

TO RESPOND OR NOT TO RESPOND: T CELLS IN ALLERGIC ASTHMA

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The incidence of allergic asthma has almost doubled in the past two decades. Numerous epidemiological studies have linked the recent surge in atopic disease with decreased exposure to infections in early childhood as a result of a more westernized lifestyle. However, a clear mechanistic explanation for how this might occur is still lacking. An answer might lie in the presently unfolding story of various regulatory T-cell populations that can limit adaptive immune responses, including T helper 2 (T_H2)-cell-mediated allergic airway disease.

T HELPER 1/ T HELPER 2 (T_H1/T_H2). Functional subsets of $CD4^+$ T cells that express T-cell receptor- $\alpha\beta$ and produce either type-1 cytokines (interferon- γ and other cytokines that support macrophage activation, the generation of cytotoxic T cells and the production of opsonizing antibodies) or type-2 cytokines (interleukin-4 (IL-4), IL-5, IL-13 and other cytokines that support B-cell activation, production of non-opsonizing antibodies, allergic reactions and expulsion of extracellular parasites).

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The recent increase in atopic disease has been described as epidemic^{1,2}. There has been an almost doubling in the incidence of asthma, atopic dermatitis and hayfever in industrialized countries over the past two decades^{2,3}, with the present cost of care for asthmatics being estimated at about six million US dollars per year³. Although it is clear that atopic individuals have an underlying genetic predisposition to become sensitized to commonly encountered allergens, the rate at which the incidence of allergic disease is rising implicates a recent change in environmental influences on this process. Several hypotheses have been put forward to explain this trend, including the 'hygiene hypothesis', which has received the most attention recently^{4,5}. This hypothesis proposes that decreased exposure to immune-stimulating infections in early childhood is a cause of the increased prevalence of allergic disease. The epidemiological data, upon which this hypothesis was based, showed a lower incidence of allergic sensitization among children with a higher number of older siblings, which was attributed to a greater exposure to infections in early life of these children⁴. Several studies have since confirmed that there is an inverse correlation between the incidence of allergic disease and, not only sibling number, but also other indicators of early childhood exposure to infections, such as day-care attendance⁶⁻⁸. What remains unclear, however, is the mechanism by which this could occur. In other words, how might infections in early life influence the tendency to become sensitized to otherwise innocuous antigens in

the environment? To answer this, we must first gain a better understanding of how allergic responses are initiated at the sites of natural allergen exposure.

Although it is certain that $CD4^+$ T HELPER 2 (T_H2) effector T cells have an important role in generating the inflammation that characterizes allergic disease, including airway eosinophilia and mucus hypersecretion in atopic asthmatics, less is known about how these T_H2 -cell responses are first induced. Furthermore, what role other T-cell populations might have in either facilitation or downregulation of T_H2 -cell-mediated airway inflammation is yet to be established. Two relatively new areas of investigation, regarding the immunoregulation of allergic disease, focus on the role that innate-immune-system signals might have in the generation of T_H2 -cell responses, and the involvement of regulatory T-cell populations that can downregulate inflammatory responses. Indeed, these two areas are closely intertwined and might provide the information required to link the epidemiological observations of allergic prevalence with an immunological mechanism. A better understanding of all the components that are involved in the immunoregulation of allergic-airway inflammation is also required to help generate new therapeutic strategies.

Allergic asthma and T_H2 cells

Asthma is defined as a chronic inflammatory lung disease that is characterized by airway hyperreactivity and mucus hypersecretion that results in intermittent airway

