

The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences

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Atopic asthma is characterized by infiltration of the bronchial mucosa with eosinophils and T helper 2 (Th2)-type cells, circulating specific immunoglobulin E (IgE) antibodies and positive skin tests to common aeroallergens, and airway hyper-responsiveness. Stimulation of IgE synthesis by B cells and mobilization of eosinophils is believed to be driven by interleukin 4 (IL-4) and IL-5, respectively. Since Rackman's clinical classification of asthma, it has been widely accepted that a subgroup of asthmatic patients are not demonstrably atopic – the so-called 'intrinsic' variant of the disease¹. Intrinsic asthmatics show negative skin tests and there is no clinical or family history of allergy. Furthermore, serum total IgE concentrations are within the normal range and there is no evidence of specific IgE antibodies directed against common allergens. These patients are usually older than their allergic counterparts and have onset of symptoms in later life, often with a more severe clinical course^{1–3}. There is a preponderance of females and the association of nasal polyps and aspirin sensitivity occurs more frequently in the non-atopic form of the disease^{1–4}. Whereas some authors suggest that around 10% of asthmatics are intrinsic, the Swiss SAPALDIA survey (8357 adults, 18–60 years old) found that a third of total asthmatics were non-allergic (intrinsic)^{4,5}.

Ever since the first description of intrinsic asthma, there has been debate about the relationship of this variant of the disease to atopy⁴. One suggestion is that intrinsic asthma represents a form of autoimmunity, or autoallergy, triggered by infection as a respiratory influenza-like illness often precedes onset. Some authors have suggested that intrinsic asthmatics are allergic to an as yet undetected allergen and could therefore benefit from allergen avoidance, as previously demonstrated in atopic asthmatics^{6,7}.

Our viewpoint is that although intrinsic asthma has a different clinical profile from extrinsic asthma it does not appear to be a

Intrinsic asthma shows no clinical or serological evidence of IgE-mediated allergy to common environmental agents. Similar to extrinsic asthma, bronchial biopsies from such patients show enhanced expression of Th2-type cytokines, CC chemokines and Iε/Cε compared with controls. These findings suggest there might be local IgE production directed against unknown antigens, possibly of viral origin or even autoantigens, in this important clinically distinct variant of the disease.

distinct immunopathological entity. In a series of bronchial biopsy studies using *in situ* hybridization and/or immunohistochemistry, both variants of the disease were characterized by: (1) infiltration of eosinophils and Th2 cells secreting IL-4 or IL-5, or both; (2) the presence of CC chemokines and FcεRI⁺ cells; and (3) cells that express mRNA for the ε germ-line transcript (Iε) and the ε heavy chain of IgE (Cε). The only difference seemed to be a strong macrophage signal in biopsies from intrinsic asthma patients compared with those from extrinsic asthmatics. This could represent macrophage dysfunction or simply be a reflection of age and length of disease (the intrinsic asthmatics were significantly older) rather than a basic difference in the pathological mechanism between these two forms of asthma. Thus,

there appears to be more similarities than differences between extrinsic and intrinsic asthma. Both could be IgE-mediated diseases, although in the intrinsic patients, the putative antigen, or allergen, is unknown and IgE production appears to be local rather than generalized, as in atopy.

Patient and control groups

This review focuses on the findings of several recent studies^{3,8–15} and involves bronchial biopsies on four groups of subjects (summarized in Table 1).

Atopic (AA) and non-atopic asthmatics (NAA) were matched in terms of asthma severity, baseline lung function and histamine PC₂₀ (Refs 3, 8–10, 16). Non-atopic (intrinsic) asthmatics were significantly older than their atopic counterparts. Although intrinsic asthmatics had serum IgE concentrations within the normal range (0–150 IU ml⁻¹) and no evidence of specific IgE antibodies against common allergens, total serum IgE concentrations were significantly higher than those observed in normal controls⁸. Blood eosinophil

