Chronic inflammation in asthma

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It is now widely accepted that chronic airway inflammation plays a key role in asthma [1]. This fundamental feature has been included in the most recent definitions of the disease: hence the Global Strategy for Asthma Management and Prevention reports that "asthma is a chronic inflammatory disease of the airways in which many cell types play a role, in particular mast cells, eosinophils and T-lymphocytes. In susceptible individuals the inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough, particularly at night and/or early morning. These symptoms are usually associated with widespread but variable airflow obstruction that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli" [2]. Based on this consensus all treatment guidelines focus on the importance of anti-inflammatory drugs (mainly inhaled corticosteroids) to control the disease process [2, 3].

Eosinophilic airways inflammation in asthma

Eosinophils are potent inflammatory cells which secrete a number of lipid mediators and proteins relevant to the pathophysiology of asthma including leukotrienes (LT)C$_4$, D$_4$, and E$_4$, platelet-activating factor (PAF) and basic proteins (major basic protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), and eosinophil peroxydase (EPO)) [4]. LT play an important role in asthma through their ability to induce a variety of effects including bronchoconstriction and inflammatory cell recruitment. Basic proteins induce direct damage to the airway epithelium [5] and promote bronchial hyperresponsiveness [6]. Eosinophils are also able to produce pro-inflammatory cytokines and thereby amplify the inflammatory reaction (transforming growth factor (TGF)β, tumour necrosis factor (TNF)-α, interleukin (IL)-4, -5, -6, -8, granulocyte-macrophage colony-stimulating factor (GM-CSF), RANTES (regulated on activation, T-cell expressed and secreted, eotaxin) [4, 7].

Derived from myeloid progenitors in the bone marrow, mature eosinophils circulate briefly in the peripheral blood and home to the site of inflammation under the action of several factors including cytokines and chemokines (see below) [4]. Eosinophil production and maturation are regulated by eosinophil-active cytokines IL-5, IL-3 and GM-CSF [4, 8]. Eosinophils may be activated by factors such as IL-5, PAF, GM-CSF and release toxic basic proteins (MBP, ECP, *etc.*) [4].

There is strong circumstantial evidence that eosinophils are important pro-inflammatory cells in the asthma process, irrespective of the patient's atopic status

[9, 10]. It is well known that blood and sputum eosinophilia are commonly associated with asthma. Moreover, the numbers of eosinophils in peripheral blood, bronchoalveolar (BAL) fluid and bronchial biopsies in a group of asthmatics were elevated when compared to normal controls and it was possible to demonstrate an increasing degree of eosinophilia with clinical severity [9]. Furthermore, immunostaining of the bronchial mucosa of patients who had died from severe asthma revealed the presence of large numbers of activated eosinophils and considerable amounts of MBP deposited in the airways [11]. Increased concentrations of MBP were found in BAL fluid from atopic asthmatics when compared to normal controls and correlations were found between the concentrations of MBP and the numbers of denuded epithelial cells in BAL fluid [12]. In atopic asthmatics, late-phase bronchoconstriction was accompanied by an influx of eosinophils in BAL fluid [13]. This was not observed in individuals developing an isolated early-phase response. Lastly, airway eosinophils are very sensitive to corticosteroid therapy, and their disappearance is associated with an improvement in bronchial hyperresponsiveness [14].

T-lymphocytes in asthma

T-cells have a central role to play in an antigen-driven inflammatory process, since they are the only cells capable of recognising antigenic material after processing by antigen-presenting cells [15]. CD4+ and CD8+ T-lymphocytes activated in this manner elaborate a wide variety of protein mediators including cytokines which have the capacity to orchestrate the differentiation, recruitment, accumulation and activation of specific granulocytes at mucosal surfaces. T-cell derived products can also influence immuno-globulin production by plasma cells. There now exists considerable support for the hypothesis that allergic diseases and asthma represent specialised forms of cell-mediated immunity, in which cytokines secreted predominantly by activated T-cells (but also by other leukocytes such as mast cells and eosinophils) bring about the specific accumulation and activation of eosinophils [10].

