some time. The

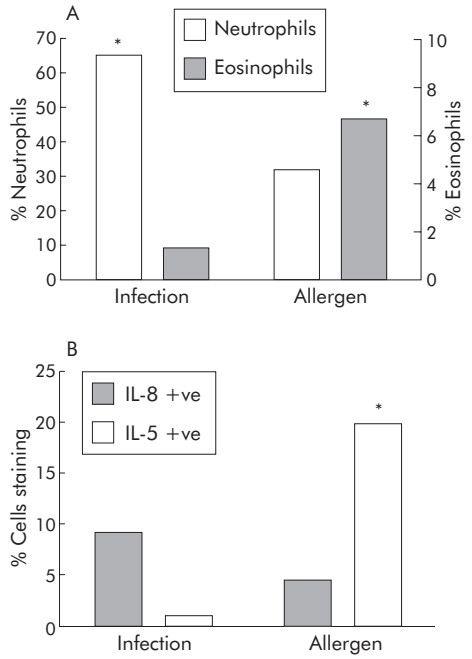

Figure 1 Cellular cytokine patterns in asthma exacerbation triggered by viral infection and allergen (thunderstorm asthma). (A) Induced sputum neutrophils and eosinophils. (B) Immunocytochemistry for interleukin (IL)-8 and IL-5 positive cells in induced sputum *$p<0.05$. Adapted from Wark *et al*[83] with permission.

importance of virus infection as an acute trigger was suggested by epidemiological surveys that showed an association between symptomatic colds and acute asthma, while failing to show an association with allergen or fungal spore exposure.[20 21] However, confirmation was hampered by insensitive techniques to detect rhinoviruses and coronaviruses. The advent of sensitive polymerase chain reaction detection techniques has confirmed that viral upper respiratory tract infections (URTIs) are an important trigger of acute exacerbations of asthma. In school age children 80–85% of exacerbations are associated with viral URTI.[22 23] In adults the rates of virus detection have varied with studies, but they remain the single most prevalent trigger for acute asthma (table 1). In a large community and hospital based UK study, symptomatic colds were associated with 80% of asthma exacerbations although detection of virus from the upper airway was much lower (44%).[24] While this may reflect a difference in virus induced asthma between children and adults, it may also be accounted for in adults by lower shedding of virus from the upper respiratory tract and a delay between acute infection and deterioration of asthma. In contrast, in a hospital based study of severe acute asthma in which polymerase chain reaction for common respiratory viruses was employed using induced sputum, respiratory viruses were detected in 76%[5] and, more recently, another study in adults detected respiratory viruses in 78%.[25] In both adults and children, the virus most frequently identified with acute asthma exacerbations is rhinovirus (RV). In keeping with this is the strong epidemiological evidence that links asthma exacerbations to the recommencing of school, a recognised feature of RV induced colds.[26 27] The questions these studies raise is how respiratory viruses, in particular RV, can induce acute asthma and why asthmatics are so predisposed to the effects of infection.

RVs are single strand RNA viruses belonging to the picornavirus family and are transmitted by direct contact and via the respiratory route with inoculation and replication occurring in the epithelium of the upper airway.[28] In vitro

Table 2 Characteristics of the airway response in asthma exacerbation

Trigger	Airway response	Mechanism
Virus	Neutrophilic bronchitis	Epithelial chemokine activation
Allergen	Eosinophilic bronchitis	Th2 lymphocyte activation with IL-5 release
Occupational	Eosinophilic and/or neutrophilic bronchitis	Not known
Pollution	Neutrophilic bronchitis	Epithelial/macrophage chemokine activation
Medication: aspirin	Severe bronchospasm	Arachidonic acid shunting via 5-LO pathway, increased leukotriene production

IL, interleukin; 5-LO, 5 lipoxygenase; Th, T helper.

