

Controversies in Experimental Dermatology

Section Editor: Ralf Paus, Hamburg

What are the most promising strategies for the therapeutic immunomodulation of allergic diseases?

Tokura Y, Röcken M, Clark RAF, Maurer M, Grabbe S, Haliasos E, Takigawa M, Sinha AA. What are the most promising strategies for the therapeutic immunomodulation of allergic diseases?
Exp Dermatol 2001; 10: 128–140. © Munksgaard, 2001

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Specific immunotherapy and other immunomodulatory strategies have long been a stronghold in the management of allergic diseases. In particular, “immunodeviation-therapy” or “vaccination for allergies”, i.e. the redirection of Th2-type immune responses towards a Th1-response pattern, has become an ever more popular concept. The present feature of CONTROVERSIES complements our previous discussion of atopy (Röcken et al., Exp Dermatol 7: 97–104, 1998), and is dedicated to a critical analysis of the general problems and limitations one faces

with the main immunomodulatory strategies traditionally considered in this context. We also explore alternative approaches that appear promising in order to achieve both a more effective and/or a more specific immunotherapy of allergic diseases. Given that the mast cell remains a key protagonist in the pathogenesis of allergic diseases finally, this feature examines how innovative, more selectively mast cell-targeted strategies may be developed for the management of allergic diseases.

Viewpoint 1

This Viewpoint essay will focus on discussing the validity of several established or currently explored therapies for atopic dermatitis (AD) in the light of our current understanding of the role for T cells in the development of skin lesions of AD.

The mechanism underlying atopic dermatitis (AD) involves complex interactions between various cells and cytokines. Cell-mediated responses are performed by T cells, Langerhans cells, mast cells, eosinophils, and monocytes/macrophages. In initial allergic reactions, the majority of pathogenetic T cells are T helper type 2 (Th2) cells producing interleukin (IL)-4, IL-5, and IL-13 but not IFN- γ or IL-2. These cytokines regulate IgE synthesis, promote eosinophil differentiation and survival, and induce vascular endothelial adhesion

molecules, thus contributing to allergic inflammation (1, 2).

Various immunomodulatory therapies have been established or explored for the treatment of AD. Since T cells play a central role in the pathophysiology of AD, immunomodulation of T cells or targeting of their cytokines *per se* deserve consideration in this allergic disease and Table 1 summarizes therapies relevant to T cell immunomodulation. Given that AD patients have a Th2-skewing immunologic balance, pharmacological agents or treatment modalities that act on T cells can be divided into the following categories:

1) Th1-derived cytokines, represented by interferon- γ (IFN- γ) (3–8); 2) immunosuppressants or cytokine transcription inhibitors, including cyclo-

Table 1. Th1-derived cytokine and T-cell-modulatory agents for the treatment of AD

| | Drugs or modalities | Category |
|----------------------------------|----------------------|----------------------------------|
| Th1-derived cytokine | IFN- γ | Cytokine |
| Cytokine transcription inhibitor | Cyclosporine A | Immunosuppressant |
| | Tacrolimus | Immunosuppressant |
| Th2 cell inhibitor | Suplatast | Anti-allergic |
| Th1-polarizing agent | PUVA | Photochemotherapy |
| | Hochu-ekki-to | Japanese/Chinese herbal medicine |
| | CpG oligonucleotides | Experimental level |

Promising:

Anti-T cell antibody

Anti-cytokine antibody

Cytokine receptor antagonist

Chemokine receptor antagonist

sporin A (9, 10) and tacrolimus (11–13) (the former is used orally and the latter topically; 3) novel Th2 cell inhibitors, such as an anti-allergic drug, the dimethylsulfonium derivative suplatast (14, 15); and 4) various Th1-polarizing modalities, including psoralen and ultraviolet A (PUVA) therapy (16) and even Chinese-Japanese herbal medicine, e.g. Hochu-ekki-to (17); and 5) other promising but as yet unestablished therapies, including anti-T cell (18)/cytokine (19) monoclonal antibodies, and cytokine (20, 21)/chemokine (22, 23) receptor antagonists. These drugs/modalities are different from each other in the intensity of therapeutic action and adverse effects. For example, while both the clinical benefits and side effects of cyclosporin A and tacrolimus are pharmacologically high, those activities of the Chinese-Japanese herbal medicine are only mild.

Is suppression of Th2 cells effective?

Th2 cells are generally known to mediate allergic diseases. This concept has led to acceptance of the idea that downregulation of the polarized Th2 response or enhancement of production of Th1 cytokines such as IFN- γ is therapeutically effective.

