

Novel immunotherapeutic approaches for allergy and asthma

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Abstract

The immune response is a tightly regulated process, which normally results in protection from infection and tolerance of innocuous environmental antigens. However, in allergic disease, the activated immune response results in a chronic pro-inflammatory state characterized by antibody secretion (IgE) and T cell activation to normally well-tolerated antigens. Currently, the treatment of allergic disease is focused on the suppression of key inflammatory mediators or inflammatory cell populations and include anti-histamines, anti-leukotrienes, β_2 adrenergic receptor agonists and corticosteroids. However, these approaches only provide a temporary suppression of disease symptoms. Successful long-term treatment can only be provided by allergen-specific immunotherapy (allergen-SIT), which restores normal immunity against allergens. This review will discuss novel approaches to the management of allergy and asthma by targeting the T regulatory cell via modulation of the commensal microbiota and allergen-SIT.

Keywords: *Allergy, Asthma, T regulatory cells*

Abbreviations: SIT, Specific Immunotherapy; T_{reg} , T regulatory; T_H , T helper; PAMPs, Pathogen-associated molecular patterns; PRR, Pattern recognition receptor; TLR, Toll-like receptor; CLR, C-type lectin receptor; IL, Interleukin; mAbs, Monoclonal antibodies; AD, Atopic dermatitis; SEB, Secreted enterotoxin B; SLIT, Sublingual immunotherapy

Introduction

Atopic allergic sensitization is characterized by production of IgE against environmental antigens such as house dust mites, grass pollen, and animal proteins and can lead to a range of allergic disorders including asthma, rhinitis, and atopic dermatitis (AD) [1]. These disorders affect 15–25% of the Western populations, and their prevalence has doubled in the last 10–15 years. While many hypotheses have been proposed to explain this phenomenon, it is clear that there is a strong environmental influence on the incidence of these disorders. Originally, the hygiene hypothesis proposed that allergic diseases were prevented by early infectious exposure introduced by contact with older siblings [2].

The mechanism was thought to include the potential effect of pathogenic microbes on polarizing the type 2 T helper (T_H2) cell-biased cytokine response of the human neonates toward a type 1 T helper (T_H1) cell response. More recently, the hygiene

hypothesis has expanded beyond the involvement of pathogenic microbes to include the commensal microbiota, which are essential participants in normal immunological development and function. Understanding of the mechanisms has also evolved in the context of altered T regulatory (T_{reg}) cell activity, which is now considered to be a critical feature of the immune deregulation associated with allergy [3,4]. In addition, lifestyle factors such as diet and physical activity are thought to be important, and it is likely that multiple environmental factors with currently unappreciated interactions contribute to the atopic state [5].

When immune tolerance is not established in response to a new antigen, the sequential processes of immune cell sensitization, migration to tissues, survival, and reactivation followed by the execution of immune-cell effector functions lead to the establishment of chronic inflammation. In the sensitization phase, inappropriate presentation of allergens by antigen-presenting cells (e.g. dendritic cells)

stimulates the clonal expansion of specific T and B cells and the production of specific antibodies [6,7].

Polarizing signals drive the differentiation of naive responding T cells into T_H1 , T_H2 , T_H9 , T_H17 , or T_H22 cells [8–16]. The selection of an appropriate cytokine secretion pattern by the immune system is dependent on a number of factors but is significantly influenced by the binding of microbial ligands, termed pathogen-associated molecular patterns (PAMPs), to pattern recognition receptors (PRRs) such as toll-like receptors (TLR) and C-type lectin receptors (CLR). The differential binding of specific PRRs activates a number of intracellular signaling pathways that ultimately result in cytokine secretion and/or cellular maturation (Figure 1).

Certain intracellular pathways have been well described (e.g. the TLR-4 pathway), while others are still being explored. However, *in vivo*, multiple dendritic cell PRRs are simultaneously activated and the co-operation or competition between the resultant signaling cascades is not well understood. The specificity of these responses is achieved through the activation of a particular mosaic of PRRs, which is determined by the available PAMPs and the innate immune cells involved. Dendritic cells express a wide variety of PRRs, and aberrant stimulation of these receptors on dendritic cells during initial allergen presentation may be critical for the skewed T_H2 response in allergic individuals. Priming of allergen-specific $CD4^+$ T_H2 cells results in the production of T_H2 cytokines (such as interleukin (IL)-4 and IL-13) that are responsible for class switching of antibody

isotypes to the ϵ heavy chain for IgE antibody production by B cells.