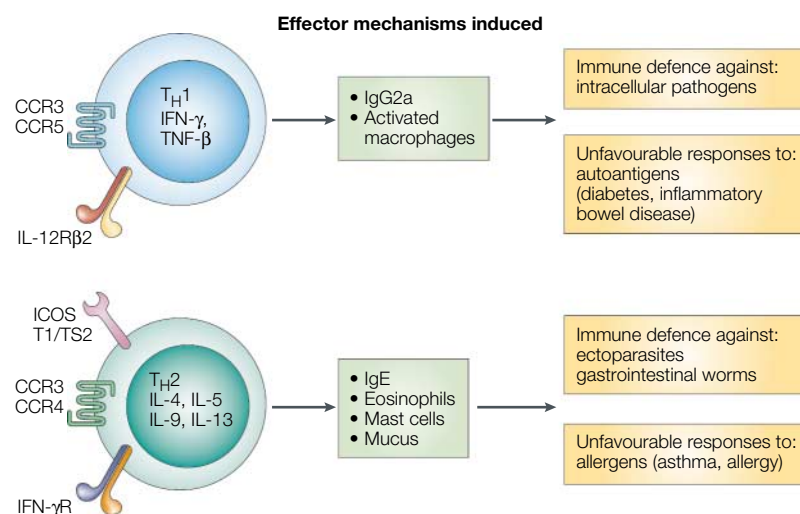


Figure 1 | Phenotypic distinctions and differential functions of T_H1 and T_H2 cells. Although originally defined by differences in cytokine production and function, T_H1 and T_H2 cells are now known to express different cytokine and chemokine receptors. Effector functions of T_H1 and T_H2 cells mainly indicate their differences in cytokine-secretion profiles, leading to both beneficial effects in immune defence and unwanted inflammatory reactions. CCR, CC-chemokine receptor; ICOS, inducible T-cell co-stimulator; IFN- γ , interferon- γ ; IL, interleukin; TNF, tumour-necrosis factor.

obstruction⁹. Although the clinical syndrome of asthma might result from various aetiologies, atopic individuals can develop a form of the disease that is exacerbated by exposure to aeroallergens. These atopic asthmatics have characteristic allergic airway inflammation with high numbers of lymphocytes and eosinophils, together with mucus hypersecretion⁹. It has been known for a long time that atopic individuals, including those with atopic dermatitis, allergic rhinitis and asthma, have an inherited predisposition to become sensitized to commonly encountered environmental allergens and to develop high levels of immunoglobulin E antibodies. However, the reason for mounting these IgE responses was not well understood until the discovery of T_H1 and T_H2 subtypes of $CD4^+$ T helper cells^{10,11}. These subsets are characterized by distinct cytokine-secretion patterns and associated effector functions (FIG. 1). Given that both IgE production and recruitment of allergic-type inflammation is associated specifically with T_H2 cells, it became clear that the underlying genetic predisposition in atopic individuals was the development of T_H2 -type immune responses.

The high levels of T_H2 -type cytokines that are found at sites of allergic inflammation^{12–18} are consistent with a T_H2 -cell-based aetiology of atopic disease. Furthermore, studies in mouse models of asthma have shown that allergic airway inflammation is dependent on $CD4^+$ T cells and, more specifically, is seen when T-cell receptor-transgenic T_H2 , but not T_H1 , cells are adoptively transferred to mice^{19–22}. Finally, the absolute requirement for T_H2 cells in directing allergic airway inflammation has been shown by the use of interleukin-4 (IL-4)-deficient mice. In these studies, defective priming of T_H2 cells in the absence of IL-4 resulted in a failure to generate allergic inflammatory responses after subsequent airway

challenge^{21,23–25}. Of note, if IL-4 was blocked only during inhaled antigen challenge, airway inflammatory responses were intact^{23,25}, indicating that once T_H2 -cell priming has occurred, IL-4 is no longer necessary for airway inflammation. This has also been confirmed by studies in which effective T_H2 -cell sensitization was achieved despite the absence of IL-4. Specifically, we have shown²⁶ that IL-4-independent T_H2 -cell responses with high levels of IL-5 and IL-13 production can be generated in IL-4-deficient mice by epicutaneous exposure to soluble protein. In this system, mice showed no deficit in airway eosinophilia or mucus secretion following inhaled antigen challenge. So, the main role of IL-4 in allergic airway inflammation is during the initial priming of T_H2 -effector cells, whereas IL-5 and IL-13 have been shown, in numerous studies in both mice and humans, to be more directly responsible for the characteristic eosinophil infiltrates and mucus hypersecretion. The individual roles of the T_H2 -cell cytokines in allergic airway inflammatory responses are summarized in TABLE 1. Although other cell types might participate to some extent in certain aspects of asthma pathophysiology — for example, airway hyperresponsiveness^{27,28} — $CD4^+$ T_H2 cells are the main orchestrators of allergic-type airway inflammation.

Despite their clear role in the pathogenesis of allergic asthma, little is known about how T_H2 -cell responses are regulated. An overall shift in the balance towards more abundant T_H2 -type responses could result from an increase in positive, as well as a loss of negative, influences on this process. Furthermore, these regulatory effects could operate during *de novo* generation of T_H2 -cell responses or at the time of activation of established T_H2 cells. So, when considering reasons for the sharp increase in the incidence of atopic disease over the past few decades, as well as potential therapeutic targets, all of the events that lead to the establishment of T_H2 -cell-mediated inflammation and the possible regulatory influences on each of these processes must be looked at. To begin to dissect these questions, we discuss several recent areas of investigation that focus on the immunoregulation of T_H2 -cell-mediated allergic asthma.

