

The role of antigen-presenting cells in the regulation of allergen-specific T cell responses

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Allergic reactions in atopic patients follow from a generalized enhanced polarization of Th cells, predominantly imposed by factors derived from antigen-presenting cells from a pathogen-stressed tissue; these sample information not only on antigen structures but also on the nature of the stress. Antigen-presenting cells of atopic individuals show aberrant characteristics which, through a highly interactive communication network, play an active role in aberrant Th-cell polarization. This generalized bias may follow from intrinsic abnormalities of antigen-presenting cells and also from a low degree of cross-regulation by micro-organisms.

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Abbreviations

APC	antigen-presenting cell
DC	dendritic APC
GM-CSF	granulocyte-macrophage colony-stimulating factor
IFN	interferon
IL-12R	IL-12 receptor
LC	Langerhans cell
PGE₂	prostaglandin E ₂

Introduction

Immunity depends on two major types of specific immune responses: firstly, cellular responses mediated by inflammatory CD4⁺ and cytotoxic CD8⁺ T cells; and secondly, humoral responses mediated by CD4⁺ Th cells and the immunoglobulins produced by B cells. Depending on the type of pathogen or (in case of micro-organisms) the life cycle stage, effective protection relies on either strong cellular or strong humoral responses. The balance between cellular and humoral responses is orchestrated by cytokines produced by CD4⁺ Th cells. Th1 cells make the 'type 1' cytokines interferon (IFN)- γ and tumor necrosis factor which promote inflammatory cellular immunity, as required both for protection against many intracellular micro-organisms and for the effective killing of tumor cells. Th2 cells make the 'type 2' cytokines IL-4 and IL-13 which promote humoral immunity, which is required for the elimination of many extracellular pathogens and reduces the risk of Th1-cell-mediated autoimmunity by counteracting inflammatory responses. Populations of CD4⁺ T cells may simultaneously produce all of these cytokines, but effective cellular or humoral responses require the selective activation of highly

polarized Th1 or Th2 cells, respectively. The failure to develop highly polarized Th cells when needed or the development of aberrantly polarized Th cells may lead to disease — for example chronic infections, tumors, autoimmunity or allergy. Whereas accumulating evidence suggests that the paradigm of protective or harmful responses biased towards Th1 and Th2 cells in infection, autoimmunity or transplantation is not fully explanatory, there is less doubt about the role of Th2 cells in the sensitization phase of atopic allergy.

Atopic allergy to normally harmless proteins is related to the development of highly polarized Th2 cells, with high production of type 2 cytokines (IL-4, IL-5 and IL-13) but without simultaneous production of the type 1 cytokine IFN- γ . The inflammatory late-phase response in allergic rhinitis and asthma is causally related to the high expression of IL-5; this promotes the maturation, recruitment and activation of eosinophils; these in turn will cause local tissue damage. Due to the high expression of IL-4 and/or IL-13 without IFN- γ , Th2 cells induce B cells to switch to IgE production. In the normal situation, abundant IgE production does not occur because low levels of IFN- γ block the IgE switch induced by IL-4 or IL-13. The enhanced levels of serum IgE in atopic patients are essential for immediate hypersensitivity responses. The biased polarization of the response towards Th2 cells in atopics is generalized and in some of the patients appears to be inherited. For instance, the response to mycobacterial antigens — although dominated by IFN- γ — is less polarized towards Th1 cells in atopics as compared to control subjects [1]. A crucial question concerns the mechanisms by which Th2-type profiles develop in atopic subjects. Answering this question requires knowledge both of the factors that polarize the Th-cell cytokine profiles and of the extent to which these factors operate aberrantly in atopic disease.

In general, polarization of the production of type 1 or type 2 Th-cell cytokines can result from various conditions. On the molecular level, it involves different signals to which Th cells are susceptible — primarily during, or shortly after, their activation. As Th cells are activated upon the recognition of antigen-derived peptides presented in the context of MHC molecules expressed by antigen-presenting cells (APCs), the tuning of the balance between type 1 and type 2 cytokines is highly determined by factors associated with APCs. In fact APCs play a central role, as they transfer information to the T cells from an infected microenvironment; this information is crucial to select the most effective immune response to the pathogenic antigens associated with the microenvironment.

