

REVIEW

Dysregulation of IgE responses and airway allergic inflammation in atopic individuals

M. RICCI and O. ROSSI

Institute of 'Clinica Medica III', University of Florence, 'Policlinico di Careggi', 50134 Florence, Italy

Introduction

The clinical importance and the high incidence of allergic diseases of the respiratory tract are well known and hence the great research effort over the past 20 years on problems related to the pathogenesis of these syndromes. Cellular cloning and molecular biology techniques, and also the characterization of the many mediators involved in tissue inflammation have made it possible to highlight the importance of the interactions among mediators, cytokines, neuropeptides and neurotransmitters in the triggering and maintenance of allergic inflammation.

In this review, first we will briefly describe the recent acquisitions regarding the physiological aspects of IgE regulation in humans; secondly, we will discuss the possibility that certain alterations are responsible for the enhanced and persistent IgE antibody production in atopics as well as for the airway allergic inflammation. An integrated view is now made possible by the recent evidence of some relationships between the cellular and molecular mechanisms involved in the dysregulation of IgE responses and those responsible for the initiation and maintenance of tissue inflammatory lesions.

Physiological aspects of IgE antibody regulation in humans

Experimental models have shown that IgE production is tightly controlled by T lymphocytes [1]. In humans the importance of interaction between T and B cells has been demonstrated by the use of alloreactive T-cell clones capable of recognizing MHC class II molecules of allogeneic B cells through the specific T-cell receptor (TcR), and then developing a true *cognate interaction* with them, which in turn leads to both T-cell clone activation and B-cell proliferation and differentiation [2,3]. It has also been shown that stimulation of the TcR-associated CD3 molecular complex can reveal the capability of a portion of T cells of inducing *in-vitro* IgE

synthesis by B cells from both allergic and nonallergic subjects [4]. The need for T-B cell physical contact was definitively shown in co-culture experiments with double chambers (separated by microporous membranes) in which IgE production was only observed when T and B cells were in close contact in the same compartment [5]. It is possible to assume that only previously activated T lymphocytes are capable of forming the above-mentioned T-B cell conjugates and of performing helper functions for either resting or memory B cells [6]. It is possible that the first activation of T cells occurs through the recognition of antigenic peptides within the context of class II molecules on the membrane of macrophages and dendritic cells (classical antigen presenting cells: APCs). This type of priming allows the activation and proliferation of specific T-cell clones. This clonal expansion obviously facilitates the interaction with the appropriate B cells.

Recent studies have shown that the interaction between T and B lymphocytes can also occur through binding which is independent of the typical cognate interaction. In fact, it has been demonstrated that B cells can produce IgE following stimulation by T-cell clones, even independently of a specific recognition through the TcR, provided that IL-4 is present in the micro-environment [5]. T-B cell interaction irrespective of specific recognition and genetic restriction could account for the synthesis of polyclonal IgE antibodies which accompanies the production of specific IgE during, for example, intense allergic responses or parasitosis.

One of the most significant acquisitions is the proof that IL-4 produced by T cells represents an essential signal for B cells to switch towards IgE synthesis [7]. The importance of IL-4 in IgE production has been demonstrated in both murine and human models [7-10]. Specifically, two types of signals appear necessary for B cells to produce IgE: the first signal is the T-B cell interaction ('cognate' or 'non-cognate'), while the second one is IL-4. Other cytokines may play a role in the induction of IL-4 and T-B contact-dependent IgE synthesis [5]. IFN- γ , IFN- α , TGF- β , and PGE₂ have been found to inhibit the IL-4-dependent IgE synthesis [7-9]. It is important to

Correspondence: Prof. Mario Ricci, Direttore dell' Istituto di Clinica Medica III, Università di Firenze, Viale Mozgagni, 85, 50134 Firenze, Italy.

note that the inhibitory effect of IFN- γ can also be observed *in vivo*. In addition to IgE production, this modulation also involves Fc ϵ RII expression (Fig. 1).