Can T_H1 -cell responses prevent asthma?

In addition to their distinctive functional phenotypes, T_H1 and T_H2 $CD4^+$ T cells each have the ability to suppress the generation and activation of the other²⁹. It might be inferred, therefore, that a relative deficiency in T_H1 -type immune responses could allow for the generation of greater T_H2 -type responses. Indeed, a leading interpretation of the hygiene hypothesis has been that it is the decreased exposure to T_H1 -type-inducing infections, for example, with mycobacteria or viruses, that leads to the unconstrained development of T_H2 -cell responses and the increased incidence of allergic disease^{30–32}. However, there are problems with this simple explanation. First, not only has T_H2 -cell-mediated allergic disease been on the rise in recent years, but the prevalence of several T_H1 -associated autoimmune disorders, including INFLAMMATORY BOWEL DISEASE and TYPE 1 DIABETES, has also risen over the same time period^{33–35}.

INFLAMMATORY BOWEL DISEASE

A group of conditions, of unknown aetiology, in which the intestinal mucosa is chronically inflamed. Includes Crohn disease and ulcerative colitis.

TYPE 1 DIABETES

(Insulin-dependent diabetes mellitus). A severe form of diabetes mellitus that is usually of abrupt onset during the first two decades of life and requires insulin therapy. It is characterized by an immune-mediated destruction of pancreatic β cells.

Table 1 | Individual roles of T_H2 cytokines in allergic airway inflammation

Effects on allergic airway responses	T _H 2 cytokines*	References
Acute effects in the lung		
Airway eosinophilia	IL-5 IL-13 (IL-4) (IL-9)	38,88–91 92–95 42 96–100
Mucus hypersecretion	IL-13 (IL-9)	92–94,100,101 96–100
Airway hyperresponsiveness	IL-13	92,93,95
Airway remodelling/pro-fibrotic effects		
	IL-4 IL-13	102–104 94,104,105
General effects on T_H2-type responses		
T _H 2-cell differentiation	IL-4 (IL-13)	106–109 26,110–112
IgE isotype class switching	IL-4 (IL-13)	113–115 93,111,116

*Cytokines that have been shown to enhance, but are not required for, these effects are shown in parentheses. IL, interleukin; T_H, T helper.

Furthermore, populations with high rates of helminth infection, which induce strong T_H2-cell responses, are also protected from the development of allergic disease^{36,37}. So, if the hygiene hypothesis holds true, it seems probable that some other consequence of early childhood exposure to infections limits the development of both unwanted T_H2- and T_H1-type immune responses.

Regardless of whether the development of T_H2-type immune responses to environmental antigens is naturally prevented by a high degree of T_H1-cell activation in early life, the question remains as to whether deliberate generation of T_H1 cells could help to suppress T_H2-mediated airway inflammation. In other words, can the

ability of T_H1 cells to suppress T_H2-cell responses be taken advantage of for therapeutic purposes? Unfortunately, the evidence from mouse models of allergic asthma has not been promising. Several groups, using adoptive-transfer systems, have shown that antigen-specific T_H1 cells can suppress T_H2-cell-mediated airway eosinophilia, as assessed by analysis of cells in bronchoalveolar lavage (BAL) fluid^{38–40}. However, histological examination showed that equivalent numbers of T_H2 cells and eosinophils were present in lung tissue, even though decreased numbers of eosinophils were recovered by BAL when T_H1 cells were transferred^{39,40}. Interestingly, a similar situation has been observed in IL-4-deficient mice, in which decreased numbers of BAL eosinophils do not always indicate decreased eosinophil-mediated inflammation in lung tissue^{41,42}. Furthermore, this phenomenon was shown to be mediated by interferon- γ (IFN- γ)⁴². So, an increase in IFN- γ , whether owing to the presence of T_H1 cells or the loss of IL-4-mediated suppression, can limit the inflammatory response to the lung parenchyma and prevent the egression of eosinophils into the airway, but does not prevent T_H2-cell-mediated lung inflammation altogether. Additional studies with adoptive T_H1-cell transfers have also shown that a lack of suppression, or even enhancement, of T_H2-cell-induced airway eosinophilia occurs in the presence of T_H1 cells^{43,44}. Similarly, studies with inhaled IFN- γ in humans have been disappointing^{45,46}. Not only did inhaled IFN- γ have no impact on asthma symptoms, but it also resulted in increased numbers of lymphocytes in the airways. So, T_H1 effector T cells do not seem to be capable of preventing, and might actually exacerbate, lung inflammatory responses to inhaled antigen, making this an unlikely therapeutic option (reviewed in REF. 47).