Antibody production occurs at many sites including lymphoid tissue, bone marrow, and inflamed mucosal sites, such as lung or nose [17–19]. In the final phase of chronic inflammation, antibody production by B cells in the inflamed tissue is induced; mast cells, eosinophils, neutrophils, and macrophages are activated and exert their effector functions; secretory glands are activated and tissue remodeling, loss of cell function, and apoptosis ensues. Tissue eosinophilia is maintained by features of chronic allergic inflammation such as production of T_H2 -like cytokines, for example, IL-25 and IL-33 secreted from tissue cells, in addition to IL-5 [6,20–23]. As all of these pathological events require activation of effector T cell subsets, peripheral T cell tolerance is considered to be vital for a healthy immune response and represents a mechanism to overcome chronic inflammation mediated by these T cell subsets.

Targeting T_{reg} cells

The fundamental role of T_{reg} cells in maintaining immune tolerance has been demonstrated in a wide range of animal models, in which the adoptive transfer or deliberate expansion of T_{reg} cells was shown to prevent or cure several T cell-mediated diseases, including allergy, asthmatic lung inflammation, autoimmune diseases, and allograft rejection, by restoring immune tolerance to allergens, self-antigens, or alloantigens [24]. Multiple molecular mechanisms

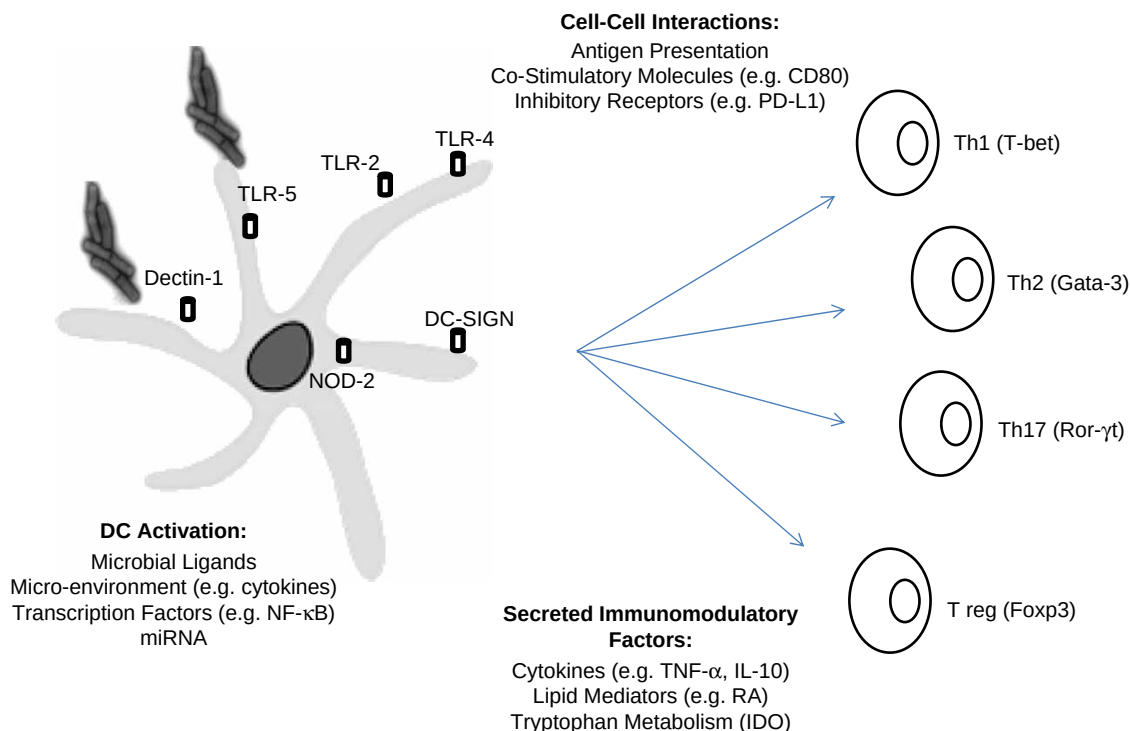


Figure 1. Following activation by microbial ligands, dendritic cells activate and polarise the adaptive T cell response.