Recent findings in the murine model attribute the secretion of different cytokine combinations (with contrasting effects on B cells) to different types of helper T cells: those able to produce IL-2 and/or IFN- γ (defined as Th1) and others producing IL-4, IL-5 and IL-6 (defined as Th2) [8]. Th1 cells would be involved in delayed-type hypersensitivity reactions and in the synthesis of IgM and some IgG subclasses. On the other hand, Th2 cells would be important in allergic-type inflammatory reactions and in the defence against parasites. Studies in humans have shown that, in addition to Th1 and Th2 clones, there are also T-cell clones able to produce IL-2 and IFN- γ along with IL-4 [11]. For those T-cell clones, the helper activity

depends on the pre-eminent production of IL-4 in respect to IFN- γ [7]. Studies on different types of helper T cells in relation to the regulation of their growth and differentiation are also of interest. It has been shown that IL-4 is able to inhibit Th1 proliferation and maturation, while IFN- γ seems capable of inhibiting the growth and expansion of Th2 lymphocytes. More recently, yet another cytokine produced by Th2 cells has been identified ('cytokine synthesis inhibitory factor': CSIF/IL-10), which is able to inhibit cytokine production by Th1 clones [12].

Dysregulation of IgE responses in atopic individuals

Genetic studies have shown that in atopic individuals there are different orders of genetic alterations including: (a) increased response to allergens dependent upon particular genes linked to the HLA haplotype; and (b) increased IgE production which is apparently independent of HLA [13]. Knowledge acquired in recent years makes it possible to suggest that the alterations of regulatory mechanisms in atopics are multiple, that they have a genetic basis, and that various associations among them give rise to the *allergic phenotype*.

It should be remembered that despite increasingly sophisticated molecular analysis, including primary and tertiary structure, there is no evidence for characteristic structures or chemical properties of allergens associated with IgE antibody responses. All data available support the view that physical properties of allergens (low molecular weight and rapid solubility) as well as the route and the dose of immunization are key factors influencing the development of IgE antibody response in man [14].

The old problem concerning the portal of entry of allergen molecules through respiratory mucosae has recently been solved after the description of highly developed dendritic cell networks in human airway epithelium. Class II MHC-bearing dendritic cells, similar to the Langerhans cells of the skin, are ideally positioned to function as an intra-epithelial trap for inhaled allergens and they appear to represent the primary point of contact between inhaled aero-allergens and the immune system. An involvement in allergen transport to regional lymph nodes for these cells appears likely [15,16].

The number of dendritic cells in nasal epithelium of patients with grass pollen allergy is significantly higher during the grass pollen season [16]. As proposed for Langerhans cells, dendritic cells could migrate from a surface location to the lymphoid structures where they could acquire an increased immunostimulatory ability [17,18]. Surface dendritic cells could bind to and process allergen molecules; lymph node dendritic cells could possess the ability to present allergenic peptides and to stimulate also unprimed T cells.