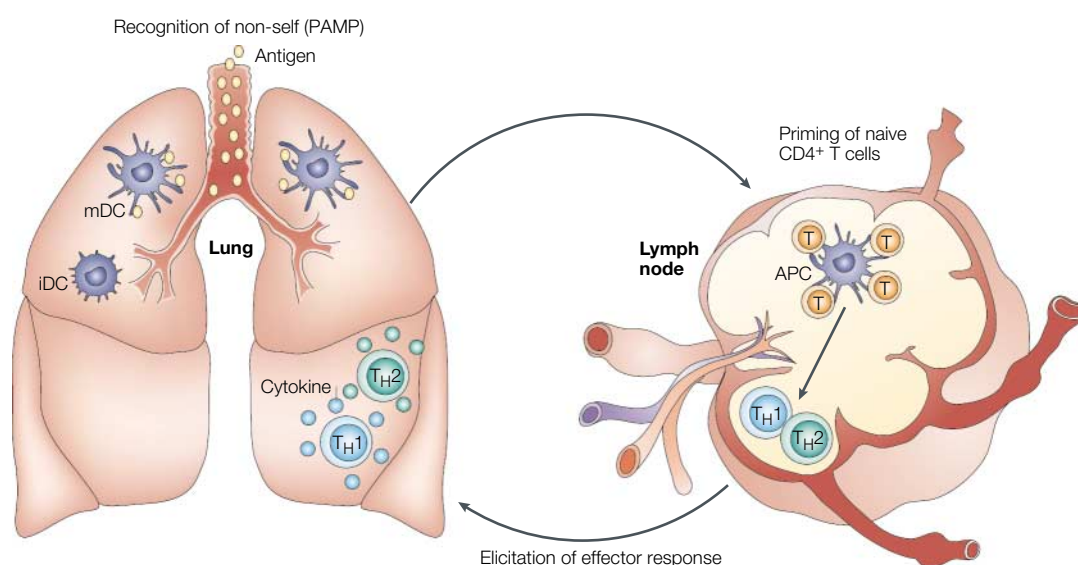


Figure 2 | Requirement for PAMP exposure to elicit an effector response to inhaled antigen. Immature respiratory dendritic cells (DCs) are activated and induced to migrate to draining lymph nodes after exposure to antigen (microbial or allergen) and pathogen-associated molecular patterns (PAMPs). CD4⁺ T-cell priming occurs in the lymph node followed by subsequent differentiation and egression of the T cells back to the lung. These effector cells can then mediate a T helper 1 (T_H1)-type (neutrophil-mediated) or T_H2-type (eosinophil-mediated) inflammatory response. APC, antigen-presenting cell; iDC, immature dendritic cell; mDC, mature dendritic cell.

To respond or not ... that is the question

For the reasons outlined previously, simple T_H1/T_H2 -cell counter-regulation does not seem to be a probable explanation for how increased exposure to infections in early life could protect from the development of allergic disease. Several groups have proposed alternative mechanisms to explain the hygiene hypothesis, which instead indicate a role for regulatory T cells^{48,49}. These cells have been described under several names and with varied phenotypes, but all share the ability to suppress unwanted adaptive immune responses, whether T_H1 - or T_H2 -type^{50,51}. Therefore, we refer to this family of cells as regulatory T cells. At least two main functions have been proposed for regulatory T cells. The first is part of a homeostatic mechanism that is designed to shut down immune responses to infectious agents. In other words, regulatory T cells are thought to be naturally generated as part of the host defence mechanism that limits the pathogen-directed immune response before it becomes overwhelming and causes inadvertent tissue damage. As discussed further later, the presence of particular PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPs) on the surface of microbial agents has been implicated in directing this process^{52,53}. The second function of regulatory T cells is the induction of a state of unresponsiveness to non-microbial and self-antigens, which seems to relate to the absence of signals from the innate immune system, such as those induced by PAMPs^{54–56}. These two different scenarios for development of regulatory T cells, with one requiring the presence of pathogen-associated innate-immune-system signals and the other the absence, have been difficult to resolve. Before we can address this issue, however, we must first consider how adaptive immune responses are generated normally and what role PAMPs have in this process.