Antigenic peptides are presented to T-cell receptors as a high-affinity complex of peptide and major histocompatibility complex (MHC) molecules. T-cells can be broadly divided into two groups based on their recognition of peptide in the context of either MHC class I gene or MHC II gene products. T-cells recognising endogenously generated peptides, presented with class I molecules, express the CD8 molecule which binds to class I molecules thus increasing the avidity of the interaction. Most cytotoxic T-cells have the CD8+ phenotype. The expression of CD4 by T-cells indicates recognition of peptides in the context of class II molecules to which CD4 is able to bind. Peptides presented in the context of class II MHC proteins generally elicit a T-helper (CD4+ T-lymphocyte) response. T-helper cells can be further subdivided according to the pattern of cytokines elaborated following activation [16, 17]. Great progress in the knowledge of phenotypic and functional activities of different T-cell subsets in mice and humans has been made recently. T-cells secreting cytokines such as IL-2, interferon (IFN)-γ and TNF-β are referred to as T-helper (Th)1 cells. The cytokines produced by these cells promote cytotoxic T-cell and delayed-type responses and inhibit allergic reactions. T-cells producing IL-4, IL-5, and IL-10 but not IFN-γ are referred to as Th2 cells. These cells are critical to allergic diseases and asthma, as they provide B-cell help for isotype switching to immunoglobulin (Ig)E and eosinophil maturation, survival and activation. T-lymphocyte activation and expression of Th2-type cytokines is believed to contribute to tissue eosinophilia and local IgE-dependent events in allergic diseases and asthma [10].

The demonstration of primed circulating blood T-lymphocytes in acute severe asthma

is interesting as it presumably reflects the presence of activated cells in the bronchial mucosa, the major site of the asthmatic inflammatory process [18]. In allergic individuals, circulating blood CD4+ T-lymphocytes produce high levels of Th2-type cytokines including IL-5, GM-CSF and IL-3 and may therefore promote eosinophilic inflammation [10, 19]. Moreover, elevated numbers of CD4+ T-lymphocytes expressing IL-5 messenger ribonucleic acid (mRNA) have been demonstrated in the airways from asthmatics compared with nonasthmatic controls [20]. More precisely a Th2-like cytokine profile has been identified in bronchial samples from atopic and nonatopic asthma [21, 22]. This is in agreement with the demonstration that CD4+ and to a lesser extent CD8+ T-cell lines grown from BAL cells from atopic asthmatics produce more IL-5 protein than in control subjects [23].

Activated T-lymphocytes are usually sensitive to corticosteroid therapy and improvement of bronchial hyperresponsiveness and reduction in airway eosinophils parallels reduction of activated CD25+ T-lymphocytes and Th2-type cytokines including IL-4 and IL-5 [14]. However some patients with chronic severe asthma are refractory to corticosteroids [24]. Pharmacological targeting of T-cells has been proposed as a novel approach to the treatment of corticosteroid-dependent or corticosteroid-resistant asthma. A 12-week randomised, double-blind, placebo-controlled, crossover trial established that cyclosporin A improves lung function in patients with corticosteroid-dependent chronic severe asthma [25]. Compared with placebo, a 36-week treatment with cyclosporin A resulted in a significant reduction in median daily prednisolone dosage and total prednisolone intake [26]. In addition morning peak expiratory flow rate improved significantly in the active treatment group but not in the placebo group [26]. Using placebo-controlled, double-blind conditions Sihra et al. [27] showed that cycloporin A inhibited the late, but not the early, bronchoconstrictor response to inhaled allergen challenge of sensitised mild atopic asthmatics. These data support the concept that T-cells play a crucial role in asthma, as cyclosporin A exerts its immunosuppressive action primarily by inhibition of antigen-induced T-lymphocyte activation and the transcription and translation of mRNA for several cytokines including IL-2, IL-5 and GM-CSF [28]. More recently a single intravenous infusion of a chimeric monoclonal antibody that binds specifically to human CD4 antigen has been evaluated in severe corticosteroid-dependent asthmatics. This randomised double-blind, placebo-controlled trial demonstrated significant increases in morning and evening peak flow rates in the highest dose cohort [29]. Additional experiments showed that keliximab infusion induced a rapid and effective binding to all CD4+ T-cells with a transient reduction in numbers of circulating CD4+ T-cells and modulation of CD4 expression, further suggesting that therapy aimed at the CD4+ T-cell may be useful in asthma [30].

