

T regulatory cells in childhood asthma

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Asthma is a chronic disease of the airways, most commonly driven by immuno-inflammatory responses to ubiquitous airborne antigens. Epidemiological studies have shown that disease is initiated early in life when the immune and respiratory systems are functionally immature and less able to maintain homeostasis in the face of continuous antigen challenge. Here, we examine the cellular and molecular mechanisms that underlie initial aeroallergen sensitization and the ensuing regulation of secondary responses to inhaled allergens in the airway mucosa. In particular, we focus on how T-regulatory (Treg) cells influence early asthma initiation and the potential of Treg cells as therapeutic targets for drug development in asthma.

Programming respiratory function in early life

Asthma is an inflammatory disease of the conducting airways that results in compromised lung function that manifests as hyper-responsiveness to inhaled environmental stimuli; the range of which expands with disease progression. There are several forms of asthma, with the most frequently encountered being atopic asthma, in which disease exacerbations are associated with cycles of inflammation involving the combined effects of activated mast cells, eosinophils and cytokine-secreting, aeroallergen-specific T helper (Th)2 memory cells [1–3]. The prevalence of atopic asthma is highest amongst school children, and in a large proportion of affected subjects, the disease persists into adulthood [4,5].

The approach that has proven most successful in elucidating the mechanisms underlying initial development of the asthma phenotype has involved tracking of birth cohorts throughout childhood, documenting the onset of early disease manifestations and identifying associated risk factors [6]. A key finding from these studies has been that respiratory function ‘tracks’ stably over time throughout childhood unless lung maturation is perturbed, for example, by exposure to environmental insults, particularly inflammatory stimuli [4]. Such temporary interruptions in the orderly growth and differentiation of lung tissues can result in permanently compromised respiratory functions, that is, the functional phenotype of the adult respiratory system can be ‘programmed’ via events occurring in early childhood [4]. A relevant analogy is immunological memory, which can also be programmed semi-permanently as a result of exposure to environmental signals during this same life period.

An important concept that has arisen from the recent epidemiological studies is that episodic airway inflamma-

tion is extremely common during early life, but it is the severe events that are most strongly associated with the drive towards asthma pathogenesis. Here, we review the control mechanisms that potentially regulate the intensity of inflammatory events in the airways, as opposed simply to the mechanisms responsible for their initial triggering. In particular, we focus on how T regulatory (Treg) cells influence early asthma initiation, as well as the potential of Treg cells as therapeutic targets for drug development in asthma.

Asthma inception during childhood: epidemiological evidence

As a consequence of the high susceptibility of rapidly growing lung and airway tissues to inflammatory damage, early postnatal programming of T cell sensitization to perennial aeroallergens represents a major risk factor for the subsequent development of asthma [4,5]. Early sensitization is most frequent among children from atopic families, indicating the importance of underlying genetic factors, although these remain incompletely understood. Part of this genetically-determined sensitization risk is attributable to delayed postnatal maturation of Th cell function [7], and follow-up studies have extended these findings to include developmental defects within the innate immune system [3,8] and Treg cells (discussed in detail later). It is noteworthy that these maturational defects in innate and adaptive immune competence additionally predispose to early life respiratory infections [9–11]; the significance of which is also discussed below.

Prospective monitoring of aeroallergen-specific antibody responses in children during the preschool years, over which initial encounters with environmental allergens occur, indicates that active immunological recognition of aeroallergens by the infant immune system is the norm. This initiates transiently cycling low-level IgE antibody production over the ensuing 2–3 years, which either stabilizes at around the assay minimum detection limits (in non-atopics), or increases progressively until amounts exceed the threshold for expression of symptoms [12]. This pattern of transient Th2-associated immunity during early exposure of infants mimics what is observed in experimental animals undergoing immunological tolerance induction in response to repeated exposure to aerosolized allergen [2]. The cycling phenomenon probably reflects ongoing cross-regulation between Treg and Th2 cells driving IgE class-switching. We hypothesize that replacement of this cycling pattern with one of progressively increasing IgE titres reflects the failure of underlying tolerance mechanisms, and the epidemiological evidence indicates that this

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failure is associated with a markedly increased risk of asthma development.