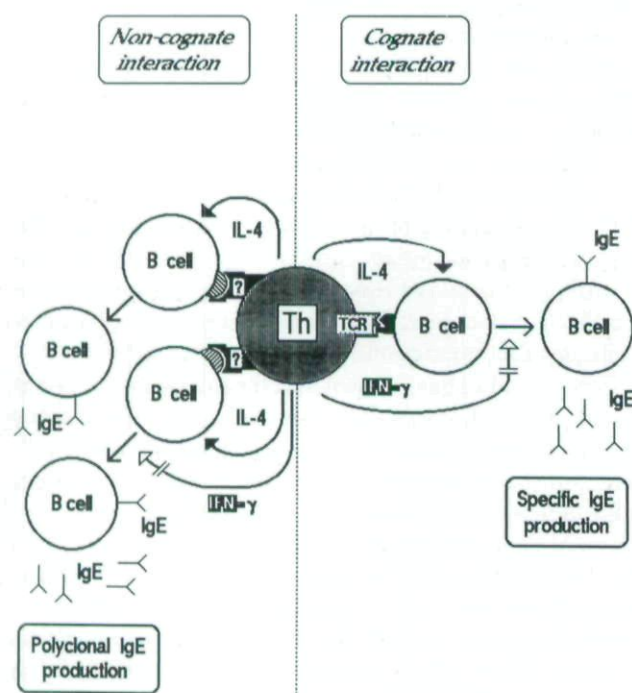


Fig. 1. Schematic representation of the cellular and cytokine interactions that regulate human IgE synthesis. B cells require a first signal delivered by a physical interaction with T cells. Such a contact can consist of cognate interaction (recognition by the TcR/CD3 complex of the antigenic peptide in combination with MHC class II determinants), but it may also involve non-cognate interactions. Another signal required for IgE synthesis is provided by IL-4 released by activated Th2-type cells. Other cytokines and factors may play a role in T-B cell interactions leading to IgE synthesis. IFN- γ , IFN- α , and, probably, TGF- β negatively regulate the IgE production. This scheme does not take into account the role of antigen-presenting cells other than B cells in the initiation of the immune response. Adapted from [52].

HLA-class II molecules peculiar to atopic individuals, present on the membrane of APCs and therefore also on dendritic cells, may preferentially bind allergenic peptides to form bimolecular complexes that can easily be recognized by the TcR of specific lymphocytes. Thus, a genetic trait peculiar to atopic subjects could be their inheritance of particular amino acid sequences within HLA-class II molecules which, when expressed on the membrane of the dendritic cells of the respiratory mucosa, become capable of creating stable and preferential binding with some allergenic peptides. It should also be remembered that CD1 antigens are present on the membrane of the intra-epithelial dendritic cells [16]. However, it is very likely that these cells use class II molecules for binding micro-environmental antigens or allergens.

Significant associations between particular HLA types and specific immune responses toward several different highly purified allergens have been observed [13]. HLA-DR2/Dw2 was found to be significantly associated with responsiveness to all three *Amb* V homologue (allergens from three species of *Ambrosia*—ragweed—pollen) [19] and DR3/Dw3 was found associated with responsiveness to *Lol p* I, II, and III (allergens from *Lolium perenne*—rye grass—pollen) [20]. Weak associations were also found with DR5 and DRw6 [20,21]. More recently, by sequence-specific oligonucleotide (SSO) slot-blot and sequence analyses of PCR-amplified genome DNA from *Lol p* III responder and non-responder subjects, the antibody responsiveness was found to be associated strongly with the sequence glu-tyr-ser-thr-ser (EYSTS), present in the first polymorphic regions of DR β I polypeptide chains of DR3, DR5, and DRw6. These findings suggest that the EYSTS sequence is important in the presentation of an epitope of *Lol p* III; other sequence(s) may be involved in the presentation of the other epitope(s) [21].

The continuous, stable and preferential presentation of certain allergenic peptides on extended surfaces of dendritic cells can considerably increase the probability of recognition by T cells bearing TcR specific for those peptides, with subsequent proliferation, expansion and colonization in lymphoid structures. The existence of this phenomenon was sustained by the observation that, even at clonal level, T lymphocytes in atopics do indeed proliferate *in vitro* with very low concentrations of purified allergens. The *in-vitro* T-cell responsiveness was shown to be allergen specific and could be inhibited by anti-HLA-DR polyclonal or monoclonal antibodies. This suggested that HLA-DR molecules are able to function as restriction elements for the presentation of allergen molecules [3,22,23].

Another peculiar alteration in atopics could be related to the progressive development of a greater proportion of Th2-like T-cell clones able to produce high amounts of

IL-4 and no or reduced amounts of IFN- γ , and therefore capable of favouring IgE antibody responses. It has been demonstrated that polyclonal T cells and CD4⁺ *Dermatophagoides* spp. (house dust mite: HDM)-specific T-cell clones derived from an atopic, HDM-allergic individual are able to support IgE synthesis by autologous B cells. The helper activity was IL-4 dependent, as only cloned T cells expressing detectable mRNA for IL-4 were able to induce IgE synthesis without the addition of exogenous IL-4 [24].