Systemic administration of IFN- γ is a direct and efficacious therapy for induction of the Th1-skewing immunomodulation, and its effectiveness has been documented in patients with AD (3–5). However, the dosage of IFN- γ , the therapeutic schedule, and the degree of clinical improvement differed greatly between studies. It was reported that most AD patients with an eosinophil percentage over 9% and an IgE level over 1500 IU/ml did not respond to IFN- γ therapy (6). Also, treated patients demonstrated reductions in total leukocyte, eosinophil, and lymphocyte counts, but not a reduction

in the elevated levels of circulating IgE levels (5–8). Interestingly, improvement more closely correlated with changes in eosinophil counts than with changes in IgE levels (3).

Therefore, it seems that IFN- γ provides therapeutic benefit to a certain group of AD patients by decreasing the eosinophil number, but not the IgE level. In our own experience, it appears that IFN- γ offers also therapeutic benefit to patients with other Th2-mediated skin diseases, such as eosinophilic pustular folliculitis (24), Wells' syndrome (25), and subacute prurigo (26).

Suplatast is a unique drug that selectively inhibits Th2 cells but not Th1 cells in their cytokine production, resulting in a decrease in the IgE level (14, 15). It is approved as a treatment modality for atopic diseases in Japan. Treatment with psoralen and UVA induces transient, but biologically active Th1-skewing cytokine production (16), which may partly account for the therapeutic effect of PUVA therapy (27) and photopheresis (28) in AD. A Chinese-Japanese herbal medicine, Hochu-ekki-to, may induce such modulation because of its IFN- γ elaborating ability (17).

However, the therapeutic effectiveness of these therapies may be limited and appears to be less impressive or intense than that of IFN- γ . New approaches to achieve downmodulation of the Th2-polarized response are currently being tested. The development of oligodeoxynucleotides containing cytosine and guanosine nucleotide repeats (CpG motif) (29) looks especially promising.

Thus, the above Th1-skewing therapeutic modalities do not necessarily produce satisfactory results in AD. This also implicates that the formation of AD skin lesions is not purely mediated by Th2 cells.

Is suppression of both Th1 and Th2 cells effective?

An analysis of cytokine expression in AD is critically dependent on the acuity and duration of the skin lesion. An *in situ* hybridization study demonstrated that although T cells in both acute and chronic AD lesions are associated with increased activation of IL-4 and IL-5 genes, acute skin inflammation in AD is associated with a predominance of IL-4 expression, whereas chronic inflammation is predominantly associated with increased IL-5 expression. The number of IFN- γ mRNA-expressing cells was not significantly increased in acute AD skin, and was slightly elevated in chronic skin as compared to uninvolved skin (30). However, a considerable number of studies has revealed that in chronic eczematous skin lesions of patients with AD, expression of IFN- γ predominates and allergen specificity of skin-infiltrating T cells is not restricted to a Th2 cytokine pattern in lesional atopic derma-

titis (31). This is consistent with the observation that lesional expression of interferon- γ is linked to the clinical course of atopic dermatitis (32).

The chemokine receptor CCR4 is known to be selectively expressed in Th2 cells. Thymus- and activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC) are the two functional ligands for CCR4. TARC is highly expressed in lesional basal epidermis in the NC/Nga mouse model for AD, whereas it is not expressed in non-lesional skin (33). Production of TARC by keratinocytes was confirmed by culturing a murine keratinocytic cell line with IFN- γ as well as with IL-1 β and TNF- α (33).

Therefore, IFN- γ may even be a potent facilitator of Th2 cell infiltration in lesional AD skin. These observations raise the possibility that, under certain conditions, IFN- γ or Th1-polarizing modalities rather induce the formation of atopic skin lesions. Consequently, therapeutic modalities that suppress both Th1 and Th2 cells may be more effective in the treatment of patients with AD than a monotherapy with IFN- γ .

Cyclosporin A and tacrolimus are immunosuppressants that affect a broad spectrum of inflammatory mediators. These drugs have proven value in treating patients with AD as systemic (9, 10) or topical (11–13) agents. To surmount the poor penetration of cyclosporin A, it was conjugated with a heptamer of arginine for topical application. This modified cyclosporin A reached dermal T lymphocytes and inhibited cutaneous inflammation (34). These two immunosuppressants downmodulate both Th1 and Th2 cells by inhibiting the transcription of various proinflammatory cytokine genes. Since even topical application exerts excellent therapeutic efficacy (11–13), suppression of both Th2 and Th1 cells seems to be a more powerful therapeutic strategy for the treatment of AD, than only Th2 suppression. Yet, in some AD patients, the serum IFN- γ levels were unexpectedly increased during cyclosporin A therapy, which – intriguingly – was correlated with clinical improvement of AD lesions (35). This implies a dominant suppression of Th2 cells, and reinforces the therapeutic value of skewing the immune response towards a Th1 pattern in AD.