Despite the undoubted importance of atopy as a risk factor for childhood asthma, it does not appear to act alone. The most compelling evidence in this regard again comes from birth cohort studies, which in this case involves prospective assessment of both atopy and respiratory tract infections [12–15]; the most important being rhinovirus [13] and respiratory syncytial virus (RSV) [15]. Viral infection is the most common cause of severe bronchiolitis in the first few years of life, and is responsible for the bulk of hospital admissions in this age group, underscoring the severity of the associated inflammation. The mechanisms underlying virus-induced immunopathology in these children are probably multifactorial, but recent evidence indicates an important role for CD8⁺ effector T cells [16], and it is noteworthy that Treg cells have been implicated in attenuation of these responses [17].

Although these factors can function independently to drive pathogenesis [14], the highest risk for asthma development is observed when they operate together [12–14]. This suggests that interactions between inflammatory pathways triggered in atopic children during viral infection are key drivers of early asthma development, and the nature of these interactions is explored in the ensuing sections.

Tolerance versus sensitization to aeroallergens: insight from animal models

Control of immune responses in naïve animals

The normal response to inhaled aeroallergens is mucosal tolerance; a process originally characterised in animal model studies from our laboratory [2], which now represents one of the established paradigms in the lung immunology area. In these studies, the selective attenuation of Th2-skewed immunity, particularly production of IgE, could be attained by repeated antigen exposure via the respiratory route, which is associated with induction of a phenotypically heterogeneous population of T cells with suppressor activity. Recently, this suppressor activity has been more specifically associated with Treg cells, and their essential requirement in the maintenance of peripheral tolerance is now unquestioned. Significantly, different animal strains display marked disparity in relation to efficiency of mucosal tolerance induction; the process being markedly less efficient in high-IgE-responder strains that require log-fold higher levels of aeroallergen exposure to induce stable tolerance. To date, there is no satisfactory explanation for these profound genetically determined differences in tolerance efficiency.

These latter observations provided the initial impetus for the search for antigen-presenting cell populations within the respiratory tract. One of the key findings in this regard has been the identification of extensive networks of airway mucosal dendritic cells (AMDCs) and elucidation of their role in local immune surveillance in the airways [2]. In the steady state, AMDCs exhibit a sentinel phenotype [18–20] that is specialised for antigen uptake via extension of dendrites through airway epithelial tight junctions [21] and subsequent transport to draining lymph nodes (DLNs) [21,22]. The immunological consequence of initial uptake of

inhaled antigen by AMDCs and CC chemokine receptor (CCR)7-dependent migration [23] to DLNs is normally the preferential induction of transient Th2-biased immunity, which is terminated via the onset of tolerance [24,25]. This initial Th2 ‘default’ response mimics that observed in non-atopic children undergoing natural tolerisation during normal environmental aeroallergen exposure [12].

The central role of DCs in the T-cell priming process underlying sensitisation is well accepted [2,19]. In particular, the adoptive transfer of *in vitro* allergen-pulsed, bone-marrow-derived myeloid DCs (mDCs) [26,27] and endogenous lung-derived DCs from allergen-exposed animals [27–29] have been shown to induce Th2 responses. Conversely, adoptive transfer of lung-derived DCs [30,31], or *in vitro*-pulsed bone marrow derived DCs [28,32] can also induce tolerance. Moreover, several different DC subtypes might contribute to tolerance induction, including CD8α⁺ DCs [33], interleukin (IL)-10-producing DCs (subtypes not specified) [30,31,33], and immature DCs that phenotypically resemble steady-state AMDCs [34–36]. Notably, tolerogenic pDCs have been implicated in tolerance induction in several studies [28,37]. Monoclonal antibody-mediated *in vivo* depletion of pDCs has been shown to promote sensitisation [28], and adoptive transfer of allergen-loaded bone marrow-derived (Flt3 expanded) DCs confers tolerance via a pathway involving programmed cell death ligand 1 [28,38]. In a further study in Flt3-deficient mice however, tolerance induction following *in vivo* inhalation exposure progressed normally, indicating that Flt3L-dependent DCs are not essential for the process [39].