An imbalance in the T-cell subsets responsible for IL-4 and IFN- γ secretion therefore seems to be one of the alterations responsible for the hyperproduction of IgE in atopics. This imbalance is quite well defined in tissue-allergic inflammatory infiltrates. It has been shown that the majority of T cells isolated from conjunctival infiltrates of patients with vernal conjunctivitis consist of Th2-type lymphocytes able to secrete IL-4 and to induce IgE synthesis, whereas the number of Th1-type cells producing IFN- γ is low [25]. Recent studies in our laboratory [unpublished data] have shown that, upon stimulation with the appropriate allergen or with phorbol myristate acetate (PMA) plus anti-CD3, allergen-specific T-cell clones derived from atopics express mRNA for IL-5 and secrete IL-4, but only reduced amounts of IFN- γ . On the other hand, virtually all T-cell clones specific for tetanus toxoid or other bacterial proteins synthesize IFN- γ , whereas only a certain number of them also secrete IL-4.

On the basis of current knowledge we can assume that in atopics the conditions favouring the expansion of Th2-type clones should be sought both at the level of interaction between the dendritic cells of the respiratory mucosa, allergenic peptides, and T cells, and also at the level of cross-regulation by some cytokines (IL-4, IFN- γ , IL-10/CSIF, others) which affect the maturation of various functional T-cell subsets. Once a Th2-type of T-cell response to allergen is activated, two events are predictable: (a) the preferential expansion of Th2 clones; and (b) the increased probability of T-B cell co-operation leading to an IgE antibody response (Fig. 2).

Most experimental data strongly suggest that the selection of the isotype expression occurs very early in the course of an immune response and that it is dictated by the chronological order of secretion of the different cytokines. A peculiar micro-environment determined by the portal of entry and dose of antigens, isolated or repeated stimulations, as well as by the hormonal influences and the properties of APCs, cytokines and adhesion molecules involved, certainly influences the differentiation of different types of Th-effector cells [18,26–28]. Dendritic cells have been identified as synergistic components in T-cell activation [18], with increased

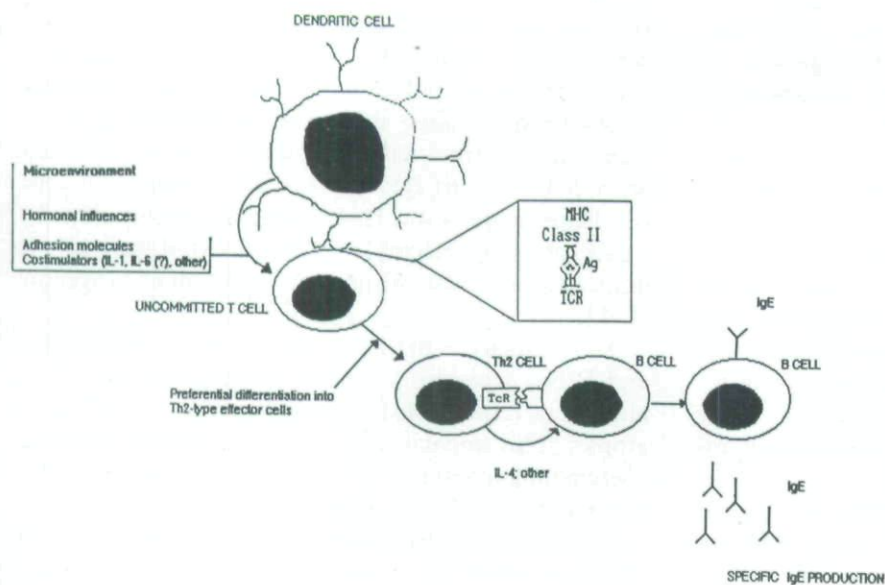


Fig. 2. A simplified view of cellular and molecular interactions which in atopic individuals favour the enhanced and persistent production of IgE antibodies specific for inhaled environmental allergens. (Detailed explanations in the text.)