Table 1. Clinical details of patients and controls^a

Patient group	Age (yr)	Gender (F/M)	Total serum IgE (IU ml ⁻¹)	Blood eosinophils (10 ⁹ /L)	FEV ₁ (% predicted)	Histamine PC ₂₀ (mg ml ⁻¹)	Aas score
Atopic asthma	33	1/9	252 ^c	0.25	83 ^e	0.34	3.5
(n = 10)	(23–55)		(57–3749)	(0.10–0.70)	(55–104)	(0.02–3.60)	(1–4)
Non-atopic asthma	53 ^b	6/4	66 ^d	0.55 ^b	76 ^e	0.64	3.5
(n = 10)	(39–62)		(17–108)	(0.10–1.10)	(58–112)	(0.12–6.00)	(1–4)
Atopic controls	27	1/8	152 ^c	0.20	100	>16	NA
(n = 9)	(18–36)		(38–808)	(0.10–0.80)	(81–125)		
Non-atopic controls	27	4/4	12	0.10	110	>16	NA
(n = 8)	(21–42)		(3–29)	(0.0–0.20)	(90–119)		

Abbreviations: Aas score, validated asthma severity scoring system¹⁶; FEV₁, forced expiratory volume in 1 s; histamine PC₂₀, histamine provocative concentration causing a 20% fall in FEV₁; NA, not applicable.

^aAll data³ are expressed as median (range) except for PC₂₀ [geometric mean (range)]. The four groups were used in order to control non-atopic asthma both for atopy and asthma. Asthma was defined as a clear clinical history with current symptoms, and evidence of more than 20% reversibility of the FEV₁ either spontaneously or after inhaled β_2 agonists and/or a histamine PC₂₀ provocation test of ≤ 6 mg ml⁻¹ in the previous two weeks. Asthma severity was assessed by a validated asthma severity scoring system (the Aas score). Atopy was defined as a positive skin-prick test to extracts of one or more aeroallergens (including house dust mite, mixed grass pollen, mixed tree pollen, mixed moulds, cat fur and dog dander). All atopics demonstrated elevated serum allergen-specific IgE concentrations (>0.70 IU ml⁻¹) to one or more of these allergens. Non-atopic subjects were defined by negative skin-prick tests to a wide range of local aeroallergens in the presence of a positive histamine control. The non-atopic controls also exhibited serum IgE concentrations within the normal range of our laboratory (0–150 IU ml⁻¹) and negative RAST tests to 25 common aeroallergens. Atopic controls were asymptomatic or had mild to moderate allergic rhinitis with no history of wheeze or chest tightness, normal baseline lung function with less than 20% reversibility of the FEV₁ either spontaneously or after inhaled β_2 agonists, and histamine PC₂₀ provocation test of >16 mg ml⁻¹. All subjects were non-smokers and had not taken oral corticosteroids for the previous two months, or inhaled corticosteroids for the previous two weeks.

^b $p < 0.01$ versus atopic asthma, atopic controls and normal controls.

^c $p < 0.05$ versus normal controls and non-atopic asthmatic subjects.

^d $p < 0.05$ versus normal controls.

^e $p < 0.01$ versus controls.

counts were higher in NAA when compared with the three other patient groups.

Bronchoscopy was performed in all subjects (asthmatics and controls) and biopsies were taken from the right middle, lower and upper lobe bronchi. This procedure was well tolerated and the safety of our bronchoscopy protocol was prospectively monitored in all patients and controls¹⁵. Bronchial biopsies were processed immediately in the bronchoscopy room and used later in immunohistochemistry and *in situ* hybridization.

Extrinsic and intrinsic asthma: similarities and differences

As expected, an eosinophil-rich bronchial inflammation was a prominent feature of all asthmatics and this was somewhat more pronounced in non-atopic asthma^{2,3,8–14}. Small numbers of basophils were also observed both in AA and NAA, but not in the two control groups¹⁷. IL-4 and IL-5 mRNA and protein-positive cells were also significantly elevated in AA and NAA when compared with controls⁸ (Fig. 1). There was a trend for greater IL-4 and IL-5 production in NAA compared with AA, but this was not significant. There were no differences in amounts of mRNA encoding IL-3 (Ref. 9), IL-13 (Ref. 12) and granulocyte-macrophage colony-stimulating factor (GM-CSF)⁹, or in the CC chemokines eotaxin, eotaxin-2, RANTES, monocyte chemotactic protein 3 (MCP-3) and MCP-4 (Refs 9, 18, 19)

when both asthmatic groups were compared with the control groups. That is, there was enhanced expression of these cytokines and chemokines in bronchial asthma, irrespective of atopy⁹.