models of RV infection of human bronchial epithelial cells (BECs) have been important in aiding our understanding of the mechanisms by which RV infection can induce acute asthma. At first RV was thought to be incapable of infecting the lower airway and its effect on asthma was thought to be indirect. However, detection of RV by bronchoscopy and confirmation of its presence in lower airway BECs in asthmatic subjects confirms that direct infection of the lower airways can occur.[29 30] In vitro cell culture models of cell lines derived from airway BECs showed that RV could infect and replicate in them.[31 32] This was also found to occur as effectively in primary BECs obtained from the airways and then cultured. In fact, there was no difference in infectivity or viral yields between upper and lower airway epithelial cells.[33] However, when epithelial cells were cultured and then differentiated, they were found to be much more resistant to infection with RV and to yield far less virus than undifferentiated primary BECs.[34] The implications for asthma may be that a damaged epithelium is more susceptible to infection and therefore the effects of infection on the lower airway are amplified (tables 3 and 4). This is supported by a recent study which compared the lower airway inflammatory response in patients with acute viral asthma and in non-asthmatic subjects with RV infection.[25] Absolute neutrophil counts from induced sputum were twofold higher in subjects with acute asthma with virus infection (317.5×10^4/ml) than in non-asthmatic subjects with virus infection (165×10^4/ml).

The intuitive influence of RV infection on asthma would be its ability to induce an inflammatory response from infected BECs and influence recruitment of inflammatory cells to the airways. In vitro infection of cell lines and primary BECs shows that RV infection leads to the release of the pro-inflammatory mediators IL-6, IL-8, TNF-α, and IL-1β[33 35] as well as RANTES and granulocyte-macrophage colony stimulating factor (GM-CSF). Increased levels of RANTES[32] and, more recently, the chemokine IP-10[36] have been shown to correlate with in vivo virus replication. In addition, at least in a cell line, RV induces the release of the eosinophil chemoattractant eotaxin.[37] RANTES is a CC chemokine with important antiviral effects and the ability to recruit lymphocytes to the airways, while IL-6 and IL-8 play important roles in neutrophil trafficking. In addition, there is evidence that RV infection upregulates the intercellular adhesion molecule 1 (ICAM-1)—incidentally the receptor for 90% of RV serotypes—which also plays a central role in the movement of inflammatory cells into the airways.[38] These in vitro pro-inflammatory effects have been confirmed in human studies in which volunteers infected with RV had increased levels of markers of eosinophilic activation, IL-8, and neutrophilia,[39 40] and infiltration of the airways with eosinophils, CD4 and CD8 lymphocytes.[41] These findings are also reflected in the effect of these experimental infections on airway physiology in asthma with increases in bronchial hyperresponsiveness[41] and a fall in forced expiratory volume in 1 second (FEV_1).[42] However, some experimental infection models have shown only modest inflammatory and physiological changes, raising concerns about how well these models reflect acute asthma[40] and whether other factors in addition to RV may be needed to trigger an acute exacerbation.

The importance of the pro-inflammatory effect of virus infection has been shown in a study of adults presenting to the ER with acute asthma in which airway inflammation was assessed by sputum induction.[5] Those with virus induced asthma had distinct airway inflammation compared with those with non-infective acute asthma, with raised sputum neutrophils, neutrophil elastase, and evidence of lower airway cell necrosis with increased levels of lactate dehydrogenase (LDH). Subjects had a lower FEV_1 at presentation, which remained lower even a month later, and a longer stay in hospital. Of these inflammatory markers, LDH—potentially a measure of direct virus induced lower airway damage—was most strongly associated with the length of hospital admission for the asthma exacerbation.

These studies have also confirmed the importance of the viral induced chemokine response with increased RANTES gene expression seen as a feature of respiratory viral infection.[25] An additional observation was the increase in airway gene expression for IL-10[25] which was seen in subjects with acute asthma with viral infection but not in non-asthmatic subjects with viral infection. The anti-eosinophilic effects of IL-10 may explain the low eosinophil numbers in viral induced asthma, and suggest a role for T cell regulation in the acute events in asthma exacerbation.