The well established 'two-signal' model of immune activation states that in addition to antigen-specific recognition, a second co-stimulatory signal is also required to produce an adaptive immune response⁵⁷. This second signal can be provided by various co-stimulatory molecules, including B7-1 (CD80), B7-2 (CD86) or B7-H2 (ICOS ligand), that are expressed on the surface of antigen-presenting cells, such as dendritic cells (DCs). Of note, recognition of PAMPs by specific cell-surface receptors, for example TOLL-LIKE RECEPTORS (TLRs), can lead to DC maturation, expression of co-stimulatory molecules and migration to lymph nodes⁵⁸. These events are crucial for the generation of an adaptive immune response, allowing interactions between DCs and naive T cells that are necessary for T-cell differentiation into effector cells, whether T_H1 -type or T_H2 -type. Egression of these mature effector cells from the lymph nodes back to the site of initial antigen encounter then occurs. An example of this process with regard to inhaled antigen is shown in FIG. 2. So, innate immune-system signals, as generated by PAMP-containing microbial pathogens, are crucial for the generation of an adaptive immune response⁵⁹.

As mentioned before, the same high level of exposure to PAMPs that contributes to the generation of adaptive immune responses to microbial pathogens also

seems to initiate a pathway for the development of regulatory T cells^{52,53}. For example, Zuany-Amorim *et al.*⁶⁰ have shown that pre-treatment of mice with a killed-mycobacteria suspension results in the development of a CD4⁺ regulatory T-cell population that is capable of suppressing subsequent airway inflammatory responses. Similarly, McGuirk *et al.*⁵² have shown that regulatory T-cell clones can be generated from lungs of mice following acute infection with the microbial pathogen *Bordetella pertussis*. Furthermore, in this study, the pathogen-derived molecule filamentous haemagglutinin was shown to induce the production of IL-10 by DCs, which promotes the induction of naive T-cell differentiation along a regulatory T-cell pathway. So, it might be that high levels of PAMP exposure, which occur during natural encounters with microbial pathogens, leads to the development of DCs with a particular regulatory T-cell-inducing phenotype⁶¹.

The second scenario for the generation of regulatory T cells, however, does not seem to involve activated DCs. Instead, it has been proposed that DCs fail to mature after encounter with non-microbial (non-PAMP-containing) antigens, which results in a state of tolerance. Given that natural encounter with allergens, as occurs in the respiratory tract, should not involve PAMP-induced innate immune signals, it would be predicted that no response is made to these antigens. In fact, tolerance induced following inhalation of soluble protein antigen has been described in animal models^{55,62}. Specifically, exposure of mice to inhaled ovalbumin (OVA), in the absence of co-stimulatory signals induced by adjuvant or the innate immune system, leads to a state of unresponsiveness to further antigen challenge. This unresponsive state has been shown to involve regulatory T cells and IL-10, and to be dependent on interactions with inducible T-cell co-stimulator (ICOS)^{56,63}. These results are consistent with the two-signal model of immune activation, which provides a means of protection from unwanted responses to non-pathogenic foreign antigens. The two proposed pathways for the natural generation of regulatory T cells that have been described are outlined in FIG. 3.

Given these scenarios of regulatory T-cell development, could a decrease in the number of these cells be a probable explanation for the hygiene hypothesis? In other words, if natural exposure to non-PAMP-containing antigens normally leads to development of regulatory T cells and unresponsiveness, then why would a high level of exposure to microbial agents (PAMP containing) be required in early life for this purpose? Furthermore, if exposure to non-microbial antigens in the absence of innate immune signals leads to non-responsiveness then under what circumstances are T_H2 -effector-cell responses to inhaled environmental allergens generated? Surprisingly, in a similar manner to encounter with microbial pathogens, PAMP-induced innate immune signals seem to have a crucial role in the generation of T_H2 cells as well. Our laboratory, as well as others, has shown that Toll-like receptor 4 (TLR4) signalling has a crucial role in allergic inflammatory responses in the lung^{64,65}. Specifically, sensitization of mice by intranasal

PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPs). PAMPs are conserved molecular patterns found in microbial pathogens, but not mammalian cells, including terminally mannosylated compounds, bacterial lipopolysaccharides, hypomethylated DNA, flagellin and double-stranded RNA. They are recognized by pattern-recognition receptors, such as the mannose receptor and Toll-like receptors.