Is suppression of CD8+ T cells, in addition to CD4+ T cells, effective?

Although activation of CD4+ T cells has been demonstrated to play an important role in allergic inflammation of the skin, a minor (or even more important) role for CD8+ T cells deserves consideration. In atopic skin lesions, the existence of a considerable number of CD8+ T cells was shown

by immunohistochemistry and by culturing T cells from skin biopsies. In addition to the CD4+ subset, the CD8+ cutaneous lymphocyte-associated antigen (CLA) + memory/effector T cells are capable of responding to superantigenic stimulation, and are appreciated to play an important role in the pathogenesis of AD (36). CD8+CLA+ T cells proliferate in response to superantigen and are as potent as CD4+CLA+ T cells in IgE induction and support of eosinophil survival. Both CD4+ and CD8+ subsets of CLA+ CD45RO+ T cells from the peripheral blood of AD patients spontaneously release IL-5 and IL-13, thereby inducing IgE production by B cells and enhancing eosinophil survival (36). Moreover, another study has shown that, in addition to CD4+ cells, CD8+ cells contribute to IgE synthesis in AD patients, presumably by secreting IL-13 (37). In AD patients with high IgE levels, type 2 cytokine expression (IL-4 and IL-13) is associated with IgE production, in both CD4+ CD45RO+ T cell and CD8+ CD45RO+ T cell subsets (38).

Thus, CD8+ T cells as well as CD4+ cells play an important role in the pathogenesis of AD lesions. This notion supports the use of cyclosporin A and tacrolimus, which suppress not only CD4+ but also CD8+ cells, so as to further improve the systemic and local immunodysregulation seen in AD.

Perspectives

The pathogenic cytokines discussed here in the context of AD may become key therapeutic targets in our future treatment of allergic diseases. The increasing availability of recombinant cytokines and cytokine antagonists (20, 21) or anti-cytokine antibodies (19) will likely lead to more wide-scale applications in AD.

Understanding the chemokine network has become another of the great challenges for researchers interested in AD (22, 23). In particular, Met-RANTES, a modified antagonist of RANTES, as well as cotaxin receptor (CCR3) antagonists, represent promising novel therapeutic agents potentially useful in atopic disorders. Thus, suppression of chemokines may interrupt the sequence of signals culminating in an allergic response (22). Infiltration of the skin by Th2 cells and increase of CCR4 mRNA in the skin coincide with the development of AD lesions. This indicates that the Th2 chemokines, TARC and MDC could be novel targets for immunointervention therapy in AD.

However, it should always be kept in mind that Th1 cells do play a substantial role in the development of AD skin lesions. Thus, therapies that ex-

clusively suppress or eliminate Th2 cells are not necessarily satisfactory in the treatment of AD.

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Viewpoint 2

Conventional, symptom-oriented pharmacotherapy of allergic diseases has progressed to a level that strongly reduces the severity of chronic and acute symptoms of allergic diseases and greatly improves the quality of life of patients with IgE-mediated allergies. Despite this progress, regular and continuous treatment with drugs that possess broad anti-inflammatory properties is required. The costs and handicaps associated with daily immunotherapies and the potential risks resulting from immunosuppressive agents that are applied over years define the need for specific immunotherapies, in the sense of anti-allergic vaccination (4).

The primary goal of specific immunotherapies is to modify selectively immune reactions that cause harm. A secondary goal is the establishment of a long lasting state of protective immunity that allows a normal life with little or no additional drug therapy. Since T cells are key mediators between innate and specific immune responses, most vaccination strategies focus directly or indirectly on T cells and their antigen receptors (1–4, 6, 10, 12–14, 30). Therapeutic vaccination is only established for IgE-mediated allergies, induced by IL-4 and IL-13 producing T cells (6, 9, 16, 23, 24, 28, 29).

A clear diagnosis proving the association between the disease manifestation and IgE-mediated immune reactions is a prerequisite for initiating specific immunotherapies. A diagnostic procedure that omits either laboratory or clinical findings does not justify the initiation of immunotherapies.

Specific immunotherapy is not indicated if the causative agent can easily be avoided, as in most patients with drug allergies, or if the allergen is poorly defined. Moreover, specific immunotherapies are not established for atopic dermatitis. 'Anti-allergic' vaccination is most successful when both the allergens involved and the antigenic structure of the allergen are well defined, such as in patients with bee or wasp venom allergy, and it tends to be satisfactory in many patients with allergic rhino-conjunctivitis. However, they frequently fail even in patients with rhino-conjunctivitis, if the clinical symptoms are caused by more than three allergens (7, 10).