A number of subtypes of Treg cells with various modes of action have been implicated in respiratory tolerance induction, and this has been recently reviewed elsewhere (for example, [40,41]). The most frequently implicated are IL-10-producing Treg (IL-10Treg) cells, which can be induced following antigen exposure via an IL-10-dependent [30–32] and (in some models) an inducible costimulator-ligand-dependent process [31,42]. Additionally, immature DCs, as exemplified by steady-state AMDCs, can also induce IL-10Treg cells [34–36]. Other Treg cell types that have been suggested to play a role include a subset whose activity is surface transforming growth factor (TGF)β-dependent [43], and those producing interferon (IFN)γ plus IL-10 [33].

Regulation of memory responses

Exacerbation of allergic asthma in sensitised/allergen-exposed subjects is associated with the reactivation of Th2 memory in the airway mucosa, and this process is AMDC-dependent [18,44]. How does this occur, given the immature phenotype of AMDCs in the steady-state? Cognate interactions between aeroallergen-specific CD4⁺ Th2 memory cells and allergen-bearing AMDCs post-aerosol challenge triggers upregulation of CD86 expression and T cell clustering properties of AMDCs. This coincides with acquisition of potent antigen-presenting cell activity that is mediated locally for a few hours before migration to DLNs [18]. The end result is local triggering of other allergen-specific Th2 memory cells encountered by the activated AMDCs during their subsequent egress from the mucosa into DLNs (Figure 1).