expression of ICAM-1 [26], are probably capable of migrating from the epithelium of the respiratory mucosa to regional lymph nodes where they could mature and acquire much more stimulatory activity, and appear to be the best candidates for the creation of more suitable requirements for the differentiation of Th-cell precursors, bearing TcR specific for allergen epitopes, into Th2-type effector cells. Also, limiting dose exposure of allergens and repeated stimulations are probably important in favouring the differentiation of Th2-type cells and in the induction and maintenance of IgE antibody responses. Recently, it has been shown that in mice, resting T cells will produce IL-2 and IFN- γ rather than IL-4 upon primary activation by antigens. The IL-4-producing T cells are cells which are already activated by environmental antigens [29].

Of interest is the demonstration that hapten-specific CD4⁺ Th lines, generated by repeated stimulation with hapten-modified cultured Langerhans cells (cLC), release IL-4 but no detectable IL-2 into the culture medium. These cells could be stimulated to proliferate by Con A and IL-1. The latter plays a critical role in the growth of IL-4-producing cells which, when cultured with syngeneic, hapten-modified small resting B cells, caused specific IgE production. IL-4-producing Th cells appeared to result from their selective stimulation by cLC, suggesting that T-cell responses elicited in this way profoundly influence the B-cell isotype pattern [30].

Cytokines play a further regulatory activity in the differentiation states of Th1 and Th2 cells. In mice, IFN- γ inhibits the growth of Th2 cells; the CSIF secreted by Th2 clones can inhibit the production of cytokines by Th1 cells

but Th2 cytokines synthesis is not significantly affected. IL-2 and IL-4 partially antagonize the activity of CSIF [8,12]. It has been demonstrated in humans that IL-4 is able to down-regulate IFN- γ production by mitogen-stimulated mononuclear cells [31].

Effector mechanisms of airway allergic inflammation

New knowledge about the mechanisms involved in the effector phase of allergic reactions and respiratory tract inflammation comes from studies on the cytology of relevant biopsies and nasal and bronchial secretions, as well as from studies on cells involved in the release of mediators and cytokines. In particular, the discovery of the multiple biological effects of cytokines has offered an opportunity for advancing a new, integrated view of how the pathophysiological alterations responsible for respiratory allergic syndromes come about.

Data obtained from a broad series of studies suggest that airways *allergic inflammation* is sustained by induction, amplification, and maintenance mechanisms which originate from complex cellular and molecular interactions. Tentative schematic representations are depicted in Fig. 3a.

Cytological and pharmacological studies favour the hypothesis that chemotactic factors released by *mast cells* (LTB₄ and PAF) should be considered as an induction mechanism of inflammation, because they are, at least partially, responsible for the recruitment of inflammatory infiltrating cells. The release of these factors represents a pathophysiological link between immediate-type and late-phase reactions [32]. There is a possibility that mast