TOLL-LIKE RECEPTORS (TLRs). TLRs are receptors present on mammalian cells, mainly on cells that are involved in the innate or adaptive resistance to pathogens. They are homologous to the Toll-receptor gene family in *Drosophila*, members of which have important roles in both embryogenesis and defence against infection. TLRs have evolved to recognize pathogen-associated molecular patterns (PAMPs) that are conserved and shared by many microbial pathogens.

exposure to OVA results in T_H2 -effector-cell responses, which are capable of mediating allergic airway inflammation after subsequent challenge, only if TLR4 signalling is intact. Moreover, low-level intranasal exposure to lipopolysaccharide (LPS) during sensitization is capable of inducing these T_H2 -cell responses, whereas higher levels of LPS result in T_H1 -cell activation⁶⁴. A probable explanation for these results is that the low dose of LPS in this system was able to stimulate DC migration and activation, without inducing the production of IL-12, whereas higher doses of LPS resulted in DC migration and activation together with increased production of IL-12 (FIGS 3,4). So, the ability of certain protein antigens to be effective allergens, in that they lead to T_H2 -cell sensitization, might be related to their ability to stimulate the innate immune system. Whether this is due to

inherent enzymatic activity that mimics microbial signalling in some way, or possibly due to contamination with a PAMP, remains to be determined. Interestingly, varying levels of exposure to a ubiquitous environmental PAMP, LPS, have been linked to both exacerbation and inhibition of asthma^{66–68}.

Pathogen-associated innate immune signals have now been implicated in both the normal host response to a microbial pathogen, with the ultimate development of a regulatory T-cell response, as well as unwanted T_H2 -cell responses to commonly encountered allergens. Why, then, are regulatory T cells not the final outcome following allergen sensitization as well? (FIG. 3). Clearly, if this were so, then a high infectious burden early in life would be required to generate this down-modulatory arm of the immune system. Results from mouse models