In general, the numbers of CD25⁺ cells were equally elevated in AA and NAA compared with non-atopic controls (NAC)². In this early study, a greater increase in CD3⁺ and CD4⁺ T cells was demonstrated in NAA compared with AA (Ref. 2).

Compared with controls, both the AA and NAA expressed elevated numbers of cells positive for mRNA for I ϵ as well as C ϵ (Table 2).

Table 2. Local expression of ϵ germline gene transcripts (I ϵ) and RNA for the ϵ heavy chain of IgE (C ϵ) in the bronchial mucosa in atopic and non-atopic asthma^a

	Atopic asthma (n = 9)	Non-atopic asthma (n = 9)	Atopic controls (n = 10)	Non-atopic controls (n = 10)
CD20 ⁺ cells	14 (5, 42)	20 (4, 29)	15 (3, 26)	16 (8, 34)
C ϵ ⁺	20 (3, 54)	10 (0, 38)	1 (0, 11)	0 (0, 1)
I ϵ ⁺	10 (2, 33)	11 (0, 31)	1 (0, 10)	0 (0, 2)

^aData expressed as the numbers of positive cells/mm² (median + IQ range) from counts in the submucosa of bronchial biopsies³¹.

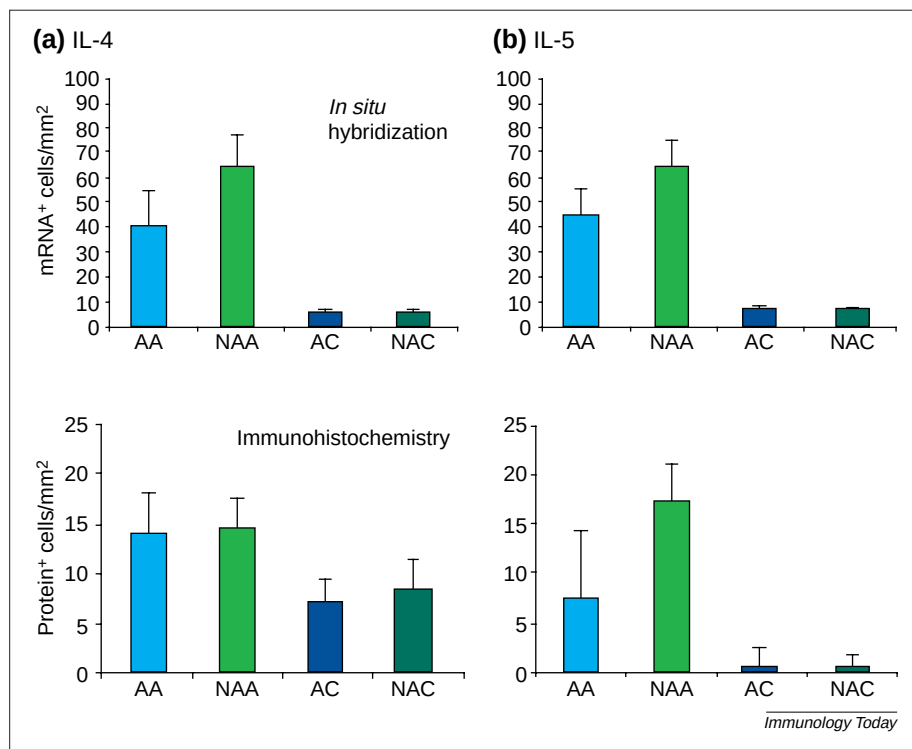


Fig. 1. Interleukins (IL) in asthma. IL-4 (a) and IL-5 (b) mRNA and protein in bronchial biopsies from atopic asthma (AA), non-atopic (intrinsic) asthma (NAA), atopic controls (AC) and non-atopic controls (NAC). AA or NAA versus AC or NAC ($P < 0.05$). There were no significant differences between AA and NAA. The bar represents the mean $\pm$ SEM. Data shown with permission from Ref. 8.