Other inflammatory cells

B-cells

Th2-type cytokine-induced B-cell activation and subsequent IgE production is believed to be a critical characteristic of patients with atopy, a disorder characterised by sustained, inappropriate IgE responses to common environmental antigens ("allergens") encountered at mucosal surfaces [31, 32]. Interaction of environmental allergens with cells sensitised by binding of surface Fc receptors to allergen-specific IgE is assumed to play a role in the pathogenesis of atopic asthma. Stimulation of IgE synthesis by B-cells is mainly driven by IL-4 [31]. It has recently been shown that in both atopic and nonatopic asthmatics, airways CD20+ B-cells have the potential to switch in favour of

IgE heavy-chain production, supporting the concept that local IgE production may occur in these patients [33]. These changes may be at least in part under the regulation of IL-4.

Mast cells and basophils

Mast cells and basophils have long been recognised as major effector cells of allergic reactions by virtue of their high affinity surface receptors for IgE (FcεRI) [1]. The early phase bronchoconstrictor response to allergen challenge of sensitised atopic asthmatics can probably be accounted for by mast cell and basophil products, mostly histamine. Mast cells can produce and store several cytokines which may play a role in the chronic asthmatic process, including TNF-α, IL-4, IL-5, and IL-6 [34]. Mast cells are also believed to be responsible at least in part of airways remodelling through fibroblasts activation. Mast cells have been described in the airways of asthmatics, and, although not necessarily increased in number, are in the activated state (degranulated) [35]. BB1+ basophils were identified in baseline bronchial biopsies of asthmatics, although eosinophils and mast cells were 10-fold higher. Similarly basophils increased after allergen inhalation in atopic asthma, but again basophils were <10% of eosinophils [36].

Macrophages

Macrophages are phagocytic cells derived from bone marrow precursors. They play a fundamental role as accessory cells and they also produce several mediators and cytokines promoting chronic inflammation. Macrophages infiltrate the asthmatic airways, especially in nonatopic patients, but also in atopics where allergen challenge activates macrophages [32, 37, 38]. This cell type may also play a role in airway remodelling through the production of growth factors such as platelet-derived growth factor (PDGF), bFGF and TGF-β [1].

Dendritic cells

Dendritic cells are specialised in antigen processing and presentation. IgE presumably plays a role in their function as they express high numbers of FcεRI. These cells are essential in the induction of immune responses within the airways and their numbers are increased in asthma. Their role in human asthma is still a matter of debate [1].

Fibroblasts

Fibroblasts are responsible for the production of collagen and reticular and elastic fibres. Myofibroblasts numbers in the submucosa correlate with subepithelial collagen deposition, supporting a role in airway remodelling [1].

Neutrophils

These cells are recruited in the airways after allergen challenge and are found in elevated numbers in cases of fatal asthma [39]. Their role in asthma however remains unclear.

Cytokines in asthma

Pro-eosinophilic cytokines

Accumulating evidence tends to show that the combined effects of a wide array of cytokines produced by different cell types including activated T-lymphocytes could play a major part in regulating the successive steps leading to a characteristic eosinophil-rich airways inflammation [10]. It is well established that tissue recruitment of eosinophils from the bloodstream requires rolling and firm adhesion of circulating cells under the control of cytokine-induced adhesion molecules (mostly of selectin and integrin families) and migration following a gradient of chemotactic substances in which the newly described family of chemokines are of utmost importance [40, 41]. In addition eosinophils can be activated by several environmental factors including eosinophil-active cytokines (IL-5, GM-CSF and IL-3) [42–44]. As a result, tissue damage is due at least in part to the release of toxic granule proteins from activated infiltrating eosinophils [5, 6].