for T_{reg} -mediated immunosuppression have been described with secretion of IL-10 being of particular importance [25]. Absence or defective function of T_{reg} cells has also been correlated with hyper IgE syndrome, hypereosinophilia, and autoimmunity in humans, whereas their presence has been associated with immune tolerance [26].

Studies on the mechanisms by which immune responses to non-pathogenic environmental antigens lead to either allergy or non-harmful immunity have demonstrated that allergen-specific IL-10 producing T_{regs} (T_{R1} cells) are the dominant T cell subset in healthy individuals [27,28]. Repeated exposure of non-allergic healthy beekeepers to bee venom antigens during the beekeeping season represents a valuable *in vivo* model to ascertain mechanisms of immune tolerance to venom antigens [29]. After multiple bee stings, venom antigen-specific T_{H1} and T_{H2} cells switch toward IL-10-secreting T_{R1} cells. This occurs in parallel to the suppression of cutaneous late-phase responses to allergens and inhibition of allergen-specific T_{H1} and T_{H2} cells. The response is observed as long as venom exposure persists and returns to initial levels within 2–3 months after the end of the beekeeping season. In the same model, the upregulation of histamine receptor 2 on specific T_{H2} cells suppressed allergen-stimulated T cells and increased IL-10 production.

Various strategies, which are designed to enhance T_{reg} function *in vivo*, are currently under investigation. These include the adoptive transfer of inducible or constitutive T_{reg} cells and their induction by specific adjuvants or immunomodulators. These approaches are attractive compared to conventional treatments, as the antigen-specific suppressor capacity of T_{reg} cells does not result in general immunosuppression and may actually lead to long-lasting antigen-specific regulation *in vivo*. Moreover, individual patient-specific treatments are possible with limited side effects. Many immunomodulators that have been developed or are under development, such as rapamycin, the CD80/CD86:CD28 co-stimulation blocker abatacept (Orencia; Bristol-Myers Squibb, Co., Uxbridge, Middlesex, UK), non-mitogenic anti-CD3 monoclonal antibodies (mAbs), and T cell depletion and anti-tumor necrosis factor- α (TNF- α) mAbs, display direct or indirect effects on T_{reg} cells, which may enhance or suppress their function [30–34].

There is a selective advantage to expand a population of T_{reg} cells that can target the organ (or the lymph nodes that drain the organ) by recognition of an allergen or an autoantigen expressed in inflamed organs in mouse models [35]. Thus, transfer of organ-specific T_{reg} cells can be effective at suppressing ongoing disease, although those T_{reg} cells do not necessarily need to recognize exactly the same autoantigen as the autoaggressive effector T cells

[36]. This has implications for therapeutic strategies aimed at targeting the T_{reg} cell arm of immune tolerance against allergens, autoantigens, or transplantation antigens. Possibilities of adoptive transfer of T_{reg} cells or small molecular compounds that induce T_{reg} cells in the tissue are being investigated [35], but no double-blind, placebo-controlled studies have been reported so far. To date, allergen-specific immunotherapy (SIT) is the only antigen-specific approach that induces T_{reg} cell production and activation in humans.

Allergen-SIT induces T_{reg} and IL-10-secreting T_{R1} -like cells, and treatment with glucocorticoids and $\beta 2$ adrenergic agonists seems to promote the number and activity of these cells [37–39]. The essential transcriptional elements regulating expression of the Foxp3 promoter have been recently reported, and these will provide new targets for the development of novel therapeutics [40,41].