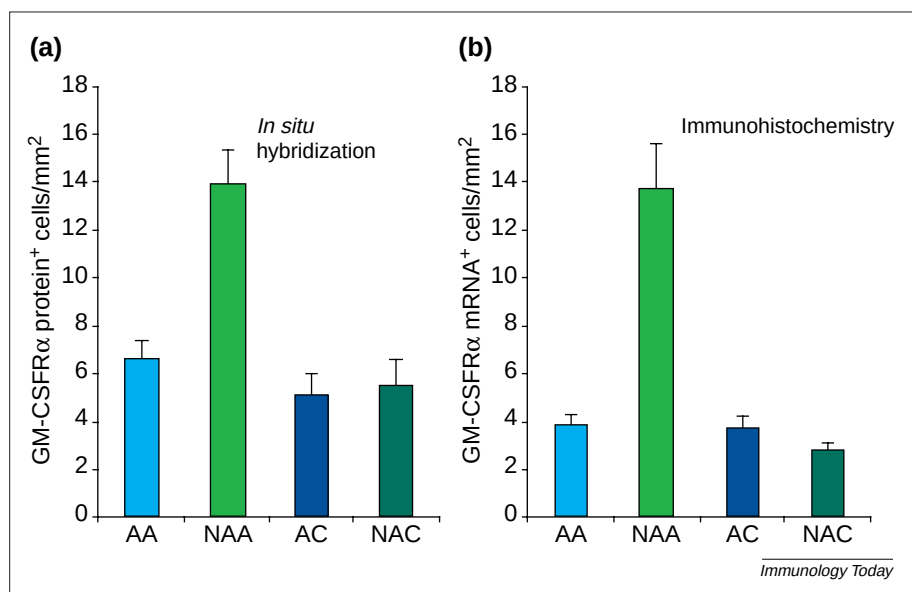


Fig. 2. Elevation of granulocyte-macrophage colony-stimulating factor receptor α (GM-CSFR α) mRNA⁺ cells and protein product in bronchial biopsies from non-atopic (intrinsic) asthma (NAA) compared with atopic asthma (AA), atopic controls (AC) and non-atopic controls (NAC). $>80\%$ of the GM-CSFR α ⁺ cells co-localized to CD68⁺ macrophages. AA versus NAA ($P < 0.001$), NAA versus AC or NAC ($P < 0.001$) for both mRNA and protein. Data taken with permission from Ref. 13. The numbers of CD68⁺ cells [median mm⁻² (range)] were NAA [94 (5–156)], AA [35 (0–75)], AC [38 (20–115)], NAC [48 (5–173)]. Data taken with permission from Ref. 3.

However, there were no differences in the numbers of CD20⁺ B cells between the four groups. Expression of Fc ϵ RI on mast cells, macrophages and eosinophils was also up-regulated in both AA and NAA when compared with AC and NAC (Ref. 3). The only difference between the two groups of asthmatics, a feature seen in two separate studies, was the marked increase in CD68⁺ macrophages in NAA compared with those in AA, AC and NAC (Refs 2, 3), as shown either by an increase in CD68 (Refs 2, 3) or GM-CSF receptor α (GM-CSFR α) subunit cells¹³ (Fig. 2). An inverse correlation between the numbers of GM-CSFR α cells and the forced expired volume in 1 second (FEV₁; %predicted) was also apparent ($P < 0.05$), suggesting that this finding has relevance to disease severity in intrinsic asthma. There was also a significant increase in the numbers of cells that expressed mRNA for total, membrane-bound and soluble IL-5 receptor α subunit in AA and NAA compared with the NAC subjects¹¹. A large majority of IL-5 receptor α subunit-bearing cells were activated EG2⁺ eosinophils, the numbers of which inversely correlated with FEV₁ (an index of airflow obstruction) in asthmatics¹¹. There was also enhanced expression of the IL-4 receptor α subunit mRNA and protein product in the subepithelium in AA and NAA compared with AC and NAC (Ref. 20). The various cellular phenotypic markers, cytokines, cytokine receptors, chemokines, IgE and Fc ϵ RI findings in AA and NAA are summarized in Table 3.