A more challenging problem is allergic asthma. The difficulties in developing specific immunotherapies for allergic asthma may be related to several factors.

One important aspect is that the airway inflammation observed in asthmatic patients differs

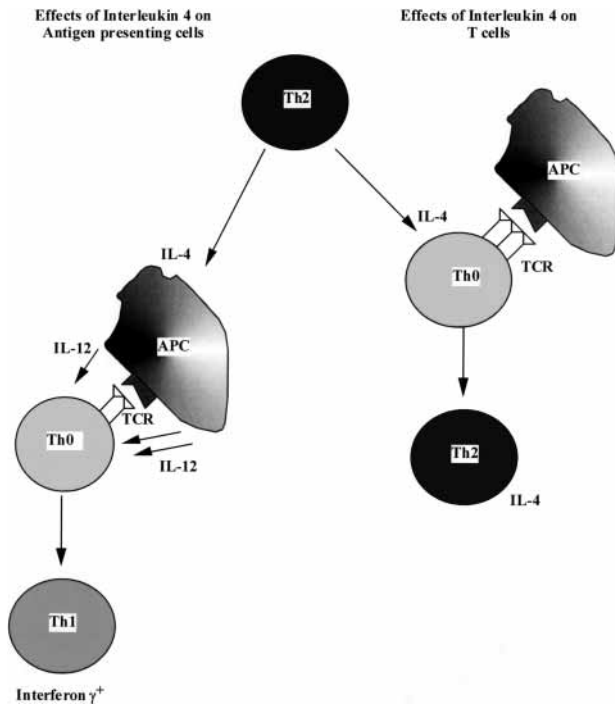


Figure 1. Potential effects of interleukin 4 on T cell differentiation.

from typical Th2-induced immediate type responses and is more complex than classical immediate type immune responses. Thus, IL-13 seems to play a more important role than during other immediate type responses, and the Th2 cells obviously exert potent pro-inflammatory effects, leading to tissue destruction (18–22). Interestingly, production of IL-10, a cytokine with strong immunosuppressive and anti-inflammatory properties, is decreased in the broncho-alveolar lavage fluid of asthmatic patients. Thus, the characteristic inflammation leading to allergic asthma might be, in part, due to a lack of IL-10 producing regulatory T (Tr) cells (5, 14). It has been suggested that this complexity is secondary to the activation of additional components of the immune system, such as mast cells or the complement pathway (27).

In addition, allergic asthma reflects a degenerate Th2-response that is no longer restricted to a small spectrum of exogenous antigens. Thus, the risk of allergic asthma is associated more closely with high levels of total serum IgE than with allergen-specific immune responses, suggesting that it is associated with the spreading of Th2-responses to multiple antigens, perhaps even autoantigens (8). Such a mechanism was recently proposed for the pathogenesis of atopic dermatitis (25, 26).

Interestingly, recent data provide a provocative outlook that might again reduce even the complexity of allergic asthma to a simple Th2-response – at least during the period of initiation.

Over the past years a series of indirect data has suggested that IL-4 may not only exert the well known ‘Th2-responses’, but may also exert potent pro-inflammatory effects that promote interferon γ -mediated Th1 responses against tumors, intracellular pathogens and allo-antigens. A series of three manuscripts now has demonstrated that IL-4 promotes not only the antigen-presenting capacity but, most importantly also primes dendritic cells for the production of IL-12p70 (11, 15, 17). IL-12p70 is the most potent signal directing T cells towards an interferon γ -producing Th1 phenotype (Fig. 1). This suggests that IL-4 is directly capable of promoting Th1-mediated immune responses and tissue destruction. If confirmed for asthma, these data will have important impact on the design of future immunotherapies (11, 15–17, 23).

Current vaccination therapies are primarily designed to redirect Th2 responses towards an interferon- γ dominated Th1-phenotype. This is justified, since interferon- γ is most potent in suppressing IgE production. However, is this concept still appropriate for treating allergic asthma? If Th2-responses induce the tissue-destruction of allergic asthma through the induction of IL-12p70, this will have two major implications: vaccination strategies should be started as early as possible. The other would be to abandon the concept of redirecting Th2- into Th1-responses and to focus strictly on the instruction of IL-10 producing Tr cells, capable of silencing both, Th1 and Th2 cells.

Early data show that specific immunotherapies currently available result in allergen-induced IL-10 production, but their efficacy is limited in patients with allergic asthma (2, 3, 10, 14). This may be related to the difficulties in growing and expanding Tr cells. Future research will thus not only focus on the biological functions of Tr cells, but will have to explore the possibilities of expanding this population in vivo.