Microbes as pathogenic factors in allergy and asthma

It is becoming increasingly clear that the host microbiota condition and prime immunological function with an unexpected level of interdependence between bacteria and the immune system. Accumulating evidence suggests that certain bacterial strains provide protective signals, while other bacterial strains stimulate aggressive and damaging immune responses. In other words, the activity of the mammalian immune system seems to be governed by the balance between symbiotic and pathogenic factors derived from our microbial inhabitants (Figure 2). This raises the possibility that dysbiosis can lead to inappropriate inflammatory responses and may contribute to the dramatic increase in several immune-mediated disorders observed in recent decades, including allergy and asthma. However, it remains unclear whether dysbiosis is the cause or an effect of the disease.

There are a number of micro-organisms that are well accepted to be differentially recognized by the immune system of patients with allergic disease. *Malassezia* spp. are members of the normal human cutaneous flora. They occur mainly on the trunk and head, and seven species have been identified (*Malassezia furfur*, *Malassezia pachydermatis*, *Malassezia sympodialis*, *Malassezia globosa*, *Malassezia obtusa*, *Malassezia restricta*, and *Malassezia slooffiae*). *Malassezia* spp. are associated with several cutaneous and systemic diseases, either as the causative agent of these conditions or associated with lesions. Diseases with which *Malassezia* is associated include pityriasis versicolor, seborrhoeic dermatitis, folliculitis, AD, psoriasis, confluent reticulate papillomatosis, and seborrhoeic blepharitis.

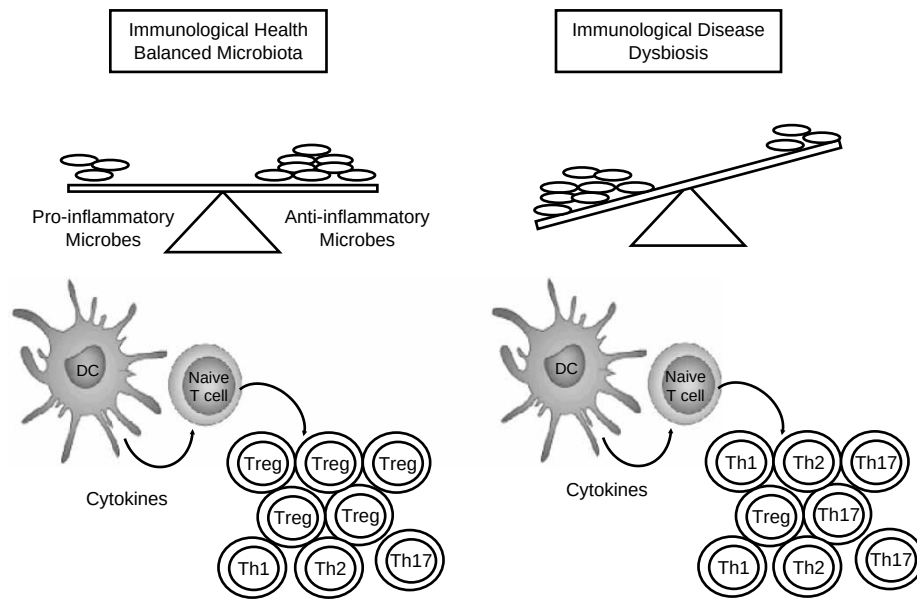


Figure 2. The activity of the mammalian immune system seems to be governed by the balance between symbiotic and pathogenic factors derived from our microbial inhabitants. In health, the correct microbial balance results in the induction of multiple T cell subsets, with T_{reg} cells dominating. When the microbiota is not correctly balanced, i.e. dysbiosis, inappropriate inflammatory responses may result due to the expansion of pro-inflammatory T cell subsets.

Malassezia spp. have also been shown to cause more deep-seated infections, including mastitis, sinusitis, septic arthritis, malignant otitis externa, fungemia, pulmonary vasculitis, peritonitis, and meningitis [42]. There is growing interest in the role of *Malassezia* as a contributory factor in the AD disease process. Patients usually have an increased sensitization to *Malassezia*, and this sensitization encompasses both the cellular and humoral immune responses. The cellular responses tend to be of T_H2 type with higher levels of IL-4 and IL-5 production by the T cells of patients than of healthy controls [43]. These cytokines may drive the continued production of IgE leading to histamine release from mast cells, and the itching associated with this would encourage scratching and so provide an opportunity for ongoing sensitization to *Malassezia*. CD1a⁺ dendritic cells, derived from peripheral blood, have been demonstrated to phagocytose whole *M. furfur* cells [44] with whole-cell uptake mediated by the mannose receptor and not influenced by IgE. In addition, dendritic cells which express the CLR minicore also recognize *Malassezia* [45].