In the sensitization phase, the transfer of information involves the challenge of a geographical barrier. Specific immune responses start in peripheral immunocompromized tissues, with the activation of immature dendritic APCs (DCs). After activation, these DCs acquire a transiently enhanced capability to take up antigen and they subsequently migrate to the draining lymph nodes. Meanwhile they undergo a process of final maturation, that provides them with the unique capacity to both effectively present antigen to naive T cells and to activate them under conditions of efficient co-stimulation [2]. In the mouse, polarized cytokine profiles in draining lymph nodes were found within a week after local infection, indicative of a polarizing activity of DCs during the primary immune response. Full polarization of Th-cell responses to infection *in vivo* may require repetitive cycles of re-stimulation of memory Th cells, either in lymphoid organs or in the infected tissues. As shown *in vitro*, memory T cells can still be polarized further upon antigen-specific re-stimulation. In contrast to naive Th cells (which can only be activated by antigen if it is presented by DCs), memory Th cells — particularly effector Th cells — can also be effectively stimulated by all other cell types that are able to process antigens and express class II MHC, irrespective of the expression of co-stimulatory molecules. Examples of such nonprofessional APCs are B cells (in the germinal centers) and macrophages, newly recruited monocytes and epithelial or endothelial cells (at the site of the antigen challenge); therefore, outside the T cell compartments of lymphoid tissues, various APC types may contribute to secondary Th-cell polarization. Once fully polarized, effector T cells may become refractory to counter-polarization due to the loss of expression of the appropriate receptors.

APCs thus provide T cells not only with an antigen-specific stimulatory signal (signal 1, i.e. ligation of the TCR) and a series of co-stimulatory signals (signal 2, i.e. ligation of CD28, leucocyte functional antigen 1 and many other surface molecules) but also with polarizing signals (signal 3, to be discussed below). The expression of these polarizing APC factors is triggered by (pro)inflammatory stress ('danger') signals that may affect the APC either directly or indirectly via the activation of other neighbouring tissue cells. Conditions that affect the polarizing function of APCs include antigen-related factors (the type, dose and site of entry of antigen), host-related factors (ongoing immune responses, genetic predisposition, hormonal balance and age) and environmental factors (natural adjuvants). Here we review the current knowledge of the role of APCs in such early signalling networks and discuss how these networks are derailed in atopic allergy.

IL-12, a crucial polarizer of Th cell responses that is derived from antigen-presenting cells

IL-4 and IL-12 are probably the two major polarizing cytokines for Th cells; they both have direct effects [3]. IL-4 promotes Th2-cell responses by upregulation of IL-4 production and inhibition of IL-12 receptor

(IL-12R) β 2 expression. Although IL-4 can be produced by various cell types, Th cells are most probably only polarized by endogenously produced IL-4 [4]. Naive Th cells produce only low levels of IL-4. The initial levels of all type 1 and 2 cytokines, including IL-4, in these cells are determined predominantly by DC-derived polarizing factors — the IL-12 p70 subunit in particular — acting at the onset of stimulation of naive Th cells [5,6]. IL-12 promotes Th1-cell responses by the selective upregulation of IFN- γ production by T cells. Remarkably, IL-12 is almost exclusively produced by APCs, although the levels vary for different APC types; IL-12 is readily produced by various macrophage types, monocytes and DCs but is absent in B cells. IL-12 production can be induced by activated Th cells, through triggering of APC CD40 by T cell CD40-ligand upon activation caused by antigen presentation [7]. A central role of APC-derived IL-12 in Th-cell polarization is underscored by the observation that several other Th1- and Th2-polarizing factors — such as IL-4, IFN- γ , IL-10 and prostaglandin E₂ (PGE₂) — exert their activity by modulating IL-12 production in APCs or, alternatively, by modulating the IL-12 responsiveness of Th cells. As discussed below, these factors may profoundly affect primary immune responses by priming the IL-12 levels in DCs.

Secondary Th cells may be further or additionally biased under the control of IL-12 production induced by these T cells in the various APC types in nonlymphoid tissues; the outcome then will depend on the type of APC encountered. IL-12 production can, furthermore, be induced via a T-cell-independent exogenous pathway, through direct infection of APCs. This mode of induction applies for infection by most bacteria and some viruses and for the action of compounds derived from them [5,6,8]. Direct infection does, however, harbour the risk of immune evasion by blocking the APC function [9•]. Pathogen-induced IL-12 production probably plays an important role at the site of infection, enhancing IFN- γ production in local natural killer cells or activated memory CD4⁺ and CD8⁺ T cells.