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Viewpoint 3

The most promising immunotherapy for atopic dermatitis (AD) is...?

a) tacrolimus, b) intravenous gamma-globulin (IVIG), c) phosphodiesterase (PDE) inhibitors, d) all of the above, or e) none of the above. As the medical community and big pharma play their version of “Who wants to be a (multi)-millionaire?” a case can be made for each of the above choices.

High dose IVIG downregulates IL-4 (1) and may have a role in severe disease. PDE inhibitors have pleiotropic intracellular effects and are inhibitory at several points along the immune cascade (2). Much fanfare has welcomed the recent FDA approval in the US of tacrolimus (FK506). SDZ ASM 981 is another new topical application that, like tacrolimus (3, 4), inhibits the expression of various cytokines in multiple cell types (5–7). In severe or persistent disease, combination therapy may be the most appropriate strategy.

However, the common drawback to each of the known and emerging therapeutic modalities of today is nonspecificity. In allergic disease, we are still in search of the holy grail of immunotherapy – Ehrlich’s ‘magic bullet’. The challenge to all – physicians, scientists, industry – will be to rise to

the next level. The most promising immunotherapy is not yet formulated – one that incorporates the fundamental immune principle of specificity and ultimately can be tailored for individual patients.

Conceptually, strategies for immune intervention can operate at 3 basic phases of the immune response: 1) effector response at the target tissue, 2) proliferation and differentiation, 3) induction (see Table 1).

Target Tissue. To mediate disease, effector cells must be deployed to the skin. Skin homing of T cells in human allergic inflammation involves the binding of adhesion molecules expressed on the surface of lymphocytes to their ligands on vascular endothelium. Cutaneous lymphocyte-associated (CLA) binding to E-selectin appears to initiate T cell migration to cutaneous tissues (8). VLA-4/VCAM-1 and LFA-1/ICAM-1 interactions are also relevant (8). Each of these molecules should be explored as potential targets for immunotherapy.

Numerous chemokines, including IL-16, the C-C chemokines (RANTES, MCP-4, eotaxin) and CTACK/CCL27 (9–13) have been implicated in the infiltration of immune cells to inflammatory skin lesions. Potential immunomodulatory strategies

Table 1. Potential targets for immunotherapy of atopic dermatitis. Note: this table does not represent an exhaustive list

| Induction | Proliferation and differentiation | Target tissue |
|---|--|---|
| <ul style="list-style-type: none"> • co-stimulatory molecules B7.2/CD28 CD3 CD4 • antigen presenting cells IgE receptor FcεRI • T cells T cell receptor antigenic ligand | <ul style="list-style-type: none"> • Th2 cytokines IL-4 IL-5 IL-13 • Th1 cytokines IFN-γ IL-12 IL-18 • cAMP phosphodiesterase | <ul style="list-style-type: none"> • adhesion/trafficking CLA-4/E-selectin VLA-4/VCAM-1 LFA-1/ICAM-1 • Chemokines IL-16 RANTES MCP-4 CTACK/CCL27 CCR3 CCR4 Leukotriene B4 |

could involve blocking their action, perhaps by antagonists of CCR3 and CCR4, chemokine receptors reported to be more highly expressed in atopic skin.

Leukotriene B4 also appears to act as a chemoattractant for the influx of skin inflammatory cells (14) and antagonists such as zafirlukant may prove efficacious in AD (15).

Proliferation and differentiation. Given the central role of TH2 cytokines in the development of allergic skin inflammation, treatment with IFN- γ , IL-12, and/or IL-18 may allow a shift towards a TH0 balance. Specific blockade of Th2 cytokines is another approach. A humanized anti-IL-5 mAb has been used in a monkey model of asthma and should be explored in atopic skin disease (16). Similarly, inhibition of IL-4 by specific antibodies or the administration of soluble IL-4 receptor molecules may offer another immunomodulatory angle.

Atopic mononuclear cells are known to have an enhanced cyclic AMP-PDE enzyme activity, allowing for increased IL-10 and prostaglandin (PG) E2 secretion, which in turn contributes to increased IgE synthesis in B cells and increased IL-4 and decreased IFN- γ production in T cells. PDE inhibitors (eg. Ro 20-1724) have been shown to decrease IL-10 and PGE2 in monocytes and demonstrate clinical benefit in pilot studies (2).