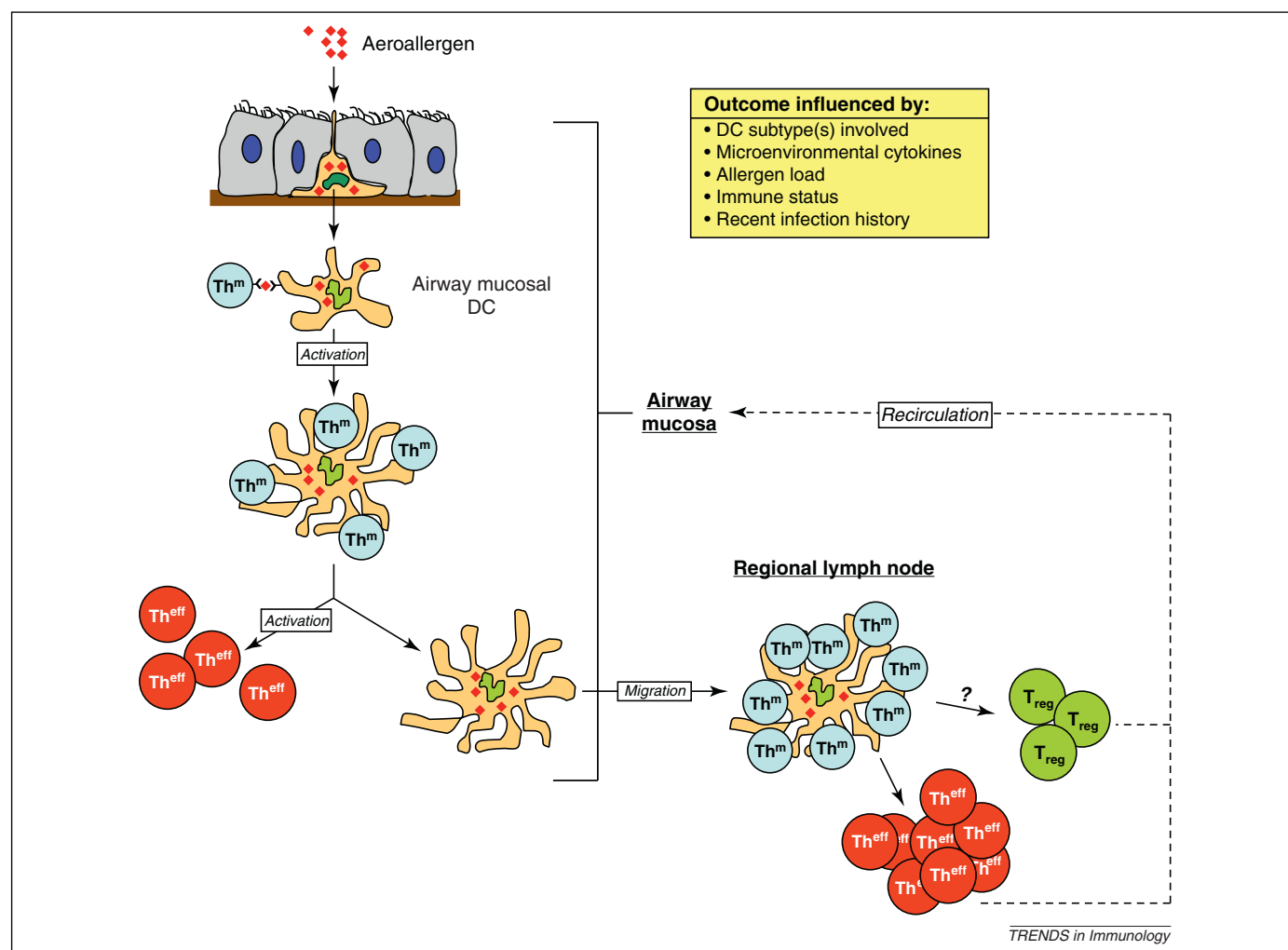


Figure 1. Reactivation of aeroallergen-specific Th memory responses in the airway mucosa. Resting AMDC sample aeroallergen from the luminal surface of the airways during their brief sojourn (24–36 h) within the epithelium. If, during subsequent migration through the underlying mucosa towards lymphatic ducts, they encounter aeroallergen-specific Th memory cells, initial weak cognate interactions occur, resulting in rapid upregulation of T cell clustering and co-stimulatory properties and accelerated mobilisation of peptide-loaded MHC II to the AMDC surface; subsequent encounters between these emigrating AMDC and incoming Th memory cells result in efficient local Th cell activation. Later encounters with Th memory cells after the arrival of the AMDCs in DLNs results in generation of additional T effector cells, which can potentially migrate back to the airway mucosa. During this time-frame Treg cells also accumulate, first in DLNs and then in the airway mucosa; the source of these Treg cells remains to be established, but based on human adoptive transfer data (see [110]), it is likely that significant numbers arise from the aeroallergen-specific Th memory clones themselves Th^{eff}. Th effector cell: Th^m. Th memory cell.

Resolution of allergic airways inflammation and re-establishment of homeostasis in the inflamed airway mucosa following aeroallergen challenge of sensitized rodents is a tightly controlled process that involves interplay between allergen-specific Th memory cells, AMDCs and inducible Treg cells [20,45]. In particular, it is clear that Treg cells are capable of damping the expression of airway hyper-responsiveness (AHR), which is one of the hallmark sequelae of uncontrolled inflammation in the airways. Recent studies that have established these principles include the demonstration that depletion of CD4⁺CD25⁺ Treg cells enhances allergic airway disease [46], whereas administering these cells (or their precursors) systemically [20,33,46] and/or intratracheally [47] is protective. An important target for Treg cells in this context is Th-mediated upregulation of expression of the co-stimulator CD86 on initially quiescent resident AMDCs [20,48]. Importantly, instituting control of allergic inflammation via CD4⁺CD25⁺ Treg cells has also been shown to reverse established inflammation, and has been

linked to prevention of airway wall remodelling and decreased mucus hypersecretion [49], which are key markers of the asthma phenotype.