By the use of double-staining procedures, 70% of message for IL-4 and IL-5 within the bronchial mucosa of AA and NAA co-localized with CD3⁺ T cells, the majority of which were CD4⁺ (Ref. 10). CD8⁺ T cells, tryptase⁺ mast cells and EG2⁺ eosinophils also expressed IL-4 and IL-5 mRNA in both the atopic and non-atopic variants but to a much lesser degree¹⁰. Thus, elevated numbers of T cytotoxic (Tc2-type or CD8⁺/IL-4⁺) cells do not appear to be a prominent feature of either AA or NAA.

Comparative analysis

Eosinophils

This group of findings highlighted more similarities than differences in immunopathology

between AA and NAA. For example, eosinophils, although classically associated with 'allergic' inflammation, were also abundant in the bronchial submucosa of non-atopic (intrinsic) asthmatics, perhaps in even greater numbers than in atopic asthmatics for a given degree of disease severity^{2,3}. This can be explained in both groups of patients, at least in part, by local expression of the pro-eosinophilic cytokines IL-3, IL-5 and GM-CSF, which recruit, activate and prolong the survival of circulating eosinophils (reviewed in Ref. 21).

IL-4 and IL-5

Our data appear to conflict with those of Walker and colleagues²²⁻²⁴, who showed that whereas NAA and AA IL-5 protein concentrations were elevated compared with controls in peripheral blood T-cell culture supernatants and concentrated bronchoalveolar lavage (BAL) fluid, detectable elevation of IL-4 concentrations in these compartments was apparent only in AA. It was suggested that the apparent lack of elevated IL-4 secretion in NAA might explain why these patients do not have detectable, circulating allergen-specific IgE. The reasons for these discrepant findings are unclear but might reflect methodological problems (variable protein recovery following concentration of bronchoalveolar lavage fluid or the possible presence of inhibitors that interfere with the protein assay). Alternatively, it could be speculated that IL-4 is transcribed, translated and stored within the bronchial mucosa of intrinsic asthmatics but is somehow not released. Another possibility is that the IL-4⁺ cells in intrinsic asthmatics produce the non-functional alternative splice variant of human IL-4 (Ref. 25).

IgE

By contrast with the general agreement that eosinophils might play a role in asthma in both clinical settings, the possible role of IgE and IgE-mediated mechanisms, especially (but not exclusively) in intrinsic asthma, is less clear. Based on the relationship, at the population level, between total serum IgE concentrations and the incidence of asthma or airway hyper-responsiveness, some authors have questioned the existence of intrinsic asthma, suggesting that all asthmatics have an IgE-dependent component to their disease^{26,27}. This relationship need not, however, be causal, and could reflect equally well the possibility that individuals who have a propensity to develop asthma also have a predisposition to produce IgE inappropriately. However, the NAA patients recruited in this group of studies did have elevated total serum IgE concentrations as compared with the NAC (Ref. 3), despite the fact that, as a group, concentrations tend to decline with age (Table 1).

IL-4 or IL-13 are required absolutely for IgE-switching in B cells, a prerequisite for elevated IgE synthesis, and thus 'atopy'^{28,29}. However, understanding of the possible significance of local elevated IL-4 and IL-13 expression in the asthmatic bronchial mucosa is confounded by a lack of more basic knowledge about the regulation of IgE synthesis *in vivo*. For example, it is uncertain whether or not ongoing elevated IL-4/IL-13 synthesis is required to maintain inappropriate IgE synthesis by memory B cells once initial switching to IgE

Table 3. Summary of immunopathological similarities and differences between atopic and non-atopic asthma

	Atopic asthma	Non-atopic asthma
Phenotypic cell-surface markers		
CD45	→	→ or ↑
CD3	→	→ or ↑
CD4	→	→ or ↑
CD8	→	→
CD25	↑	↑
EG2 ⁺ eosinophils	↑	↑
BB1 ⁺ basophils	↑	↑
CD68 ⁺ macrophages		↑
Th2 and eosinophil-associated cytokines		
IL-3	↑	↑
IL-4	↑ ^a	↑
IL-5	↑	↑
IL-13	↑	↑
GM-CSF	↑	↑
Cytokine receptors		
IL-4Rα	↑	↑
IL-5Rα	↑	↑
GM-CSFRα	→	↑
CC chemokines		
Eotaxin	↑	↑
Eotaxin-2	↑	↑
RANTES	↑	↑
MCP-3	↑	↑
MCP-4	↑	↑
IgE/FcεRI		
FcεRI ⁺ cells	↑	↑
Iε/Cε	↑	↑