Eosinophil active cytokines (IL-5, GM-CSF, IL-3). T-lymphocytes are thought to orchestrate eosinophilic inflammation in asthma through the release of cytokines including "eosinophil-active" cytokines (IL-5, GM-CSF and IL-3) which promote eosinophil maturation, activation, hyperadhesion and survival. The relevance of IL-5 to asthma has been highlighted by the demonstration of elevated numbers of bronchial mucosal activated (EG2+) eosinophils expressing the IL-5 receptor α-chain mRNA in asthmatics and by positive correlations between the numbers of cells expressing IL-5 mRNA and markers of asthma severity such as bronchial hyperresponsiveness and asthma symptom (Aas) score [9, 45, 46]. Moreover aerosolised *Ascaris suum* extract-induced airways inflammation and bronchial hyperresponsiveness in nonhuman primates are dramatically reduced by the intravenous infusion of an anti-IL-5 monoclonal antibody (TRFK-5) prior to parasite extract inhalation [47]. However, preliminary data in human asthma indicate that anti-IL-5 dramatically reduces allergen-induced eosinophilia although no significant effect was observed on the magnitude of the late-phase reaction and bronchial hyperresponsiveness [48].

Using double immunohistochemistry and *in situ* hybridisation, 70% of IL-5 mRNA+ signals co-localized to CD3+ T-cells, the majority of which (>70%) were CD4+, although CD8+ cells also expressed IL-5 [20]. The remaining signals co-localized to mast cells and eosinophils [20]. In contrast double immunohistochemistry showed that IL-5 immuno-reactivity was predominantly associated with eosinophils and mast cells. However, numbers of IL-5+ cells detected by immunohistochemistry were relatively low, raising the possibility that insufficient protein accumulated within T-cells to enable detection by immunohistochemistry [20].

GM-CSF and IL-3 are also thought to participate to the bronchial pro-eosinophilic cytokine network in asthma [43, 44]. T-cell lines grown from BAL cells in patients with atopic asthma have the capacity of producing elevated quantities of GM-CSF [23]. Recently, IL-5, IL-8 and GM-CSF immunostaining of sputum cells in bronchial asthma and chronic bronchitis has shown that the numbers of IL-5 and GM-CSF immuno-stained cells was increased in asthma, a condition characterised by elevated sputum eosinophila, compared to chronic bronchitis where elevated IL-8 expression paralleled sputum neutrophilia [49]. Others have shown that bronchial epithelial cells are also able to participate to the production of GM-CSF in asthma, emphasising that noninflam-matory cells can participate actively to the local inflammatory process [50]. Interestingly, inhaled corticosteroid attenuates both epithelial cell GM-CSF expression and the numbers of epithelial activated eosinophils, suggesting that inhaled corticosteroids could

attenuate airways inflammation partly by down-regulating epithelial cell cytokine expression [51]. Lastly, GM-CSF could also act on macrophages, as suggested by elevated αGM-CSF receptor expression on CD68+ macrophages in nonatopic asthmatics [32, 52].

Cytokine-induced upregulation of adhesion molecules. To migrate from the bloodstream to the bronchial mucosa, eosinophils must adhere to vascular endothelial cells, extracellular matrix components and tissue cells. Cell recruitment to the inflamed tissue consists of at least three events: rolling, firm adhesion and transendothelial migration [40]. Granulocyte margination and diapedesis at sites of inflammation seem to be principally under the control of the cytokine-induced upregulated expression of several endothelial adhesion molecules including P-selectin, E-selectin (ELAM-1), intercellular adhesion molecule (ICAM)-1 (CD54) and vascular cell adhesion molecule (VCAM)-1. The leukocyte receptors for the P- and E-selectins exist on most leukocytes [53]. The leukocyte receptors for ICAM-1 are LFA-1a (CD11a/CD18) and Mac-1 (CD11b/CD18) and those for VCAM-1 are VLA-4.