Many experimental studies have focused principally on short-term aeroallergen exposure, but it is also important to understand how Treg cells are maintained and contribute to control of allergic asthma during chronic exposure. Treg cells are generated in mucosal DLNs in response to repeated antigen challenge and accumulate progressively thereafter in the airway mucosa [20,50]. The maintenance of airway mucosal Treg cell activity in this context is linked to continuing antigen exposure, because antigen withdrawal results in rapid return to baseline Treg numbers in the mucosa [20]. This pattern is mirrored in other systems; a notable example being the human studies showing that repeated allergen exposure via the skin in beekeepers is associated with expansion of Treg cell populations that returns to normal after the pollen season [51]. Additional human studies that have emphasised this point are discussed in [Box 1](#).

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Box 1. Treg cells in human asthma

In human asthma, AHR induced during asthma exacerbations can persist for up to several weeks and the length of this period largely determines the severity of short- and long-term clinical sequelae. To date, studies on the role of Treg cells in human allergic asthma have yielded conflicting results, and although it is likely that Treg cells do contribute to suppression of clinically relevant airway disease, the precise details of the underlying mechanisms, and in particular, the basis for the apparent uncoupling of Treg cells from Th2 effector responses in asthmatics, remain unclear. In the peripheral blood of patients with asthma, the numbers of CD4⁺CD25⁺ Treg cells have been reported variously to be equivalent, higher or reduced, relative to non-atopic controls [2,40]. Many of the earlier human studies are difficult to interpret because phenotyping was restricted to assessment of CD4 and CD25, however, studies that in addition have examined Foxp3 expression suggest that the decrease in asthma patients might be real [101,102]. Studies on Treg cells in atopic patients have also yielded conflicting data in relation to their functional capacity. Some studies have reported decreased suppressive capacity of CD4⁺CD25⁺ T cells from patients with active allergic airway disease [101,102], whereas others have reported no differences between asthmatics and controls. These human studies have focused almost exclusively on peripheral blood mononuclear cells, which is not ideal given the accumulating evidence that microenvironmental factors exert dominant influences over local cellular functions. A notable exception is a recent study demonstrating a reduction in numbers of Treg cells in the bronchoalveolar lavage of asthmatic children [101].

Acute severe asthma-induced exacerbation

As already noted, the highest risk for initial asthma development in childhood is associated with respiratory viral infections that occur against a background of sensitisation to aeroallergens. The occurrence of the most severe grades of acute exacerbations in older subjects with established asthma disease, particularly episodes that require hospitalisation, are also associated with this combination of risk factors [6]. In particular, affected children are invariably virally infected and atopic (reviewed in [6]), and the basis for this comorbidity has hitherto been unclear. However, recent studies might explain these findings. Animal studies have demonstrated that during airway mucosal viral infection, the turnover of local (predominantly myeloid) DCs is accelerated, leading to a major draw on bone marrow precursor populations [52,53], and locally produced type 1 IFN from infected epithelial cells and/or recruited pDCs mediates rapid upregulation of FcεR1 on resident AMDCs [54].

FcεR1 expression markedly enhances the T cell stimulatory capacity of DCs by upregulating their allergen uptake/processing functions [55,56], and comparable upregulation of FcεR1 on AMDCs from virus-infected atopic patients would be expected to amplify Th2 memory cell reactivation in the airway mucosa, relative to that occurring in response to aeroallergen exposure alone. In this regard, it has been demonstrated in a recent study of asthmatic children hospitalised with virus-induced acute severe exacerbations, that virtually all subjects were strongly sensitised to perennial indoor aeroallergens that are present continuously in the environment [57] (see also [6]). During the peak of the exacerbation, a Th2-associated gene expression signature was prominent in myeloid cell populations migrating from the bone marrow, including expression of genes encoding elements of FcεR1, and

enhanced receptor expression was confirmed by flow cytometry and reproduced by *in vitro* exposure of blood mononuclear cells to Th2 cytokines [57]. The underlying mechanism is likely to involve migration to the bone marrow of Th2 cells activated in the airways, as demonstrated earlier in relation to IL-5-mediated upregulation of eosinophil precursors in aeroallergen-challenged atopic asthmatics [58]. As shown in Figure 2, this provides a source of FcεR1-prearmed replacements for the rapidly turning over mDCs and pDCs in inflamed airway tissues, potentially sustaining and amplifying an already highly pathogenic response. An additional consequence of this might be the blunting of local Th1-associated antiviral defence mechanisms via immune deviation, as has been observed with other pathogens [59,60], and in this case, also including attenuation of type 1 IFN production by pDCs via FcεR1 activation [61].