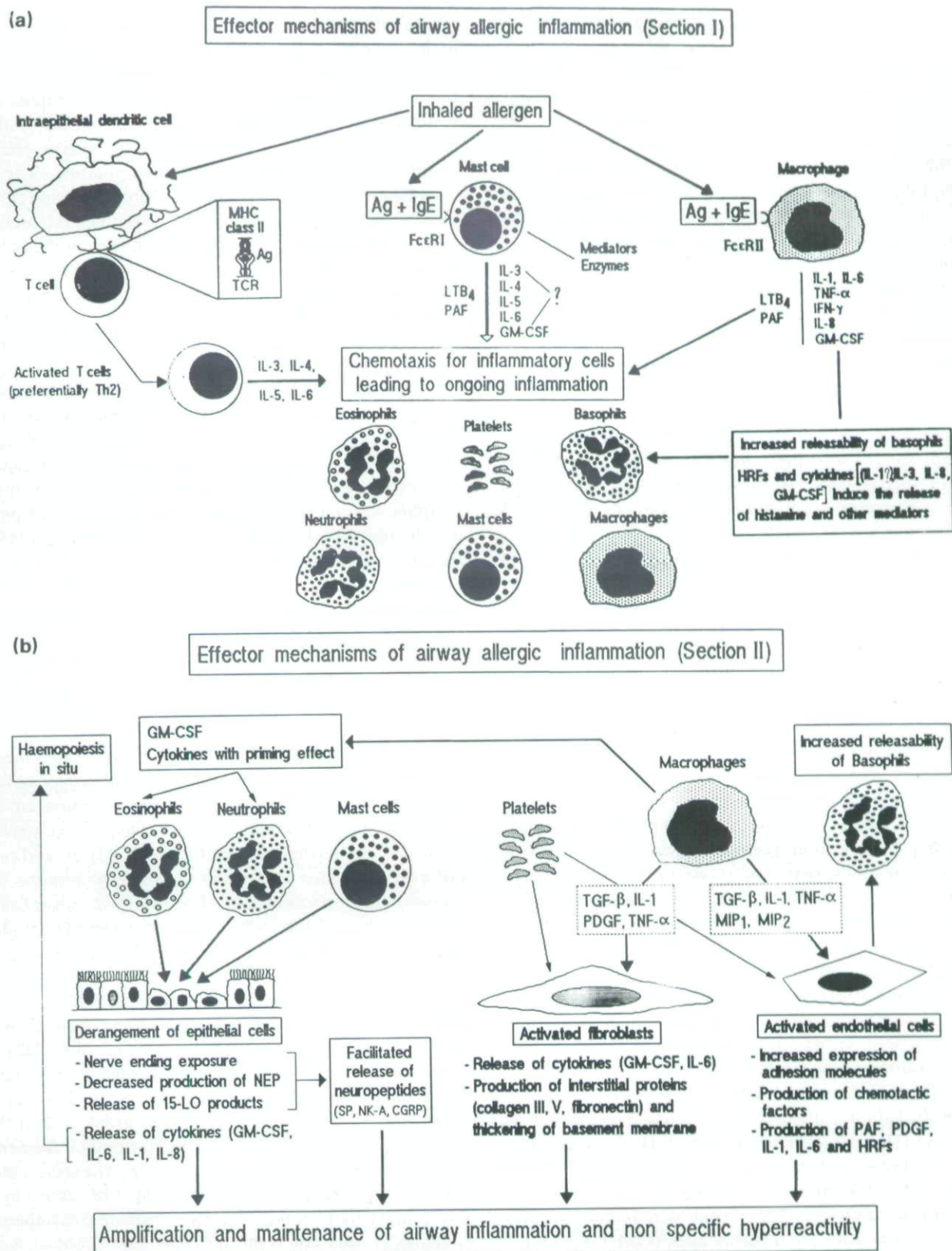


Fig. 3. A tentative scheme of (a) the main mechanisms involved in the initiation of airway allergic inflammation, and (b) the effector mechanisms involved in the amplification and maintenance of allergic inflammation (for explanation see text).

cells, as shown in mice [33], release pro-inflammatory cytokines (IL-3, IL-4, IL-5, IL-6, GM-CSF) similar to those produced by Th2-type lymphocytes.

The expansion of allergen-specific Th2-type lymphocytes makes the continuous production of IgE possible; these cells could also be capable of influencing the inflammatory cells by the production of cytokines acting on or influencing them [34,35]. Dendritic cells of the respiratory mucosa may provide the initial signal to the T-cell system during the sensitization phase of allergy, and may also function in local activation of primed T cells in the airway wall during the effector phase of allergic reactions [15].

It has been shown that lymphocytes accumulate during the first few hours of allergic tissue reactions in the skin and lung, and there is direct and indirect evidence that T-lymphocyte activation occurs *in vivo* in the late-phase reactions. T cells are attracted to sites of allergic inflammation, become activated and induce phenotypic changes in endothelial cells. A close association was found between eosinophil activation and numbers of CD4⁺ T cells [36].