The uptake of the yeast by dendritic cells induces maturation and a significant increase in the production of TNF- α , IL-1 β , and IL-18, but not IL-10 or IL-12 [46]. In addition, *M. sympodialis* has been co-cultured with dendritic cells from AD patients or healthy controls, and gene expression is analyzed. Although there were no genes exclusively upregulated in either patients or controls, there were differences in the magnitude of the upregulation between the two groups. Six genes were upregulated more than fivefold in dendritic cells from the patient group. These genes

(IL-8, CD54, CD83, IL1R, BTG1, and MDC) are involved in cell adhesion, costimulation, and chemoattraction, which suggest increased cell traffic and stimulation of dendritic cells in response to *Malassezia* in patients with AD [47].

In support of this concept, *M. sympodialis* has been shown to differently affect the level of antimicrobial components secreted by dendritic cells (in particular the cathelicidin LL-37) from patients with AD compared to dendritic cells isolated from healthy volunteers [48]. These data support the concept that *Malassezia*-activated dendritic cells may contribute to the allergic state, and a better understanding of the underpinning molecular mechanisms will be useful in the design of novel immunotherapeutic and antimicrobial strategies.

Sensitization to *Aspergillus* species is quite common in patients with asthma (about 20–25% of patients display skin-test reactivity), and among the molds involved in pulmonary complications, *Aspergillus fumigatus* plays a predominant role [49]. *A. fumigatus*-related pulmonary diseases can be broadly classified according to their clinical conditions into systemic mycoses, saprophytic colonization, and allergic diseases. *A. fumigatus*-related allergy includes rhinitis, sinusitis, allergic asthma, and allergic bronchopulmonary aspergillosis [50]. *A. fumigatus* is recognized by a range of dendritic cell PRRs including TLR-4, TLR-9 and DC-SIGN, while dectin-1–TLR-2 collaboration is required for efficient phagocytosis [51]. Appropriate PRR signaling is essential for protection from this mold as TLR-4^{−/−} mice die more quickly following infection [52]. In addition, patients sensitized to fungal allergens, such as thioredoxin,

exhibit a high degree of cross-reactivity with their homologous human self-antigens, strongly supporting the involvement of IgE-mediated autoreactivity in the pathogenesis of chronic atopic disorders [53].

Staphylococcus aureus has been implicated in a variety of clinical diseases. *S. aureus*-secreted enterotoxins (SEs) are a large protein family composed of SEs A–Q and toxic shock syndrome toxin 1, which may act as superantigens. Skin of patients with eczema is frequently colonized by enterotoxin-excreting *S. aureus* strains which can cause higher disease activity compared with non-toxigenic strains [54]. Direct application of Secreted enterotoxin B (SEB) to skin elicits local inflammatory response in both healthy volunteers and subjects with eczema. Adults with allergic rhinitis are four times more likely to show IgE sensitization to SEs than healthy controls (25 vs. 6.3%), while rhinitis severity increases in SE-sensitized compared with non-sensitized patients [55]. SE sensitization in patients with dust mite allergy and rhinitis may contribute to a higher mite-specific IgE response. Furthermore, there is growing evidence that SEs may be implicated in the pathogenesis of asthma. Adult patients with asthma have higher specific IgE levels to mixture of SE-specific IgEs (SE-mix) than controls, and the level of SE-mix-specific IgE correlates with severity of symptoms [56]. Patients with allergic asthma have higher SEA- and SEB-specific IgE compared with patients who only have eczema or rhinitis alone [57].