An interaction between pre-existing allergic sensitisation and inflammation may influence the pathogenesis of virus induced asthma (tables 3 and 4). In children, increased nasal eosinophilic inflammation and serum IgE increased the risk of wheezing with colds.[23] While the inflammatory and physiological effects of experimental RV infection were enhanced in subjects with evidence of allergic sensitisation

Table 3 Mechanisms of the exaggerated response in asthma exacerbation

Trigger	Effect	Mechanism
Virus	Enhanced lower airway damage	Deficient IFN-β response
Allergen	Enhanced eosinophil response	Allergic sensitisation
Occupational	Increased eosinophilic and/or neutrophilic bronchitis	Sensitisation
Pollution	Neutrophilic bronchitis	?
Medication: aspirin	Severe bronchospasm	?

IFN, interferon.

Table 4 Cellular mechanisms of susceptibility of people with asthma to the effects of rhinovirus (RV) infection

	Healthy	Asthma
Binding of RV		
ICAM-1 expression	Low	High
Epithelial integrity	Intact	Disrupted
Post-binding RV		
IFN-β response	Early, effective	Deficient
Cell lysis *v* apoptosis	Apoptosis	Impaired apoptosis Increased cell lysis
Inflammatory mediator release	Present	Enhanced (?)
Immune response		
Neutrophil recruitment	Present	Enhanced
Th1 response	Effective (IFN-γ)	Deficient (IFN-γ)

IFN, interferon; Th, T helper; ICAM, intercellular adhesion molecule.

(higher IgE),[43] the greatest increases in hospital admissions for asthma were seen in asthmatic subjects who were infected and both sensitised and exposed to allergen.[44] Similarly, enhanced physiological and inflammatory responses to allergen were seen in experimental RV infections in allergic subjects.[45 46]

Susceptibility to viral infection

People with asthma do not appear to be more likely to develop symptomatic colds than non-asthmatic individuals, but they are more likely to develop lower respiratory tract symptoms and these symptoms are more prolonged.[47] While this may represent the effect of virus infection on asthmatic inflammation, it may also indicate an increased susceptibility to virus infection in asthmatics. Traditionally, antiviral responses have been characterised by a Th1 phenotypic response with raised levels of IFN-γ and recruitment of CD8 cells. This is in contrast to the Th2 response thought to be dominant in asthma, with increased levels of IL-4, IL-5 and IL-13. Subjects infected with RV who have a Th2 characteristic response, as seen by a lower ratio of IFN-γ to IL-5 in sputum, were less efficient at clearing the virus.[48] Infection of peripheral blood monocytes (PBMCs) from subjects with atopic asthma and non-atopic controls with RV also showed differential responses.[49] Non-asthmatic PBMCs responded with vigorous release of IFN-γ and IL-12, while this response was lower in asthmatic PBMCs which had higher levels of the anti-inflammatory cytokine IL-10 and a small increase in IL-4 levels (which was not induced at all in non-atopic cells).

An abnormal innate immune response to RV has also been shown in atopic asthmatic BECs.[50] Asthmatic cells were more susceptible to infection with RV, with significantly higher levels of RV replication which was linked to increased cell lysis, although healthy control BECs appeared protected. Control BECs limited virus replication by undergoing early apoptosis in response to infection, an effect related to the release of IFN-β. In contrast, asthmatic BECs failed to undergo early apoptosis and had a deficient IFN-β response, although when IFN-β was replaced, asthmatic BECs underwent apoptosis and virus replication was limited. Such a deficient response in innate immunity now clearly needs to be demonstrated in clinical asthma, but it does offer a plausible explanation for the susceptibility of asthmatics to RV infection and an important therapeutic target for intervention (table 4 and fig 2).[51]