Th-cell polarization thus depends on the ability or inability of APCs to produce IL-12, which is highly determined by regulatory signals. Th-cell-induced IL-12 production occurs firstly via CD40 ligand and, secondly, is strongly upregulated by IFN- γ , IL-4 and bacterial compounds [10–12]. High IL-12 production by APCs thus requires two signals; in DCs this is a requirement for any IL-12 production [12]. It is to be expected, therefore, that either an additional exogenous pathogenic trigger (such as that provided by certain bacterial or viral molecules) or an additional endogenous trigger (such as that mediated by IFN- γ or IL-4) contributes to further polarization of Th cells in inflamed tissue. IL-12 production is downregulated by a variety of factors — including PGE₂, IL-10, vitamin D, glucocorticoids [5,6] and probably others. IL-10 and glucocorticoids, in contrast to PGE₂, also affect antigen presentation either by preventing optimal expres-

sion of class II MHC [13] and the co-stimulatory B7.1 and B7.2 molecules [14] or by limiting uptake and/or processing of antigen [15]. These factors therefore have a dual effect: they downregulate the activation of naive Th cells, in the case of IL-10 leading to tolerance [16]; and they polarize the remaining response towards type 2 cytokines.

In vitro experiments have shown that IFN- γ can prime monocytes for high IL-12 production upon subsequent activation [17]. Similarly, PGE₂ and IL-10 administered at the onset of final DC maturation prime only low IL-12 production by mature DCs [18,19]. The *in vivo* implication is that the early inflammatory-tissue response to pathogen-induced stress not only induces the migration and final maturation of DCs but also determines the development of functionally distinct DC subsets with a high (type 1 or DC1 subset) or a low (type 2 or DC2 subset) capability for IL-12 production upon subsequent contact with antigen-specific T cells — inducing Th1- or Th2-polarized primary responses, respectively [19]. Comparable to polarized effector B and T cells, the production profile of these polarized mature DCs is stable and refractory to further (counter)polarization.

Other polarizing factors derived from antigen-presenting cells

In addition to IL-12, Th-cell polarization by APCs is regulated via various other pathways; these include surface expression of B7.1 or B7.2 [20] and OX40 [21], which ligate CD28 and OX40 ligand on the surface of Th cells. There are several examples of secreted molecules that also play a role: PGE₂, IL-18 and IFN- α . PGE₂ selectively downregulates IFN- γ production by Th cells and drives Th2 responses [22,23]. DCs do not produce detectable amounts of PGE₂, suggesting that this factor has no direct role in the regulation of primary immune responses; however, it still may affect naive Th cells indirectly because PGE₂, produced by macrophages and stromal cells, primes for the development of type 2 DCs (as discussed above). The role of IL-18 is especially noteworthy as it synergizes with IL-12 in Th1-cell polarization [24,25]. To affect Th cells, IL-18 requires the presence of IL-12 to induce the expression of the IL-18Rs on T cells. In contrast to IL-12, relatively little is known about the conditions of induction and regulation of IL-18 production.

Are there aberrant antigen-presenting cells in atopic patients?

Blood monocytes from patients with atopic asthma phenotypically resemble tissue macrophages [26] and have a lower production of IL-12 in response to bacterial compounds compared to control monocytes [27]. IL-12 production by monocytes from patients with atopic dermatitis is not altered [28,29] but, interestingly, monocytes from these patients show a considerably elevated PGE₂ production [29,30]. Indeed, by decreased levels of IL-12 and/or by

enhanced levels of PGE₂, monocytes of atopic patients drive Th2-cell responses *in vitro* [27,30]. In addition, newly recruited monocytes with enhanced PGE₂ production may promote the generation of type 2 DCs in peripheral tissues in patients with atopic dermatitis.

These data suggest either an intrinsic defect or a different priming of monocytes from atopic patients. Factors that prime monocytes for either IL-12 production or (via activation of cyclo-oxygenase-2) for PGE₂ production include IFN- γ [17] and IL-4 [31], respectively. As the levels of these cytokines are known to be aberrant in sensitized atopic subjects, monocytes from atopic patients may be primed as the result of feed-back regulation by Th cells. This tight inter-relation between APCs and Th cells indicates that it is impossible to attribute an intrinsic failure to one of these cell types, at present.