In the asthmatic airways, "pro-inflammatory" cytokines such as TNF-α can upregulate ICAM-1 and E-selectin expression and therefore granulocyte recruitment [40, 54]. More specifically, the expression of VLA-4 on lymphocytes and eosinophils but not on neutrophils, has led to the hypothesis that VCAM-1 may be the predominant endothelial regulator of the chronic asthmatic bronchial mucosal inflammation. VCAM-1 is upregulated by several cytokines including IL-4 and IL-13 [55, 56]. IL-4 and IL-13 have been detected in the asthmatic airways [46, 57], emphasising the fact that specific eosinophilic recruitment through an IL-4 (and/or IL-13) induced upregulation of VCAM-1 endothelial expression could participate to chronic bronchial mucosal inflammation. Animal models of asthma and IL-4-deficient mice have shown that this cytokine might be critical to the development of an allergic eosinophilic response [58].

Eosinophil chemokines. Classical chemoattractants such as C5a act broadly on neutrophils, eosinophils, basophils and monocytes. The past few years have seen the discovery of a group of chemoattractive cytokines (termed chemokines) with similarities in structure whose principal activities appear to include chemoattraction and activation of leukocytes including granulocytes, monocytes and T-lymphocytes [41]. Chemokines are polypeptides of relatively small molecular weight (8–14kDa) which have been assigned to different subgroups by structural criteria. The α- and β-chemokines, which contain four cysteines, are the largest families. The α-chemokines have their first two cysteines separated by one additional amino acid ("CXC chemokines": IL-8, *etc.*), whereas these cysteines are adjacent to each other in the β-chemokine subgroup ("CC chemokines": eotaxins, monocyte chemotactic proteins (MCPs), RANTES). Interestingly chemokines are distinguished from classical chemoattractants by a certain cell-target specificity: the CXC chemokines tend to act more on neutrophils, whereas the CC chemokines tend to act more on monocytes and in some cases basophils, lymphocytes and eosinophils [59]. Owing to the effects of some CC-chemokines on basophils and eosinophils, their ability to attract and activate monocytes, and their potential role in lymphocyte recruitment, these molecules have emerged as the most potent stimulators of effector-cell accumulation and activation in allergic inflammation [41]. The CC chemokines interacting with the "eotaxin receptor" CCR3 (eotaxin-1, eotaxin-2, RANTES, MCP-3, MCP-4) are potent pro-eosinophilic cytokines which are believed to play an important role in asthma [60]. Since eosinophil chemokines all stimulate eosinophils *via* CCR3, this receptor is potentially a prime therapeutic target in asthma and other diseases involving eosinophil-mediated tissue damage. Antagonising CCR3 may be particularly relevant to asthma, as this

receptor is also expressed by several cell types playing a pivotal role in this condition, including Th2-type cells, basophils and mast cells.

Eotaxin mediates eosinophil (but not neutrophil) accumulation *in vivo*. Recently, eotaxin and CCR3 mRNA and protein product have been identified in the bronchial submucosa of atopic and nonatopic asthmatics [61]. Moreover eotaxin and CCR3 expression correlate with airway responsiveness. Cytokeratine-positive epithelial cells and CD31+ endothelial cells were the major source of eotaxin mRNA whereas CCR3 co-localized predominantly to eosinophils [61]. These data are consistent with the hypothesis that damage to the bronchial mucosa in asthma involves secretion of eotaxin by epithelial and endothelial cells resulting in eosinophil infiltration mediated *via* CCR3.

RANTES, MCP-3, and MCP-4 have all the properties that are needed to mobilise and activate basophils and eosinophils and currently available evidence suggests a primary role for them in allergic inflammation [60]. A combined expression of eosinophil chemokines (eotaxins, MCPs and RANTES) together with eosinophil active cytokines (IL-5, GM-CSF and IL-3), has been demonstrated in asthma, indicating that these cytokines could act in synergy to promote the elaboration of an eosinophil-rich bronchial mucosal infiltrate [61, 62]. Indeed, priming eosinophils with IL-5 increases the chemotactic properties of RANTES on eosinophils [63]. The cell sources of RANTES and MCPs in asthma also include primarily epithelial and endothelial cells, as well as macrophages, T-lymphocytes and eosinophils [61]. Interestingly, bronchial epithelial cell production of RANTES is downregulated by inhaled corticosteroids [64].