The rate-limiting step in this potentially self-perpetuating cycle of inflammation is the continuous recruitment/activation of aeroallergen-specific Th2 memory cells, and the available data suggest that the normal mechanism for control of this process is via Treg cell activity [20,37,40,41]. Treg cells thus are likely to play a central role in the reinstitution of local homeostasis following severe asthma

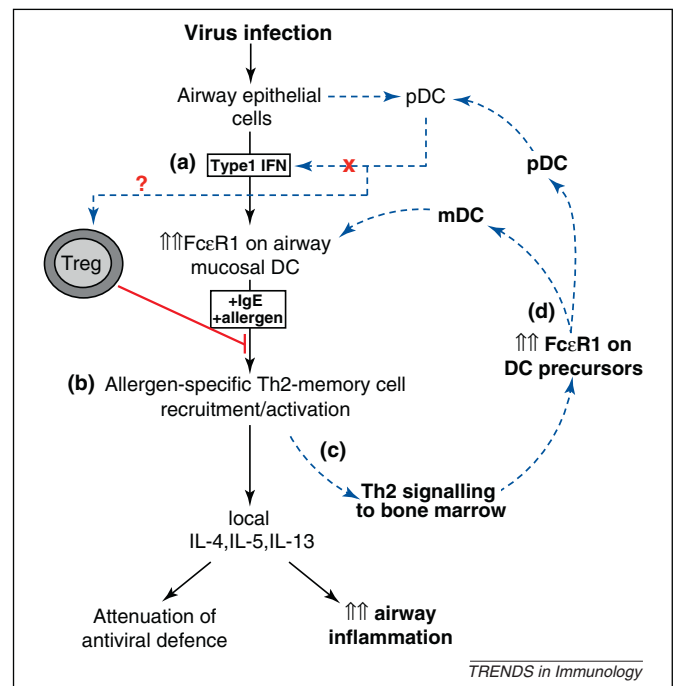


Figure 2. Interactions between virus- and atopy-associated inflammatory pathways. Respiratory viral infection in aeroallergen-sensitised atopic patients has the potential to trigger an inflammatory cascade that progresses through the following stages (as detailed in [57]): (a) initial direct upregulation of FcεR1 expression on resident AMDCs via type 1 IFN derived from infected epithelial cells and/or recruited pDCs; (b) FcεR1-driven enhancement of local aeroallergen-specific Th2 memory cell activation, leading to an initial surge in local Th2 cytokine secretion; (c) transmission of IL-4 and IL-13 (and type 1 IFN) signals to myeloid precursor populations in bone marrow; (d) programming and release of CCR2⁺ lung-homing mDCs, pDCs and monocytes pre-armed with FcεR1, further amplifying/sustaining this inflammatory cycle. One additional consequence of the latter might be FcεR1-mediated downregulation of the type 1 IFN-production capacity of pDCs (highlighted via 'X' in the Figure) (detailed in [61]). pDCs have also been implicated in generation of Treg cells, which counter-regulate aeroallergen-specific Th2 cells [28], but it is not known whether this function (note '?' in the Figure) can be modulated via FcεR1 triggering.

attacks, and we propose that they are positioned centrally in this cascade (Figure 2).