AMBIENT AIR POLLUTION AND ACUTE ASTHMA

Ambient air pollution is another important trigger of acute asthma and, like viral respiratory tract infection, there is compelling epidemiological evidence linking it to acute asthma. Poor air quality can result from a mixture of particulate matter, carbon compounds, volatile organic compounds, metals, and levels of endotoxin, all of which may induce airway inflammation and acute respiratory symptoms.[52]

Exposure to increased levels of environmental ozone is an important trigger of acute ER presentations with asthma in school age children.[52]. The ability of increased ozone levels to directly influence airway inflammation has been shown by an experimental study in which exposure to inhaled ozone induced a fall in FEV_1 and increased sputum neutrophilia.[53]

One of the greatest changes to ambient pollutants has been the prolific increase in vehicular traffic that has occurred in the last 50 years in both developed and developing nations. Experimental exposure to diesel exhaust particles can produce wide ranging inflammatory effects such as increased IgE production from B cells,[54] increased release of IL-8 and GM-CSF from epithelial cells,[55] and increased IL-8, RANTES and TNF-α from PBMCs.[56] In keeping with these experimental findings, it has recently been shown that children admitted to hospital with acute asthma are more likely to reside in an area with a high level of exposure to traffic.[57]

Nitrogen dioxide (NO_2) is both an indoor and outdoor pollutant. Increased levels of exposure have been associated with bronchitic symptoms in asthmatic children,[58] while elevated personal levels are associated with increased severity of viral induced exacerbations, pointing to a possible synergistic effect of these two inflammatory stimuli.[59] These associations are important in demonstrating epidemiological links between pollutants and acute asthma and their in vitro ability to induce airway inflammation. They also show that there appears to be an intricate association between allergenic factors, viral stimuli, and particulates in acute asthma.

Smoking

Over 30% of adults with asthma are smokers, and smoking is not uncommon among ED attendees with acute asthma.[60] The Institute of Medicine concluded that there is sufficient evidence of a causal relationship between exposure to environmental tobacco smoke and exacerbations of asthma. Smoking in asthma induces a non-eosinophilic phenotype and relative corticosteroid resistance.[61] The possible mechanisms of this include alterations in airway inflammatory cell phenotypes (for example, increased neutrophils or reduced eosinophils), changes in the glucocorticoid receptor α to β ratio (for example, overexpression of glucocorticoid receptor β), and increased activation of pro-inflammatory transcription factors (such as nuclear factor-κB) or reduced histone deacetylase activity.[59]

Allergen exposure

Eosinophilic infiltration of the airways together with lymphocytes expressing a Th2-like phenotype, secreting increased levels of IL-4 and IL-13, have characterised what is now regarded as the allergen induced inflammatory component of asthma. Allergen challenge models in sensitised individuals clearly demonstrate the potential relationship between allergen exposure, immune activation, and the physiological asthmatic response. First described in 1952,[60] sensitised individuals when exposed to an allergen develop an early response with a fall in lung function largely mediated by preformed histamine release but, in a substantial proportion of subjects with asthma, this is followed by a late response characterised again by a fall in FEV_1 along with airway infiltration by eosinophils and lymphocytes.

The acute symptoms and inflammation induced by experimental challenge require a dose of allergen that is too high to be clinically relevant, with the exception of a few situations. In the unique phenomenon of thunderstorm asthma, acute