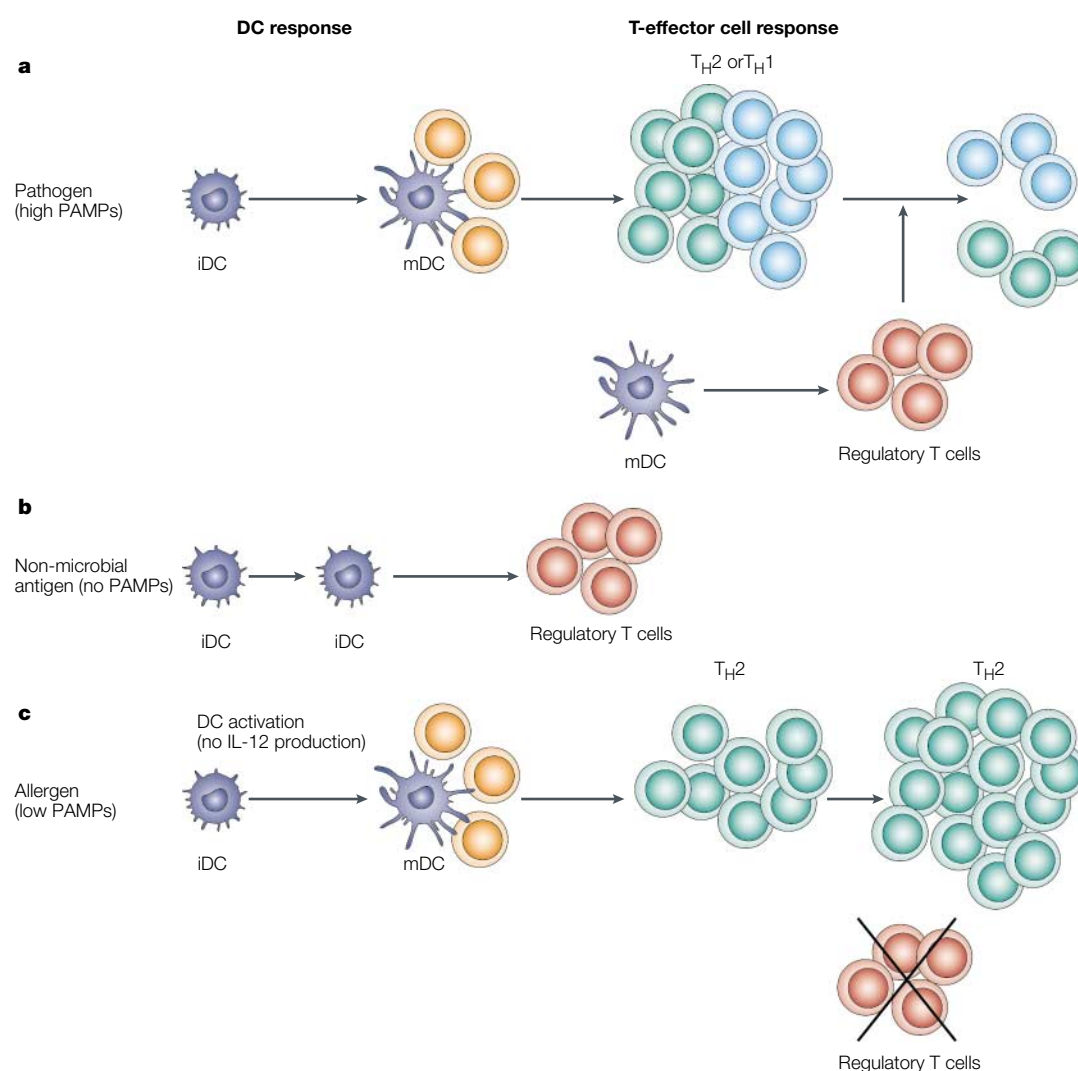


Figure 3 | Pathways for the natural generation of regulatory T-cell populations. Two models for the generation of regulatory T cells have been described. **a** | In one model, strong microbial signalling (high-level exposure to pathogen-associated molecular patterns, PAMPs) leads to both effector $CD4^+$ T-cell responses (T_H1 or T_H2) and induction of regulatory T cells. This is believed to be part of a natural homeostatic mechanism that regulates the level of immune responses. It has been proposed that a particular dendritic-cell (DC) phenotype might contribute to the generation of regulatory T cells in this situation. **b** | In the second model, exposure to antigen in the absence of PAMPs fails to generate effector T cells but leads to the induction of regulatory T cells. In this case, the lack of DC activation has been implicated in regulatory T-cell generation. **c** | By contrast, allergens seem to generate effector T_H2 cells without the induction of regulatory T cells. iDC, immature dendritic cell; IL-12, interleukin-12; mDC, mature dendritic cell; T_H , T helper.

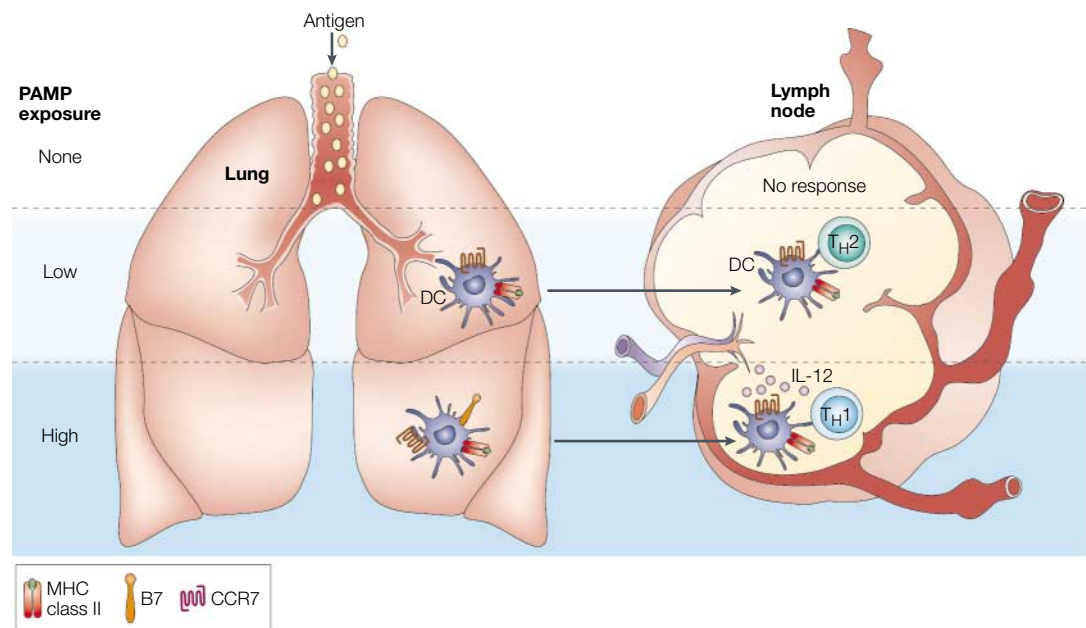


Figure 4 | **A schematic of the role of PAMPs in sensitization to allergens.** The response to inhaled antigen is only seen in the presence of a pathogen-associated molecular pattern (PAMP). However, the dose (level) of PAMP exposure determines the type (T_H1 versus T_H2) of T-cell response that is generated. CCR7, CC-chemokine receptor 7; DC, dendritic cell; IL-12, interleukin-12; T_H, T helper.

of effective T_H2-cell sensitization at sites of natural allergen exposure support this, with no evidence, so far, indicating that regulatory T cells are induced in situations where effective T_H2-cell priming has occurred in the absence of adjuvant. A possible explanation could lie in the apparent requirement for multiple rounds of stimulation to generate regulatory T cells^{52,69}. In other words, live pathogens, as a result of their ability to persist in a host for an extended period of time, might allow regulatory T-cell development over time, whereas exposure of the immune system to allergens might not be as prolonged. Alternatively, it might be that certain categories of pathogens are particularly good at stimulating the production of IL-10, which has been shown to be crucial for the generation of these regulatory T-cell populations^{70–73}.