Abbreviations: BB1, a basophil granule-specific marker monoclonal antibody; EG2, cleaved form of eosinophil cationic protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-3, interleukin 3; MCP, monocyte chemotactic protein; →, no difference compared with atopic controls (AC) and non-atopic controls (NAC); ↑, elevated when compared with AC and NAC.

^aElevated in AC compared with NAC, by RT-PCR (reverse transcriptase polymerase chain reaction) not *in situ* hybridization⁸.

synthesis has occurred. Furthermore, important sites for IgE synthesis *in vivo* have not been clearly defined, and it is unclear whether or not putative elevated local synthesis of IgE is always reflected by elevated IgE concentrations in the peripheral blood. Evidence for local IgE synthesis has been demonstrated in CD20⁺ B cells in the nasal mucosa of patients with hayfever³⁰ and there is elevated expression of Iε and Cε mRNA⁺ in cells in the bronchial mucosa of AA and NAA. This suggests that local bronchial mucosal IgE production might indeed occur in so-called intrinsic asthma³¹. Confirmation of synthesis will require demonstration of IgE protein colocalized to

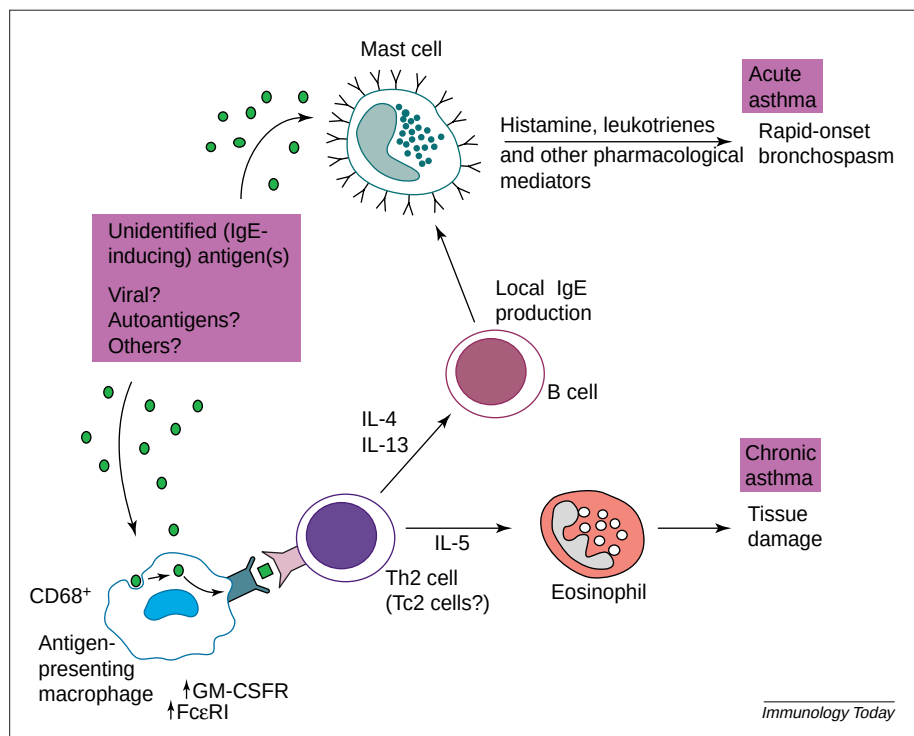


Fig. 3. A hypothesis for mechanisms in non-atopic (intrinsic) asthma. Upregulation of interleukin 4 (IL-4), IL-5, ϵ germ-line transcript (I ϵ), immunoglobulin E (IgE) ϵ heavy chain (C ϵ) and IL-13 in the absence of atopy suggest local immunoglobulin E (IgE) production with specific IgE against unknown antigens that might be of viral origin or even autoantibodies. Such antigens could presumably trigger Fc ϵ RI⁺ mast cells, as in atopic asthma, leading to the release of pharmacological inflammatory mediators that cause acute rapid-onset bronchospasm. However, the major pathway of mucosal damage is likely to be through the activation of antigen-specific CD4⁺ T helper 2 (Th2) [and to a lesser extent CD8⁺ T cytotoxic (Tc2)] cells, which elaborate IL-4, IL-13 and IL-5. IL-5, together with CC chemokines such as eotaxin, RANTES and monocyte chemoattractant protein 3 (MCP-3), which mobilize and recruit eosinophils. Tissue injury results from the release of eosinophil basic proteins and of eosinophil-derived sulphidopeptide leukotrienes. The preponderance of activated [CD68⁺, granulocyte-macrophage colony-stimulating factor receptor α positive (GM-CSFR α ⁺)] Fc ϵ RI-bearing macrophages could be of particular relevance in perpetuating this severe persistent form of asthma.

CD20⁺ B cells. This, along with the elevated numbers of cells expressing Fc ϵ RI in these patients³, suggests the possibility of local IgE-mediated processes in the absence of detectable systemic IgE production. Thus, non-atopic, as well as atopic asthma could be associated with production of IgE directed against as yet unidentified allergens or antigens.