Variations in Treg cell activity in early life and risk for allergic diseases

Treg cell activity is determined by both genetic (Box 2) and environmental factors. In relation to environmental factors, the potential role of Treg cells in protection against asthma initiation is most frequently discussed in the context of the 'hygiene hypothesis', which broadly proposes that early life exposures to microbial stimuli are protective against the tendency to develop allergic disease. This general concept is supported by a range of epidemiological studies; in particular, a series that has linked exposure to farm environments, day care and elder siblings to an ensuing lower incidence of allergy [62,63]. Moreover, these exposures appear protective against a broad range of inflammatory diseases beyond Th2-mediated allergy, arguing against microbe-induced immune deviation as the primary mechanism, but consistent with an underlying contribution from Treg cells [62,63]. It is also noteworthy that sensitisation can be prevented by prenatal exposure to environmental factors, particularly the farm environment, by influencing immune development, in particular Toll-like receptor-associated functions within the immature innate immune system [64,65]. Increased numbers and function of Treg cells in cord blood have also been associated with this maternal environmental exposure [66]. The notion that maternal microbial experience might set sensitivity thresholds in the offspring via programming of Treg-associated functions during foetal life is an exciting concept that is now being pursued vigorously [67], because it has implications with respect to susceptibility to a broad range of immuno-inflammatory diseases.

Box 2. Genetic variation in Treg cell activity

Some of the most persuasive evidence for the importance of Treg cells in prevention of allergic disease, including asthma, is related to gene mutation studies. The *FOXP3* gene was first identified through studies of the human X-linked inherited disease designated IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome – an early onset lymphoproliferative disease that affects several organ systems. Loss-of-function mutations in *FOXP3* result in IPEX syndrome and many patients suffer from severe atopic diseases [103]. In experimental animals, scurfy mice (mouse homolog of IPEX) show allergic dysregulation [104], and several animal models have also demonstrated a fundamental role for Treg cells in maintaining tolerance and in the re-establishment of homeostasis following disease exacerbation [40,41]. With specific regard to lung immunoregulation, an important role for Foxp3-expressing T cells can be inferred from the reports on reactive airway disease in children with *FOXP3* deficiency [105].

Additional genetic variation in Treg cell activity independent of the IPEX mutation has been identified as being associated with disease risk in children; a notable example being a reduction in the number of Treg cells in cord blood of infants with a hereditary risk of allergy [106]. In particular, it is recognised that transmission of susceptibility to allergy is strongest via the maternal route, and recent studies have suggested that this is associated with impairment of Treg cell activity in the cord blood of the offspring of atopic mothers [107,108]. An illustration of the significance of these findings is the demonstration of a strong association between endogenous Treg cell activity and spontaneous resolution of milk allergy during early childhood [109].

These important epidemiological findings are also supported by studies in experimental animals. In mice, maternal exposure to endotoxin prevents sensitisation and airway inflammation in offspring [68]. Furthermore, depending on the immune status of the mother, the ability to transfer tolerance can be crucial in determining immune responses of the offspring to allergen [69]. Immune development can also potentially be affected by diet [70,71], including via mechanisms involving Treg cells [71]. In this context, vitamin D has an increasingly recognised role in modulating immune programming, and a number of ongoing studies are examining the effects of vitamin D supplementation during pregnancy in relation to modulation of disease risk in infants. Several different tissues are known to express the enzyme responsible for activation of vitamin D, including airway epithelial cells [72], and the local production of vitamin D at specific tissue sites might have important immunomodulatory effects. In particular, vitamin D has been implicated in development/maintenance of forkhead box p3 (Foxp3)⁺ and IL10Treg cells in humans and rodents [73,74].

An additional avenue through which Treg activity might influence early asthma initiation involves responses to respiratory infection. As noted already, inflammatory pathways triggered by host antiviral responses interact synergistically in several ways with atopic inflammatory pathways to drive asthma pathogenesis. In this context, it is known that Treg cells are induced in large numbers during host antimicrobial responses, and might play an important role in limiting tissue damage that results from excessively intense/prolonged immune responses during pathogen clearance [75–77], including in infections due to RSV [76], which are prevalent during infancy. However, their activity at infection sites in the airways might represent a double-edged sword because the theoretical danger exists that excessive local Treg cell activity might prolong infection [75,78], and in the context of this discussion, increase danger for asthma development and/or exacerbation. It is interesting to note in this regard findings that suggest that capacity to mount effective sterilising responses against pathogens might be determined in part by the activity of the proinflammatory cytokine IL-6 in overcoming Treg-mediated immunosuppression at infection sites [79].