Maintaining homeostasis

According to the model outlined, T_H2-cell activation results when exposure to an inhaled allergen occurs in the setting of signals from the innate immune system. However, this does not necessarily lead to the development of regulatory T cells. Instead, the host must rely on a certain level of encounters with natural pathogens to generate regulatory T cells that then promote a 'down-modulatory' immune environment and limit unwanted immune responses, such as T_H2-cell-mediated allergic responses. This scenario would provide a possible explanation for how increased exposure to infectious agents early in life could affect both the level of allergic sensitization, as well as the development of autoimmune disease. Although most studies showing the *in vivo* inhibitory capacity of regulatory T cells on immune responses have been in mouse models of autoimmune disease^{74–76}, suppression of a T_H2-cell response has also

been reported⁷⁷. Similarly, the unresponsive state that is induced by bee- or wasp-venom immunotherapy, which is associated with decreased levels of allergen-specific IgE and increased levels of IgG4, has been shown to involve secretion of IL-10 by a regulatory T-cell population^{78–80}. IL-10, one of the main cytokines that is implicated in regulatory T-cell function, has also been shown to suppress airway inflammation^{81,82}. Taken together, these data support the notion that regulatory T cells can limit, or even prevent, the development of T_H2-cell-mediated allergic inflammation. Furthermore, there are situations where regulatory T-cell populations do seem to arise naturally in the setting of T_H2-cell-mediated responses when high levels of antigen exposure occur. This can occur in individuals with heavy parasite burdens and in beekeepers who have received a high number of bee stings, both of whom are protected from allergic disease^{36,37,78,83}. However, until recently, there was still no direct evidence that regulatory T cells could suppress allergic inflammation in the lung.

The results from several studies in mice now show that regulatory T cells can indeed prevent allergic airway inflammatory responses. In a study using exposure to killed *Mycobacterium vaccae* before antigen sensitization to induce regulatory T cells, Zuany-Amorim *et al.*⁶⁰ were able to show suppression of airway inflammation after subsequent inhaled-antigen challenge. This included a decrease not only in the number of eosinophils, but also in all inflammatory cell types in the airway. Moreover, they showed that this effect was mediated by a CD4⁺CD45RB^{low} T-cell population and involved both IL-10 and transforming growth factor- β (TGF- β). Akbari *et al.*⁶³ have also shown that the transfer of a CD4⁺ regulatory T-cell population two days before inhaled-antigen challenge markedly reduces both lung

ANTERIOR-CHAMBER-ASSOCIATED IMMUNE DEVIATION (ACAID). Systemic antigen-specific tolerance that develops after inoculation of antigen into the immune-privileged site of the anterior chamber of the eye.

inflammatory responses and airway hyperresponsiveness. Furthermore, this inhibitory effect was blocked with an antibody specific for IL-10. These findings are consistent with another report from this laboratory⁸⁴ that indicated that CD4⁺ T cells genetically engineered to produce IL-10 could also reduce both lung inflammation and airway hyperreactivity. Finally, prevention of T_H2-cell-mediated lung inflammatory responses has also been reported following the induction of ANTERIOR CHAMBER-ASSOCIATED IMMUNE DEVIATION (ACAID). Previous studies in this area had focused mainly on the inability to generate T_H1-cell-mediated responses following the induction of ACAID. However, Katagiri *et al.*⁸⁵ have clearly shown that T_H2-cell-mediated lung inflammatory responses are also impaired following the induction of ACAID. Although not formally shown in this study, previous reports have identified an important role for IL-10 in ACAID^{86,87}. So, several groups have now reported that regulatory T cells can indeed prevent allergic airway inflammation, with a crucial role for IL-10.

Taken together, these regulatory T-cell populations most closely resemble what have been described in the literature as 'T regulatory type 1' cells, although the expression of CD25 in most of these cases was not examined.

Concluding remarks

The data described here support the notion that a relative decline in regulatory T-cell induction, owing to a decreased exposure to infectious agents, could be responsible for the recent rise in atopic disease. The concomitant increase of certain T_H1-cell-associated autoimmune diseases would also be explained by the lack of these same regulatory T-cell populations. In other words, this provides an immunological mechanism to explain the hygiene hypothesis. Beyond this, however, could benefit be derived from these findings with regard to therapeutic approaches to atopic disease? Can regulatory T cells be induced in a targeted fashion to shut down unwanted allergic responses? The answers to these questions are yet to be resolved.

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