Although a Th2 cytokine bias has been much heralded in atopic disease, there appears to be a shift towards a Th1 pattern during the evolution from acute to chronic disease (17–19). This may explain the dramatic success of tacrolimus (and SDZ ASH 981) which have been shown to decrease both Th1 and Th2 associated cytokine expression. More specific cytokine-directed therapies need to be considered in the context of the phase of clinical disease.

Induction. The induction of allergic responses requires the interaction of T cells with antigen presenting cells (APC), including Langerhans cells (LC) and B cells. Numerous co-stimulatory molecules involved at this phase of the immune response are potential targets for immunotherapy.

The generation of Th2 cells is critically dependent upon the interaction of CD28 with B7.2 molecules on APC (20) (whose expression is increased in AD patients) (21, 22). Anti-B7.2 mAb may be of value in patients. Blocking of T cell markers CD3 and CD4 (either with antibodies or soluble receptors) represent other potential strategies.

IgE bound (via high affinity IgE receptors, Fc ϵ RI) to the surface of LCs facilitates the capture and internalization of antigens for processing and presentation required for the activation of Th2 cells. Humanized anti-IgE antibodies may be useful in downregulating IgE mediated allergic responses (23). However, their effectiveness in the context of high titers of circulating IgE in atopics remains to be determined.

Clearly, there are numerous existing and further potential targets for immune-based therapy in allergic disease. Mining of genome-wide expression data in atopic skin generated by high throughput microarray analysis will no doubt substantially increase this number.

However, despite the early promise of tacrolimus and the potential to target several other immune regulatory molecules, there are no truly ‘smart bombs’ in our current therapeutic arsenal. The specter of global immunosuppression, with associated risk of infection and neoplasm, looms for antigen nonspecific treatments (24, 25). In order to shift focus to antigen/allergen-specific directed therapies, we need more detailed knowledge regarding the fine specificity of disease-associated lymphocytes.

Recent studies demonstrating preferential T cell receptor V β usage and oligoclonal accumulation of T cell in lesional skin support the relevance of antigen-driven response in AD (26, 27). The development of T cell clones from lesional, nonlesional, and circulatory populations is possible (7, 28–34) and could be expanded to obtain large data sets from multiple patients. Extensive T cell receptor sequencing and fine epitope mapping will be required to delineate disease-associated peptide ligands derived from the potential pool of candidate allergens (see Table 2). More sensitive meth-

Table 2. Possible antigen-specific triggers of atopic dermatitis (28, 35–57). T cell and/or B cell (IgE associated) epitopes within each candidate allergen may be relevant for disease. Precise epitopes have not been determined in most cases. Note: This table does not represent an exhaustive list.

| Microbial | Food | Aero | Auto |
|--|---|--|---|
| <ul style="list-style-type: none"> • <i>S. aureus</i> Superantigens enterotoxins A+B TSST-1 • <i>Malassezia furfur</i> | <ul style="list-style-type: none"> • casein • egg protein • peanut protein • wheat protein • soy protein • birch pollen related | <ul style="list-style-type: none"> • horse dander • timothy grass • ragweed pollen • alternaria • house dust mite (Der p 1) | <ul style="list-style-type: none"> • Human skin dander (Hom s 1) |

odologies (spectratyping, tetramers) may facilitate the analysis of antigen-specific T cell responses in primary lesional and circulating cells. Recently, an IgE reactive 55 kD cytoplasmic keratinocyte protein (Hom s 1) was isolated by expression cloning (35). This technique represents a viable strategy for the mapping of B cell epitopes.

The precise delineation of antigenic triggers of allergic disease may facilitate targeted disruption of specific allergic responses without risk of compromising broader immune functions. Therapeutically, 2 general strategies could follow: 1) induction of antigen/allergen specific tolerance or, 2) blocking of immune induction with altered T cell and/or IgE specific ligands.

The emergence of the 'next big thing' in the immunotherapy of allergic disease may well be at the point furthest upstream – disease initiation. The importance of early intervention in clinical care foretells the importance of preventative therapy. What doesn't begin, doesn't matter. The nonspecific therapies of today clearly have associated payoffs for patient management, but may be just a step along the path to the final "final answer". The issues are more than academic. Prevalence of atopic disease is on the rise worldwide. Tacrolimus has raised the bar, but specifically speaking, the sweepstakes have just begun.

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Viewpoint 4

Current theory on atopy

The prevalence of atopy has dramatically increased worldwide. Epidemiological studies of this phenomenon has led to the *Hygiene Hypothesis*. That is, modern day cleanliness has decreased micro-organism stimulation of the immune system in the infant allowing potential persistence of a fetal immune response (1). Persistence of an immature immune response depends on the presence of certain predisposing genes and specific environmental exposures.