Natural Treg cells as therapeutic targets

Recent clinical studies have suggested that probiotic treatment via the gastrointestinal tract has the potential to attenuate local and additionally systemic immuno-inflammatory events. Concepts that draw on the principles of the 'common mucosal immune system', notably that lymphoid cells programmed in the gut subsequently home to other mucosal sites where they modulate local disease [80], underpin this emerging area of therapeutics. Exploitation of this concept is only beginning and there is a growing list of publications to suggest significant probiotic effects on human gastrointestinal and systemic diseases including allergy [81], infection [82] and asthma [83,84]. Support for these concepts is also provided by animal model studies that have demonstrated probiotic-induced increases in splenic Treg cell numbers and ensuing resistance to

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AHR [85]. Moreover, bacterial agents have been shown to induce Treg cells *in vitro* [86] and, in particular, can confer protection against allergic airway inflammation [87].

Recent studies have tested a different class of orally delivered microbial stimuli; notably a multi-component extract derived from the respiratory tract. This preparation (OM-85BV) has been in clinical use for many years and has demonstrated significant efficacy in adult chronic obstructive pulmonary disease [88,89] and in children susceptible to repeated respiratory infections and/or wheeze [90–92]. Additionally, it has recently been shown in experimental asthma models that treatment with this agent boosts systemic natural CD4⁺CD25⁺Foxp3⁺ Treg cell activity, including in airway mucosal tissues, and the treated animals display markedly attenuated AMDC responses and associated airway inflammation and AHR following aeroallergen challenge [45,93].

The underlying mechanisms are incompletely understood, but appear to involve local activation of Treg cells in the intestinal mucosa and their direct mobilisation into the peripheral circulation [45]. The precise mechanisms underlying this systemic response to OM-85BV remain unknown. However, a probable target appears to be gut mucosal CD103⁺ DCs that have been shown to mediate the local functional maturation of Treg cells via TGFβ and retinoic acid [94,95]. This conversion process might be influenced by gastrointestinal-specific environmental factors; in particular, those related to microbial stimuli. It is pertinent to note that other orally delivered, bacterium-derived preparations have demonstrated similar effects in amelioration of airway symptoms associated with respiratory infections in controlled trials [96,97]. These studies, as well as those above involving live probiotic organisms, collectively point to the potential of the gut as a treatment route for enhancement of Treg-cell-mediated protection against systemic inflammation. This area of research merits more detailed attention in the future, particularly in relation to respiratory inflammatory diseases.

Inducible Treg cells in specific immunotherapy

A variety of treatment regimens that offer beneficial outcomes in relation to symptom expression in allergic asthma have been associated with upregulation of Treg cells. In addition to the already described microbial agents, these also include glucocorticoid treatment, which is associated with enhanced *IL10* and *Foxp3* gene expression and/or Treg cell activity [98], and vitamin D, which as noted, has been linked to induction of Treg cell populations [40,74]. However, these treatments cannot reverse established atopic asthma. To date, specific immunotherapy (SIT) is the only known therapeutic approach that potentially offers a cure. A range of studies on the use of SIT in this context, most notably those on prevention of asthma development in children with rhinitis [99], have shown significant clinical effects, and the underlying mechanisms are generally believed to involve enhancement of inducible Treg cell activity [100]. Additionally, successful peptide immunotherapy in adults with established atopic asthma is also associated with induction of Treg cell pathways and IL-10 [100].

Concluding remarks

Tregs are now firmly established as important endogenous regulators of inflammatory processes in the respiratory tract, and in particular, as key players in the aetiology and pathogenesis of atopic asthma. They play a central role in the development of protective tolerance against inhaled non-pathogenic antigens exemplified by allergens, and in controlling the intensity and duration of proinflammatory T memory cell responses against these antigens in sensitised subjects. They also play equally important roles in modulating inflammatory responses to intrinsically pathogenic microbial antigens that function as important cofactors in driving asthma pathogenesis. The challenge remains to identify effective ways to exploit the therapeutic potential of Treg cells in relation to prevention and treatment of this increasingly prevalent disease.

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