Due to their cell-target specificity favouring neutrophil chemoattraction, a role for CXC chemokines in asthma is less likely although IL-8 has been shown to be a chemotactic factor for eosinophils [65]. Although eosinophils are most prominent in the airways of asthmatics, fewer eosinophils and more neutrophils have been identified in the airways of sudden-onset fatal asthma [39]. Elevated IL-8 expression has been reported in asthma [65]. In that setting, IL-8 could promote not only neutrophil accumulation but also eosinophil migration in synergy with IL-5.

Pro-atopic cytokines in asthma

Asthma is often, though not invariably, associated with atopy [66]. Since the clinical classification of asthma by RACKERMAN [67], it has been widely accepted that a subgroup of asthmatics are not demonstrably atopic, the so-called "intrinsic" variant of the disease [67]. Intrinsic asthmatics show negative skin tests and there is no clinical 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 aeroallergens. These patients are usually older than their allergic counterparts and have onset of their symptoms in later life, often with a more severe clinical course. There is a preponderance of females and the association of nasal polyps and aspirin sensitivity occurs more frequently in the nonatopic form of the disease. Whereas some authors suggest that only ∼10% of asthmatics are intrinsic, the Swiss SAPALDIA survey (8,357 adults, aged 18–60 yrs) found that one-third of total asthmatics were nonallergic [68].

Ever since the first description of intrinsic asthma, there has been debate about the relationship of this variant of the disease to atopy [32, 66]. One suggestion is that intrinsic asthma represents a form of autoimmunity, or auto-allergy, triggered by infection as a respiratory influenza-like illness often precedes onset. Other authors have suggested that intrinsic asthmatics are allergic to an as yet undetected allergen. The present authors view is that although intrinsic asthma has a different clinical profile from extrinsic asthma it does not appear to be a distinct immunopathological entity [32]. This concept is supported by the demonstration of elevated numbers of activated eosinophils [37],

Th2-type lymphocytes [69], and cells expressing FcεRI [70] in bronchial biopsies from atopic and nonatopic asthmatics, together with epidemiological evidence indicating that serum IgE concentrations relate closely to asthma prevalence regardless of atopic status [66]. IL-4 expression is a feature of asthma, irrespective of its atopic status, providing further evidence for similarities in the immunopathogenesis of atopic and nonatopic asthma [32]. IL-4 mRNA is mainly CD4+ T- cell derived [20]. Expression of αIL-4 receptor mRNA and protein is significantly elevated in the epithelium and subepithelium of biopsies from atopic and nonatopic asthmatics compared to atopic controls [71]. Recent evidence of the effectiveness of nebulised soluble IL-4 receptors in atopic asthma further support the relevance of this cytokine in this disease [72].