As stated earlier, Th2 cells can produce IL-3 and IL-4 (which favour growth, differentiation and activation of mast cells), IL-5 (which promotes eosinophil growth and differentiation), GM-CSF (which acts in synergy with IL-5), and IL-6.

Monocytes-macrophages could also be considered as cells which are potentially able to initiate and maintain allergic inflammation. Alveolar macrophages in asthmatic patients have an increased ability to produce eicosanoids and superoxide anions [37]. These cells express membrane FcεRII receptors and can be stimulated by allergens to release mediators [38]. Analysis of bronchial lavage fluid from asthmatic patients after inhaling allergens reveals a marked increase of β-glycuronidase, with a reduction of that enzyme at the intracellular level. This suggests that secretory processes concomitant with the allergenic challenge can be activated [39]. The number of monocytes in the respiratory tract increases during the 48 hr following the allergenic stimulus [40]. Moreover, in subjects with allergic asthma, circulating monocytes exhibit an increase of complement receptors after allergen inhalation [41]. It should also be noted that in asthmatic subjects, bronchoalveolar macrophages are capable of secreting LTB₄ and PAF, as well as cytokines (IL-1, IL-6, TNF-α, IFN-γ, IL-8, GM-CSF), which facilitate the formation of inflammatory infiltrate at the level of the bronchial mucosa.

Of much interest is the recent demonstration that cytokines produced by macrophages (GM-CSF and a still poorly defined polypeptide) induce eosinophil and neutrophil activation, along with the production of

leukotrienes and superoxide anions which confer cytotoxic potential to those cells in asthmatics [42].

Amplification mechanisms of inflammation may be: (a) the recruitment and activation of eosinophils and neutrophils; (b) the activity of factors which induce basophils to release histamine; (c) the active role of epithelial cells in maintaining inflammation; (d) the activation of endothelial cells and fibroblasts; and (e) the '*in-situ*' haemopoietic activity of cytokines released by various infiltrating cells. As is well known, in the typical infiltrates of allergic inflammation, eosinophils are the most frequent cell type. Proteins derived from eosinophil granules (ECP, EPX or neurotoxin, MPB) play an important role in the development of epithelial lesions during allergic inflammation.

It is possible that factors capable of inducing histamine release from basophils are part of the mechanisms that maintain inflammation [43]. These histamine releasing factors (HFRs), whose molecular structure and genetic control are still unknown, can be produced by T and B lymphocytes, endothelial cells, macrophages and platelets. In addition, IL-3, IL-8, and GM-CSF have a HRF-like effect on mast cells and basophils.

Epithelial cells are capable of playing an active role in maintaining inflammation. This can take place as epithelial cells release products of 15-lipoxygenase, facilitating the release of neuropeptides (NP), as well as growth and differentiation factors for basophils and other metachromatic cells. Haemopoietic cytokines, mainly GM-CSF and IL-6, are spontaneously released by cultured epithelial cells and fibroblasts obtained from nasal biopsies of subjects with allergic rhinitis or polyposis [44]. Products of epithelium facilitate the secretion of NP (substance P, neurokinine A and B, etc.) by the sensory nerve endings of the bronchial mucosa [45]. In addition, NP and cytokines interact in controlling immune responses and in inflammation. For example, substance P, substance K and the carboxy-terminal peptide SP (4-ii) induce the release of IL-1, TNF-α and IL-6 by monocytes [46].

The release of certain cytokines by activated macrophages can be considered responsible for the activation of endothelial cells and fibroblasts. In particular, TGF-β, TNF-α, MIP₁, and MIP₂ activate endothelial cells inducing, on the one hand, a greater expression of adhesion molecules which favour chemotaxis, and on the other hand, production of factors such as IL-8 and CFSs, which also have a chemotactic effect and induce the secretion of PAF, PDGF, IL-1 and HFRs [47,48]. The adhesion of eosinophils to endothelial cells is favoured by the expression of adhesion molecules, such as ICAM-1. Anti-ICAM-1 antibodies inhibit eosinophilia of the bronchial mucosa and non-specific hyperreactivity *in vitro* and *in*

vivo [49]. Activation of the fibroblasts of the respiratory mucosa by some cytokines induces the production of interstitial proteins (collagen III, V, fibronectin) responsible for thickening and fibrosis of the subepithelial basement membrane. This is a well-known histopathological feature of both allergic and non-allergic bronchial asthma [50].