Helper T lymphocytes are critical for elucidation of an immune response and two types exist, Th1 cells and Th2 cells, which can be distinguished by their cytokine profile. Th1 cells mediate classic delayed-type hypersensitivity reactions to micro-organisms typified by IgG-mediated cell cytotoxicity and γ -interferon production whereas Th2 cells mediate reactions to parasites characterized by IgE production and histamine release. During pregnancy, Th1 cells in the fetus decrease to prevent placental toxicity. As a result, infants are born with Th2 cells (2). *In utero*, exposure to low concentrations of allergens can sensitize Th2 cells.

The fate of these Th2 cells is dependent upon the type of antigen exposure. Neonatal bacterial infections drive helper T cells back to a Th1 profile. Furthermore, post-natal exposure to high concentrations of allergens, such as dietary allergens, leads to T-cell anergy or deletion, whereas exposure to low concentrations of allergens, such as aeroallergens, leads to either Th1 or Th2 responses.

Debate on atopic dermatitis (AD)

The debate concerning the role of allergy in AD has been particularly controversial. Gross examination of atopic lesions reveals morphology very different from urticaria and wheals, commonly thought of as dermatologic manifestations of allergic responses.

Histologic examination of acute and subacute lesions suggests a cell-mediated hypersensitivity reaction based on dermal monocyte and lymphocyte infiltration (3). However, it is now clear that mononuclear infiltrates rich in Th2 cells can promote IgE-mediated disease. On closer examination of acute AD lesions mast cells show evidence of degranulation. Furthermore, more chronic lesions contain eosinophils or their remnants (4).

Defining atopic dermatitis as an allergy me-

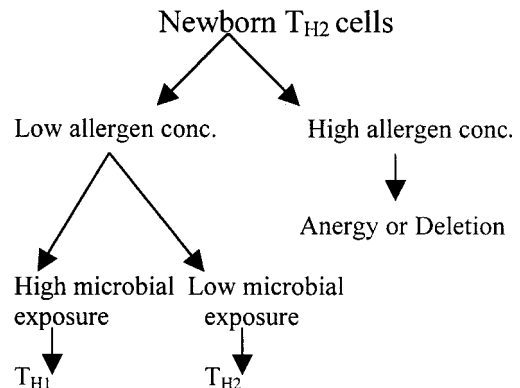


Figure 1. Proposed mechanism of immune system development.

diated disease demands a more precise analysis than pure histologic examination allows. Identification of cytokine expression by the dermal infiltrate is crucial and has provided evidence that lymphocytes in early lesions are mostly Th2 cells (5).

Basic science evidence

Allergy is defined as an antigen induced biologic response that leads to either immunity or allergic disease whereas atopy is described as an IgE mediated illness (6). IgE-mediated reactions release proinflammatory cytokines that recruit eosinophils, basophils, monocytes, neutrophils and CD4 cells (7).

Evidence that atopic dermatitis is antigen induced requires proof that allergen presentation elicits a Th2 response as seen in IgE-mediated reactions.

Kimura et al. correlated specific allergens to the induction of Th2 cytokines and symptoms of atopic dermatitis. His studies found that House Dust Mite lymphocytic proliferation (HDM-SIF) was elevated in atopic dermatitis infants. In addition, HDM-SIF positively correlated with the severity of infantile atopic dermatitis, absolute number of peripheral blood eosinophils and IL-5 production (8).

Yamada et al. performed a temporal analysis of the cytokines and dermal infiltrates present after patch testing with crude dust mite extracts on atopic dermatitis patients who had high levels of mite-specific IgE (9).

They found that 2 hours after allergen challenge, a perivascular infiltrate of small mononuclear cells appeared followed by an eosinophilic infiltration,

| Allergen | # Support/Total No. Studies | Percentage |
|------------|-----------------------------|------------|
| Pollen | 3/3 | 100% |
| Mold/Fungi | 14/15 | 93% |
| Dander | 10/11 | 91% |
| Dust Mite | 27/33 | 82% |
| Food | 54/70 | 77% |

Figure 2. Clinical studies examining the role of allergy in atopic dermatitis. (unpublished data)

which began at 6 hours and peaked at 24 and 48 hours. IL-4, 5 and TNF- α were first detected at 2 hours. Yamada concluded that Th2 cytokines elicited an eosinophilic infiltration in allergen mediated atopic dermatitis patients (9).

Leiferman et al. support the theory that eosinophils play a major role in atopic dermatitis, despite their histologic absence in acute lesions. They used immunofluorescence to detect eosinophil-derived extracellular major basic protein in the elastic fibers of the upper dermis. This major basic protein was found in greater amounts in atopic skin lesions than in unaffected areas of the skin (10).