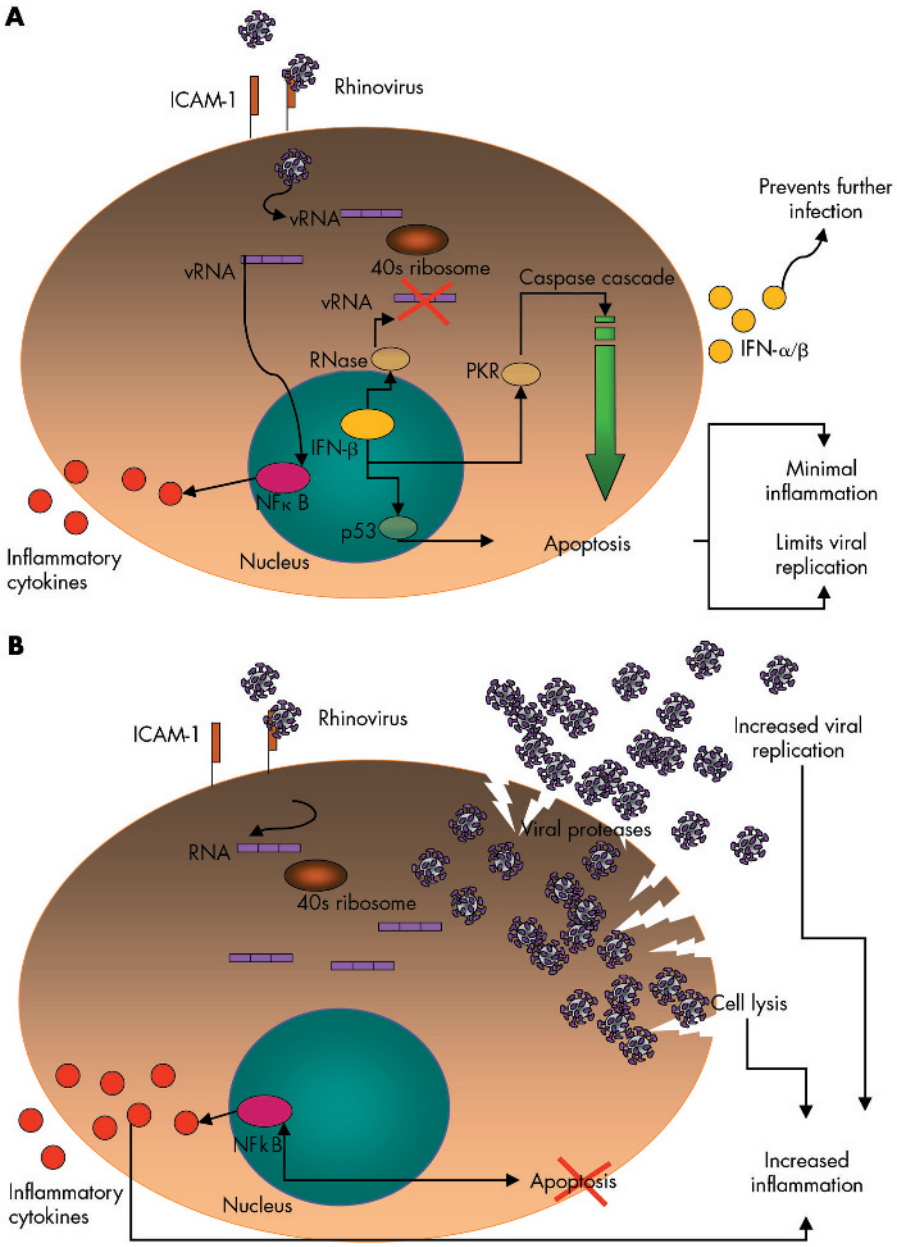

Figure 2 (A) In normal bronchial epithelial cells (BEC) rhinovirus adheres to its receptor intercellular adhesion molecule 1 (ICAM-1). It is then internalised and uncoats. Single stranded RNA replicates which, if left unchecked, would lead to the formation of vRNA and then virions. These events elicit activation of nuclear factor kappa B (NFκB) which, in turn, leads to the production of pro-inflammatory cytokines. The presence of vRNA also leads to the transcription of interferon (IFN)-β. Interferon-α/β are known to induce the antiviral protein kinase (PKR) which represses host cell protein synthesis and induces apoptosis and RNases that lyse vRNA. These type I interferons also induce activation of the tumour suppressor gene p53 in response to viral infection that leads to apoptosis. Infected cells are then induced to undergo apoptosis, limiting viral replication. In addition, released IFN-β reduces the spread of infection to neighbouring cells, in all limiting airway inflammation. (B) Proposed response in asthmatic BECs. The early events following infection proceed as described above, but the asthmatic BEC is unable to mount an effective early IFN-β response. There is no early activation of apoptosis even though there is a pro-inflammatory response. Viral replication proceeds and amplifies, and viral proteases cleave the cell membrane releasing infectious virions leading to pro-inflammatory cell lysis. Neighbouring cells become infected, enhancing the release of pro-inflammatory cytokines resulting in greatly enhanced airway inflammation.