In addition, there is an increased sensitization rate to SEs in 5-year-old children with eczema and wheeze, and the proportion of patients sensitized to SE mix increases with increasing symptom severity [58]. The mechanism of action underpinning the activity of SE is primarily related to its binding to the T cell receptor, which may activate up to 20% of the naive T cell population, thus bypassing the common antigen presentation mechanisms. Both murine models and human studies have demonstrated T_H2 -type cytokine secretion and polyclonal IgE synthesis in response to SE stimulation [59]. Although the direct impact of SEB on T cell activation has been well documented, SEB also has stimulatory effects on dendritic cells. One study has demonstrated that SEB activation of human dendritic cells in a TLR-2-dependent manner results in a dendritic cell response that promotes T_H2 T cell polarization [60]. These results were supported by another study in which SEB activates dendritic cell TLR-2 and NOD-1, resulting in expression of T cell immunoglobulin (TIM) mucin domain 4, which ligates with TIM1 on T_H2 T cells, thus stabilizing and promoting the T_H2 phenotype [61].

It is clear that certain microbes may promote inflammation and disease development. However, the absence of other potentially beneficial microorganisms (which promote appropriate immune tolerance) may also lead to the induction of

inflammatory responses and immune-mediated disease. For example, lipoteichoic acid released by *Staphylococcus epidermidis* (a cutaneous commensal microbe) inhibits both inflammatory cytokine release from keratinocytes and inflammation triggered by injury through a TLR-2-dependent mechanism [62]. The removal or depletion of such microbes from the skin would eliminate an important suppressive mechanism resulting in uncontrolled inflammation and potential sensitization to normally well-tolerated antigens. In addition, appropriate colonization of the gastrointestinal tract by commensal microbes is thought to be important for the full development of immunological function and tolerance.

Microbes as novel therapeutic options

Interest in the deliberate administration of microbes or microbial metabolites for the treatment of aberrant inflammatory activity is gaining momentum. The typical microbes which are currently being examined include *Bifidobacteria*, *Lactobacilli*, non-pathogenic *Escherichia coli*, and *Bacteroides* strains [63–68]. The protective effects associated with these microbes are probably mediated by multiple mechanisms involving epithelial cells, dendritic cells, and T cells. However, a common feature of these microbes, which is being increasingly reported, is their ability to induce T_{reg} cells. For example, encounters with a mixture of commensal microbes (VSL#3 probiotic cocktail) within the murine gut have been shown to drive the development of mucosal T_{reg} cells, which is associated with attenuation of inflammation in a murine model of colitis [69].

In addition, the consumption of a *Bifidobacterium infantis* strain promotes T_{reg} cell conversion and protects against lipopolysaccharide-induced NF- κ B activation *in vivo*, while *Lactobacillus reuteri* induces T_{reg} cells, which protect against an allergic airway response in mice [70,71]. T_{reg} cells are derived from the thymus but may also be induced in peripheral organs, including the gut mucosa [72,73]. CD103 + dendritic cells within the mucosa are largely responsible for the conversion of T_{reg} cells via TGF- β and retinoic acid-dependent processes [74,75]. The conversion is likely driven by gastrointestinal-specific environmental factors associated with the presence of large number of commensal organisms.

However, it is unlikely that all commensal microbes are equally effective at inducing T_{reg} cells *in vivo*. A recent study, comparing multiple commensal organisms (*Bifidobacterium longum* AH1206, *Bifidobacterium breve* AH1205, and *Lactobacillus salivarius* AH102), has shown that *B. longum* AH1206 induced T_{reg} cells, and was able to protect against eosinophil recruitment to the lung and blocked induction of serum IgE in murine models [76]. The other bacterial strains did not effectively induce T_{reg} cells and were not able to

protect against allergic inflammation in the same models. Therefore, the induction of T_{reg} cells may be a critical characteristic of a healthy microbiota, which is protective against the development of aberrant immunological reactivity to potential allergens.

In addition to using live microbes for the treatment of allergy, another exciting approach is to identify the microbial factor(s) responsible for the beneficial effect and to use these isolated factor(s) alone. For example, polysaccharide A derived from *Bacteroides fragilis* promotes an appropriate $T_{\text{H1}}/T_{\text{H2}}$ balance in germ-free mice following presentation by mucosal dendritic cells and protects against colitis in an animal model via IL-10-secreting $CD4^{+}T$ cells [67,77]. The continued identification of new microbial compounds which induce tolerogenic dendritic cells and T_{reg} activity will undoubtedly lead to novel therapeutic molecules for assessment in clinical studies.