In addition, IL-13 is a cytokine very close to IL-4 which exhibits activities possibly relevant to asthma: promotion of IgE synthesis, eosinophil vascular adhesion by VLA-4/ VCAM-1 interaction and promotion of Th2-type cell responses [56, 57, 73]. Importantly IL-4 or IL-13 are absolutely required for IgE-switching in B-cells, a prerequisite for elevated IgE synthesis. The present authors have reported elevated expression of IL-13 mRNA in the bronchial mucosa of so-called atopic and nonatopic asthma [57]. Therefore, although intrinsic asthma have no demonstrable atopy, they have a biological pattern of airway inflammation strongly suggesting a possible "atopic-like" status which may be restricted to the bronchial submucosa [32]. As discussed above, local IgE synthesis in CD20+ B-cells has been demonstrated in the bronchial submucosa of
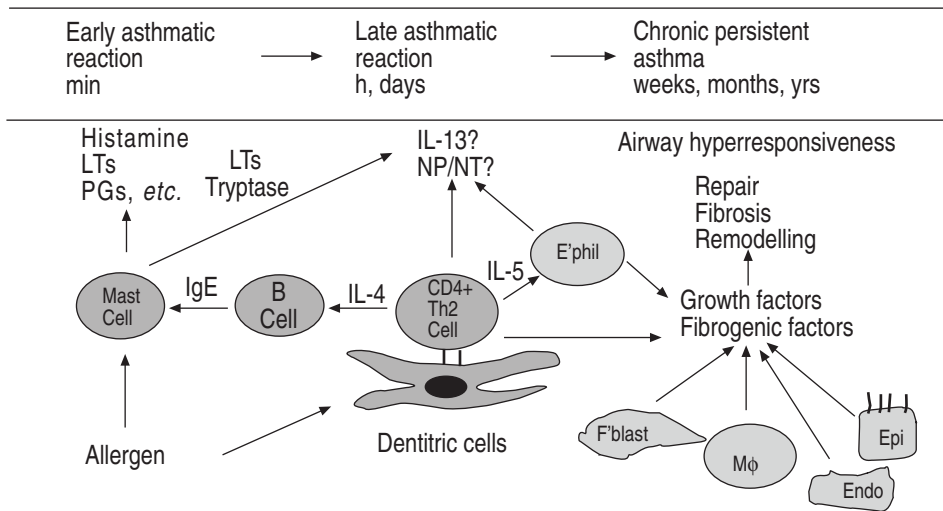

Fig. 1. – Proposed scheme for the progression of asthma in relation to pathogenesis. The progression of asthma with emphasis on the cells and mediators involved is shown diagrammatically. The early asthmatic reaction occurs within minutes and is largely due to the release of histamine and lipid mediators from mast cells following interaction of allergen with cell bound immunoglobulin (Ig)E. The late asthmatic reaction, which peaks 6–13 h after allergen challenge, is believed to be partially T-cell dependent. For example, the late-phase, but not the early-phase, was inhibited by cyclosporin A [27] and challenge with T-cell peptide epitopes induced an isolated late asthmatic reaction. CD4 cells may interact directly with smooth muscle to produce airway narrowing through the release of neurotrophins (NT) (which in turn activate neuropeptides (NP)). Interleukin (IL)-13 may also play a role in late-phase asthmatic reactions [74]. The role of the eosinophil remains uncertain. On the one hand there is much circumstantial evidence to incriminate eosinophils as pro-inflammatory cells in the asthma process. However, depletion of the eosinophils with anti-IL-5 did not influence the late-phase reaction or bronchial hyperresponsiveness in mild asthmatics [48]. Airway hyperresponsiveness is a feature of chronic persistent asthma and is due in part to airway thickening due to remodelling, fibrosis and other repair processes.These changes are brought about by the elaboration of growth factors and fibrogenic factors from various cell types including eosinophils (E'phil), fibroblasts (F'blast), monocytes (Mφ), epithelial (Epi) cells and endothelial (Endo) cells.

patients with atopic and nonatopic asthma (detection of elevated expression of ε germ-line gene transcripts and mRNA encoding the ε heavy chain of IgE) [33]. This along with the demonstration of elevated numbers of cells expressing the high affinity IgE receptor in intrinsic asthma suggests the possibility of local IgE-mediated processes in the absence of detectable systemic IgE production.

Summary

There now exists considerable support for the hypothesis that asthma represents a specialised form of cell-mediated immunity, in which cytokines, chemokines and other mediators such as leukotrienes secreted by a wide range of inflammatory cells bring about the specific accumulation and activation of eosinophils in the bronchial mucosa (the progression of asthma is diagrammatically depicted in figure 1). These observations have important implications for future therapies, since it suggests that more selective drugs than corticosteroids should be of interest in asthma.

Keywords: Cell-mediated immunity, chemokines, cytokines, eosinophils, leukotrienes.

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