uncontrolled exposure to grass pollen appears to induce such a classic inflammatory response.[61] Other events have been documented in relation to major exposure to allergenic particles such as castor bean dust[62] and soy bean dust.[63]

Occupational exposures

Workplace exposures can induce sensitisation, airway irritation, or both. These exposures frequently worsen asthma symptoms and a massive exposure could result in a severe exacerbation.[64] They are a relatively infrequent cause of asthma exacerbation but it is important that they are recognised because removal from exposure is part of the management.[65 67] The cellular mechanisms that underpin asthma exacerbations resulting from occupational exposure require more research (table 2).

Interaction between triggers

People with asthma may frequently be exposed to more than one trigger, and these appear to interact in the development of asthma exacerbations. In experimental challenge studies,

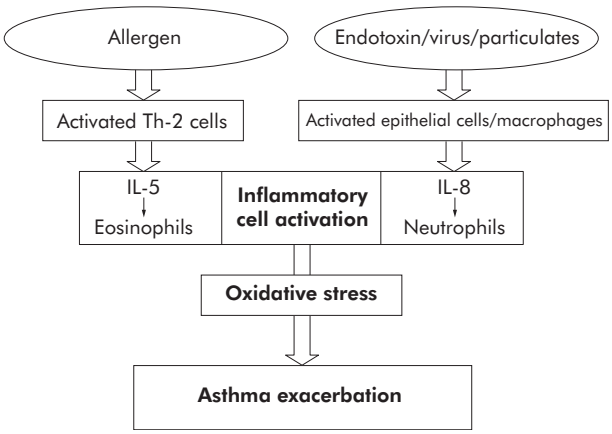

Figure 3 Environmental exposures that trigger asthma exacerbations generate specific cytokine response patterns that result in a granulocyte infiltration, activation, and oxidative stress.

allergen responsiveness is enhanced by exposure to another trigger such as air pollution[68] or smoking.[69] A similar effect has been seen with viral infection[70] but was not reproduced with frequent low dose allergen exposure.[71] Green and co-workers have reported that the risk of admission to hospital with acute asthma in adults was markedly increased with the combination of sensitisation and current exposure to high levels of sensitising allergens and the presence of viral infection.[44] Murray *et al* have extended these results to show that, in children, natural virus infection and domestic allergen exposure interact to increase the risk of hospitalisation by 19-fold.[72] These results indicate that there is a synergism between allergic sensitisation, exposure to a high level of sensitising allergen, and viral infection that induces deterioration in asthma requiring hospital admission. The mechanisms of the synergistic effect remain to be established, but suggest activation of several inflammatory pathways that lead to asthma exacerbations (fig 3).

CONCLUSIONS

Asthma exacerbations represent an exaggerated lower airway response to an environmental stimulus. Respiratory viral infection, mainly rhinovirus, is the main trigger of severe exacerbations of asthma. Airway inflammation is a key pathogenetic feature, and the inflammatory pattern is determined by the stimulus and consequent cytokine response pattern. A chemokine mediated neutrophil pattern is typical of virus induced asthma. The exaggerated lower airway response may be mediated by a deficient IFN-β response to viral infection in virus induced asthma, and by the mechanisms of allergic sensitisation in allergen induced asthma.

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