Despite encouraging animal model data, human clinical studies examining the effectiveness of therapeutic microbes for the prevention or treatment of allergic disease have not been conclusive thus far. A review of 13 randomized, placebo-controlled trials concluded that certain microbes, but not all microbes tested, could have utility particularly when administered early in life [78]. In particular, infants at high risk of atopy who received *Lactobacillus rhamnosus* GG developed AD significantly less frequently during the first 2 years of life than infants who received placebo. In these studies, mothers were administered *L. rhamnosus* GG with or without other probiotics perinatally, followed by treatment of the infants with the same probiotics for the first 6 months of life.

A more recently published study using a combination of three bacterial strains (*Bifidobacterium bifidum* BGN4, *B. lactis* AD011, and *Lactobacillus acidophilus* AD031) also demonstrated that prenatal and postnatal supplementation was effective in preventing the development of eczema in infants at high risk of allergy during the first year of life [79]. The use of microbes in the treatment of allergic disease is less promising. A Cochrane meta-analysis concluded that the microbes tested to date are not effective for the treatment of eczema [80]. In addition, clinical data on the use of microbes in the treatment of asthma and allergic rhinitis are conflicting. Thus, care should be exercised in the selection of microbes for administration in human studies, as it is likely that not all microbes are equally effective and a single microbe may not be effective for multiple disease states.

A better description of the microbial community inhabiting allergic patients and healthy volunteers will aid in the identification of those members, which are absent or those which are over-represented, thereby providing a logical rationale for intervention. In addition, significant effort needs to be focused on the elucidation of molecular pathways that are impacted by the enteric microbiota so as to select

those microbes that induce favorable immune responses. Exciting recent advances in this field already support the concept that T_{reg} cells mediate the beneficial effects of certain symbiotic organisms. Lastly, specific projects mining the microbiota for metabolites and ligands that modulate host immune function will likely lead to a new class of immunotherapeutic agents with relevance to a variety of inflammatory states, including allergy and asthma.

Novel approaches to allergen SIT

Although excellent drugs to control the symptoms of allergy and asthma are available, the only treatment able to cure allergy remains allergen-SIT. SIT is, however, rarely chosen as a therapeutic option by allergic patients mainly because it spans over a treatment period lasting between 3 and 5 years to reach protection against the offending allergen [81]. This unsatisfactory situation has strongly stimulated innovative research activities within the allergy field [82] aimed at making SIT faster and safer in order to augment patient's compliance [83]. Two main problems need to be reduced or eliminated to render SIT more attractive, that is, side effects and treatment time. Several exciting approaches to solve these issues are currently under clinical investigation.

Therapy-related SIT side effects derive from the intrinsic property of allergens to cross-link high-affinity receptors for IgE on effector cells resulting in their degranulation and release of pre-made toxic substances, like histamine and leukotrienes, leading to local or generalized anaphylactic reactions [84]. Allergoids [85], hypoallergens [86], and immunodominant allergen peptides [87] are allergen surrogates with markedly reduced IgE-binding capacity, while conserving the whole and/or the immunodominant T cell epitopes required for eliciting protective (IgG mediated) immune responses. SIT with allergoids reached the market some time ago and has yielded results comparable to those obtained with allergen extracts with a reduced side effect profile, but it still requires a long treatment time [88]. Peptide immunotherapy showed promising results in clinical trials with bee venom allergic and cat allergic individuals [89,90].

Many genetically engineered hypoallergens have shown promising results in mouse models of allergy [91,92] but have not yet reached the clinics with exception of the major birch pollen allergen, Bet v 1, which showed ambiguous results in a clinical study of limited size [93]. Perhaps the more advanced form of immunotherapy with allergens showing a favorable safety profile is sublingual immunotherapy (SLIT) [94]. SLIT still suffers from a long treatment time comparable to those of classical subcutaneous immunotherapy but is increasingly used as a therapeutic option, especially in Europe [95]. These

approaches have significant potential for improvement, particularly in combination with novel adjuvants and modified treatment regimens.