As mentioned earlier, one of the mechanisms which amplifies and maintains inflammation is the so called '*in-situ*' haemopoiesis due to some cytokines released by infiltrating cells. Such cytokines, able to promote the growth and differentiation of haemopoietic progenitors, are released by macrophages, T cells, presumably mast cells, epithelial cells, fibroblasts, and endothelial cells [44,51]. It seems quite clear that the combined action of several cells and of the several factors they produce confers the characteristics of a self-strengthening 'circular event' supporting inflammation.

A number of mechanisms can modulate allergic reactions and inflammation. Such modulatory mechanisms can operate at the level of the T-cell responsiveness to allergens, of IgE antibody synthesis, and also at the level of mediator, cytokine, and NP release, and they can have inflammatory effects. They are now under active investigation. It is easy to predict that a better knowledge of the mechanisms able to 'brake' the IgE production, the intensity and persistence of mediator and cytokine release as well as the amplifying effects of the autonomous system, will improve the therapy of allergic respiratory syndromes greatly.

Conclusion

There is evidence that in humans, IgE antibody production is dependent on two main signals provided by the T cells to the B cells. The first signal consists of physical interaction between T and B cells and the second one is provided by T-cell derived IL-4. Even though other cytokines or factors may enhance IgE antibody production, IL-4 is the signal required for the switch to IgE class. IFN- γ , IFN- α , TGF- β , and PGE₂ have been found to inhibit the IgE synthesis. Both cognate and non-cognate T-B cell interactions can support the IgE production. However, the nature of molecule(s) responsible for non-specific physical interaction occurring between T and B cells is still unclear.

Recent advances suggest that the alterations of regulatory mechanisms in atopy are multiple, that they have a genetic basis, and that the various associations among these give rise to the allergic phenotype. HLA-class II molecules present on the membrane of dendritic cells of respiratory epithelium may preferentially bind allergenic peptides to form bimolecular complexes that can easily be

recognized by TcR of specific T cells. Thus, a genetic trait peculiar to atopy could be their inheritance of particular amino acid sequences within HLA-class II molecules which, when expressed on the membrane of the dendritic cells, become capable of creating a stable and preferential binding with some allergenic peptides.

Another alteration in atopy could be related to the progressive development of a greater proportion of Th2-like T cells able to produce high amounts of IL-4 and no or reduced amounts of IFN- γ . It has recently been shown in our laboratory that allergen-specific T-cell clones derived from atopic subjects express mRNA for IL-5 and secrete IL-4 but only reduced amounts of IFN- γ . On the other hand, virtually all T-cell clones specific for bacterial proteins synthesize IFN- γ , whereas only a certain number of them also secrete IL-4. The imbalance in the T-cell subsets responsible for IL-4 and IFN- γ secretion is well defined in tissue allergic inflammatory infiltrates.

The expansion of allergen-specific Th2 lymphocytes makes enhanced and persistent IgE antibody production possible. Moreover, in the effector phase of allergic reactions Th2-like T cells could be capable of influencing the inflammatory cells by the production of cytokines acting or influencing them. Dendritic cells of respiratory mucosa may provide the initial signal to the T-cell system during the sensitization phase of allergy, and may also function in local activation of primed cells in the airway wall during the effector phase of allergic reactions. Thus, T cells, along with the mast cells and macrophages, could be considered as primary effector cells of allergic inflammation. Amplification mechanisms of inflammation involving other cells as well as a complex web of mediators, cytokines, neuropeptides, and neurotransmitters can now be envisaged. It seems quite clear that the combined action of several cells, and of several factors they produce, confers the characteristics of a self-strengthening 'circular event' supporting inflammation.

Acknowledgments

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