Bronchial biopsies from patients with allergic asthma contain a decreased number of cells expressing IL-12 mRNA, compared to similar biopsies from normal control subjects [32]; the numbers of CD1+ DCs and T cells are greatly elevated in the bronchial epidermis of patients with allergic asthma [33] and in atopic dermatitis lesional skin in animal models [34,35], suggesting that the local IL-12 production is low at the inflammatory stage of the disease. The elevation of DC numbers results from increased production of granulocyte-macrophage colony-stimulating factor (GM-CSF) by bronchial [33] and epidermal [36] epithelia of the atopics. GM-CSF is a factor known to induce local recruitment and development of DCs. Although further studies are required to establish whether such an elevated production of GM-CSF represents a primary defect of atopic epithelia, it is striking that GM-CSF production is still increased in atopic keratinocytes after five passages over several weeks of culture [36]. Another mechanism of prolonged activation of allergen-specific Th cells in atopics is IgE-facilitated allergen presentation by APCs. This mechanism involves the combination of enhanced expression of the high-affinity IgER on the APCs and the presence of elevated levels of allergen-specific IgE complexed to allergen [37,38]. The triggering of FcRs on APCs induces PGE₂ production [39] and downregulates IL-12 production, which add to the bias of the response towards Th2 cells. These FcR-mediated effects depend on intracellular Ca²⁺ mobilization [40]. Interestingly, epidermal Langerhans cells (LCs) from patients with atopic dermatitis are fully activated upon Fc ϵ RI ligation, while LCs from normal individuals fail to exhibit calcium mobilization [38]. The implication is that IL-12 production in LCs of atopic patients, in contrast to LCs of normal donors, is inhibited through the deficient expression of Fc ϵ RI.

Allergen-related polarizing factors

Although in atopic patients the bias towards Th2 cell responses appears to be generalized, the responses to

allergens show an especially high degree of polarization. This can be related to the effects of the low dose of exposure, the low biological activity and the specific site of entrance of allergens on the function of the APC. Low doses of antigen lead to low numbers of MHC molecules bearing relevant peptides on APCs, resulting in low numbers of ligated TCRs and, consequently, limited phosphorylation of intracellular kinases and limited mobilization of calcium in the T cells. *In vitro*, a low degree of T cell activation induces IL-4 production without IFN- γ production in resting human memory [41] and effector [42•] Th cells and leads to the development of Th2-cell responses in naive Th cells from TCR-transgenic mice [43]. As many allergens enter the body at low concentrations, this low-dose effect may contribute to the preferential development of Th2-cell responses as found in allergy. Interestingly, on the basis of the reactivity of allergen-specific Th-cell clones *in vitro*, the study of Carbadillio *et al.* [42•] suggests that Th cells from patients with atopic allergy require higher doses of allergen to produce IFN- γ than their counterparts from nonallergic subjects. This finding may represent another possible intrinsic abnormality underlying the generalized bias of immune responses in atopic patients towards Th2-cell responses.

The type of antigen determines the outcome of the immune response to a great extent, by affecting the function of APCs. Many pathogens display particular biological activities, which are used either by immune cells to adapt a protective type of response or by micro-organisms themselves to escape from such a protective response. Similarly, certain chemicals may affect APCs or their microenvironment, as they may not only be antigenic but induce nonspecific inflammation as well. Although various protein allergens are enzymes or otherwise biologically active molecules, they will normally not be very effective in human tissues because they enter at doses that are too low. The allergen-induced responses are highly susceptible, however, to the influence of polarizing factors they induce. Indeed allergens, for example, do induce IL-12 production in non-lesional skin of atopic dermatitis patients when applied in patch-test conditions [44]. This IL-12 production is associated with induction of IFN- γ production in local Th cells and contributes to the reversal of an early response dominated by type 2 cytokines into a late-phase response dominated by Th1 cells. This finding may explain the dominant levels of IFN- γ that are found in chronic lesions of patients with atopic dermatitis. On the other hand, a patch-test reaction requires relatively high allergen concentrations and IFN- γ production in chronic lesions may also be explained by cross-regulatory chronic infections.

The site of antigen entry is also crucial for the outcome of the immune response. Thus, to appreciate the role of APCs in the polarization of allergen-specific T cell responses it is important to know where and when sensitization occurs because APCs at different sites are

functionally different. Evidence is growing that early sensitization to allergens, to which the mother is exposed, already occurs *in utero* [45,46]. Indeed, new-borns harbour allergen-specific T cells showing a cytokine profile that is biased towards [47•] type 2; cord blood mononuclear cells show decreased IL-12 and IFN- γ production when activated cord cells are compared to activated peripheral blood mononuclear cells [48]. This bias towards Th2 cells is not surprising as the fetus is located in an immunoprivileged site, which is associated with low inflammatory responses and type 2 cytokine profiles [49]. A challenging concept is that atopic allergic reactions to these allergens during infancy and childhood follow from the inability of immune cells to sufficiently reverse these allergen-specific Th2-cell-biased responses, a process called immune deviation [46]. Alternatively, sensitization to allergen may occur after birth via breast feeding, inhalation or digestion. As mucosal DCs are known to promote responses biased towards Th2 cells [50,51], this pathway may also contribute to development of allergic reactions.