Obviously, a long treatment time strongly reduces patient's compliance, and therefore many efforts have been undertaken to reduce the number of injections (currently 50–80 are required) in order to achieve protection. Four different strategies have entered phase I/IIA clinical trials and yielded promising results: peptides covalently coupled to virus-like particles [96], A-type CpG oligodeoxynucleotides as an adjuvant [97], direct injection of allergens into lymph nodes [98], and modular antigen translocating vaccines, which directly target the MHC class-II antigen presentation pathway [99]. All these therapeutic innovations have, if confirmed in larger multi-center clinical trials, the potential to turn immunotherapy into a true vaccination approach because only a few injections are required to achieve long-lasting protection [96–100]. These approaches indicate that the problems related to the long treatment time of classical immunotherapy, which is mechanistically based on immunomodulation which requires a long time to establish, can be reduced using strong adjuvants, by changing the route of application, or by direct targeting of the antigen presentation pathways. We conclude that the limited efficacy associated with classical SIT is not closely related to the potential of the immune system to mount protective responses against allergens. There is clear evidence that low amounts of antigen, such as those encountered during natural exposure to most of the environmental allergens, favor the switch of B cells toward IgE production in predisposed individuals, whereas higher doses of antigen favor the development of protective IgE antibody responses. Therefore, the most promising approaches to faster and more successful SIT treatment regimens will most likely derive from strategies aimed at increasing the therapeutic dose of the allergen in lymph nodes, while avoiding effector cell degranulation.

Other immunomodulatory strategies under investigation

A number of anti-cytokine therapies are currently being examined. Daclizumab (an IL-2 receptor antagonist) has been examined in a phase II study in patients with moderate-to-severe asthma. Patients treated with daclizumab showed improved pulmonary function, reduced asthma symptoms and medication use, increased interval between severe exacerbations, and reduced blood eosinophils and serum eosinophil cationic protein levels [101,102]. Two humanized IL-5 mAbs – reslizumab and mepolizumab – have been studied in humans.

Mepolizumab decreased blood and airway eosinophils, but no significant sustained changes in FEV1,

asthma symptom scores, sputum eosinophils, or physician-evaluated overall condition were noted with mepolizumab or reslizumab compared with placebo [103–105]. In order to neutralize the activity of IL-4, recombinant human soluble IL-4 receptor has been examined [106]. Patients with moderate, persistent asthma had significant improvement in asthma symptom scores, rescue β -agonist use, and exhaled nitric oxide levels compared with those receiving placebo [107]. However, a follow-up study revealed that only asthma patients receiving the highest dose of sIL-4R maintained their lung function [108]. Blocking TNF- α using neutralizing antibodies improved lung function and quality of life and reduced exacerbation frequency in patients with asthma in some studies but not in all studies [109–111]. It is likely that additional cytokines (e.g. chemokines) will also be targeted in the near future for patients with allergy and asthma.

Several humanized mAb that bind to the Fc portion of the IgE molecule have been used in clinical studies, and one (omalizumab) is currently available for treatment of allergic asthma. Anti-IgE in combination with allergen-SIT resulted in a greater reduction in seasonal allergic rhinitis symptoms and rescue medication scores compared to allergen-SIT alone [112]. Importantly, the addition of omalizumab to a rush SIT protocol significantly reduced the risk of anaphylaxis [113].

Anti-histamine compounds that target the histamine receptor 1 (H1R) have been used for some time. However, the discovery of a new histamine receptor, H4R, has provided a new target for drug development. Thus far, only animal model data are available which demonstrate proof of the efficacy for H4R antagonists in models of asthma, allergic rhinitis, and pruritis [114]. Candidate molecules have been identified, which are expected to enter clinical trials shortly.

Concluding remarks

Recent advances in the elucidation of the molecular and cellular events important for the initiation and suppression of inflammatory activity have led to novel therapeutic compounds for patients with allergies and asthma. Harnessing the immunomodulatory capacity of well-selected microbes, or their symbiotic factors, will likely generate new classes of biological molecules for prevention and intervention strategies against allergic diseases. Indeed, the use of microbial factors may be most effective as novel adjuvants in combination with allergen-SIT in order to rapidly induce T_{reg} cells and tolerance to the offending allergen.

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