The present results are also compatible with a possible role for virus-specific IgE (Ref. 32) or IgG autoantibodies to Fc ϵ RI in NAA. This was previously suggested in chronic idiopathic urticaria³³, a disease characterized by basophil and mast cell release of histamine and other vasoactive mediators in the absence of any clear allergic, infectious, drug-induced or physical cause. Other autoantibodies have been detected in intrinsic asthmatics, including a circulating IgG autoantibody directed against a common 55 kDa antigen shared by platelets and cultured endothelial cells³⁴. Its role in the pathophysiology of asthma has not been elucidated.

Animal models might also help in understanding the role of IgE and atopy in asthma. Although these are concerned largely with IgE-mediated mechanisms, allergen-induced bronchial hyper-responsiveness and eosinophilic inflammation can also occur in the absence of IgE (null mutation of the C ϵ locus), as shown in a mouse model of hypersensitivity to *Aspergillus fumigatus*³⁵.

Macrophages

By contrast with the many similarities between AA and NAA, particularly with regard to the expression of Th2-type cytokines, CC chemokines and IgE, there is a potentially important difference, that is, the markedly elevated numbers of CD68⁺ cells expressing the GM-CSF receptor α subunit in NAA (Ref. 13). Do these findings support some form of abnormal macrophage activation in this variant of asthma³⁶? Many of these cells were Fc ϵ RI⁺ (Ref. 3), suggesting that there might be enhanced IgE-dependent antigen presentation in the bronchial mucosa of patients with NAA. Macrophage activation might also reflect the existence of an ongoing infectious (possibly viral) or autoimmune process in these non-atopic individuals. On the other hand the NAA were older than their AA counterparts and so the increase in macrophage activity could simply have been a reflection of a longer duration of disease. Further studies are needed to analyze the role and function of macrophages in the non-atopic variant of the disease.

Conclusions

Recent findings suggest that atopic and non-atopic (intrinsic) asthma are characterized by a broadly conserved bronchial mucosal pro-eosinophilic cytokine network in which IL-5 appears to play a key role. Moreover, inappropriate IgE-mediated mechanisms might occur in asthma, irrespective of its atopic status, as suggested by elevated serum IgE concentrations and bronchial mucosal expression of cells positive for Fc ϵ RI, IL-4, IL-13, I ϵ and C ϵ . In general, these findings support the concept that these subtypes of asthma, despite showing distinct clinical features, share many common immunopathological mechanisms. Promising future directions of research regarding intrinsic asthma include the possible identification of novel allergens or antigens, the detailed description of local bronchial mucosal IgE production and the understanding of a possible macrophage dysfunction (Fig. 3). In addition, a role for

infectious (possibly viral) or autoimmune processes has yet to be firmly identified.

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