Cross-regulation of Th2-dominated profiles by infection

In general, immune responses to biologically inactive or weakly active antigens can be cross-regulated by infection with certain bacteria or viruses. This may also apply for atopic disease, as suggested by the finding that infection by varicella zoster virus in atopic dermatitis skin lesions induces local IL-12 expression and converts a predominantly Th2-type profile into a predominantly Th1-type profile. Both locally in the lesions and systemically in the peripheral blood, specific responses against mite allergens are shifted towards a Th1 phenotype [52]. Recently, it was proposed that the increased prevalence and severity of atopic disorders inversely correlate with the extent of exposure to certain infectious micro-organisms. A mouse model of allergic asthma demonstrated that intranasal *Mycobacterium bovis* infection of ovalbumin-sensitized mice strongly reduced both local (not systemic) IL-5 production and inflammation in the lung after airway challenge by ovalbumin [53•], supporting the concept that bacterial infections have the potential to suppress the development of allergic asthma. This suppressive effect is associated with elevated levels of IFN- γ . *M. bovis* induces high levels of IL-12 [54] and allergic reactions in these models are inhibited by exogenous IL-12 [55,56], suggesting the decisive role of IL-12 levels for development or prevention of atopic allergy. An intriguing recent study with resistant and susceptible strains of mice showed that endogenous production of IL-12 is essential for resistance to antigen-induced airway hyper-responsiveness and, furthermore, showed that dysregulation of IL-12 production may lead to the development of deleterious immune responses by Th2 cells to inhaled allergens [57•].

Whereas mycobacterial infections are infrequent today, viral infections are still common. In contrast to varicella

zoster, many other viruses do not 'convert' allergic reactions. A clear relationship between upper respiratory tract infections by viruses and exacerbation of allergic symptoms has been established [58]. These findings are underscored in a mouse model showing that acute infection with respiratory syncytial virus results in increased airway hyper-responsiveness and leads to changes in immune function that can enhance the effects of airway sensitization to antigen [59]. The lack of suppression of allergic reactions after infection with most viruses may be explained by the fact that polarization to Th1-cells in response to viruses is associated with induction of only low levels of IL-12 or may not even require its production [60].

Conclusions

The bias of allergen-specific Th cells towards a Th2 phenotype in atopic allergic patients partly follows from a generalized bias in these patients. The origin of this generalized bias towards a Th2 phenotype is unknown but the high percentage of patients with a family history of atopic disease indicates a genetic basis. Recent reports suggest that the abnormal activity of APCs may be an important factor in the development of atopic allergic reactions. Atopic APCs show an aberrant production profile of factors that either do not favour Th1 responses (i.e. IL-12) or favour Th2 responses (i.e. high PGE₂). This aberrant production may be an intrinsic property of atopic APCs or may follow from an altered tissue environment, including feed-back effects of memory Th cells. On the other hand, the bias towards a Th2 phenotype probably also strongly depends on extrinsic factors, such as the cross-regulatory effects of bacterial infections which are associated with the strong induction of IL-12 production in APCs. This cross-regulation may underly the recently postulated concept that the prevalence of atopic disease correlates inversely with the occurrence of infections. Various factors — the low doses, the preferential routing via mucosal tissues and the lack of intrinsic biological activity of allergens — all add, in an APC-dependent fashion, to the generalized bias towards type 2 cytokines in atopic patients; this results in a more pronounced Th2 phenotype of allergen-specific Th cells and thus in the production of allergen-specific IgE and the generation of eosinophilia.

The present knowledge of the role of APCs and their products in the development and maintenance of Th2 responses in atopic disease may contribute to the design of new strategies of vaccination against allergens. Current studies are aimed at the improvement of the classical protocols by combining allergen not with the generally used Th2-cell-promoting adjuvant alum but with adjuvants inducing IL-12 production in APCs, thereby preventing the polarization of the allergen-specific response towards a Th2 phenotype.

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