Clinical evidence

We utilized an Evidence Based Medicine approach to evaluate the clinical studies in the English literature for the role of allergy in atopic dermatitis. Medline was searched between 1966–2000 for diagnostic, therapeutic and prognostic studies, examining atopic dermatitis and dander, dust-mite, food, fungi, or pollen. The studies were separated according to authors' conclusions into those that supported and those that contradicted the theory of allergy mediated atopic dermatitis. Fig. 2 represents a summary of the preliminary results.

The strongest studies in evidence based medicine are randomized, placebo controlled clinical trials which have a large enough number of patients to avoid α and β errors. Perhaps the most convincing clinical trials are those that exhibit improvement in atopic dermatitis after allergen avoidance measures.

One such study, utilized doubleblind placebo controlled oral food challenges on 34 patients with atopic dermatitis to diagnose food allergy. A prospective follow-up study at 1 to 2 and 3 to 4 years examined patients who adhered to allergen elimination diets. Patients who followed the diets experienced significant improvement in their eczematous lesions (11).

Another study, by Ricci et al., examined the effect of house dust mite avoidance measures in children with atopic dermatitis. This placebo controlled trial demonstrated that by encasing mattresses and pillows, weekly hot washes of bedding, frequent vacuum cleaning of living room and bedroom, no pets, and frequent washing of soft toys and carpets, the dust mite allergen load taken from the children's beds decreased as did the severity of their eczema (12).

Summary

In summary, the evidence supporting atopic dermatitis as an allergen-mediated disease is becoming increasingly apparent. Allergen avoidance measures have proven to be effective in the treatment of atopic dermatitis in some patients.

Although it appears that allergic mechanisms do not play a role in all atopic dermatitis patients, the majority of clinical studies seem to favor the hypothesis.

According to Akdis et al., approximately 10% of the atopic dermatitis patients they examined had a nonallergic form as evidenced by normal serum IgE levels and no evidence for IgE sensitization (13).

Interestingly, Valenta et al. described the molecular characterization of an autoallergen identified through IgE antibodies found in the sera of atopic dermatitis patients (14). Though further investigations are necessary, perhaps it is these patients with autoallergens that complicate studies supporting allergen-mediated atopic dermatitis.

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Commentary 1

Within the next decade, treatment of allergic diseases will completely change.

Currently, most diseases such as allergic contact dermatitis, atopic dermatitis, asthma or rhinitis are being treated almost exclusively in a symptomatic fashion, either by a nonspecific blockade of immune effector mechanisms – such as mediator release – that occur late during the course of the pathological immune response, or by inducing a state of general immunosuppression. These approaches do not account for the immune system's most distinctive feature, its ability to selectively mount different types of immune responses towards various antigens at the same time. Thus, the aim of future immunotherapy will be to specifically regulate certain immune responses while leaving the rest of the immune system unaffected.

This aim can be reached by various approaches: Firstly, more specific inhibitors of immune effector mechanisms will be designed, such as specific antibodies against cytokines (e.g. TNF) or immunoglobulins and their receptors. By this approach, immune responses can be blocked with fewer side effects and somewhat more specificity than with the broad-acting immunosuppressants that are currently being used.

Secondly, antigen-specific treatment modalities will be designed with the aim of switching a pathological immune response towards a physiological one, such as by shifting a Th2 response into a Th1 response (e.g. in atopic diseases), or by inducing regulatory T cells which will control the activation of immune effector T cells, resulting in the generation of specific immune tolerance (e.g. in allergic contact dermatitis or in autoimmune diseases).

To reach that goal, it will be necessary to better understand the mechanisms how immune responses are generated and shifted towards the various types of immune reactions, and to then use the body's own ways to generate and modulate immune responses to do this in a therapeutic or preventive fashion.

In this respect, it is beneficial if immune responses can be modulated at their very beginning, i.e. at the stage of antigen presentation. Indeed, antigen presentation not only dictates whether an

immune response is induced or not, but it also determines what kind of immune response will be generated. The outcome of an antigen presentation event is dependent upon the type and functional state of the antigen-presenting cell, the type and functional state of the responding T or B cell, the antigen itself, and the microenvironment in which antigen presentation occurs.

Thus, if we learn how to control antigen presentation we will be able to selectively generate, or prevent, or shift, the induction of immune responses to any given antigen, and to prevent the generation of pathological immune responses.

In this respect, current vaccination regimes, using simply the antigen and arbitrarily selected, poorly defined adjuvants, will be replaced by much more specific and effective ways to immunize patients in a way that not only generates some sort of immune response, but the specific type of immune response that is desired. It is likely that this will be achieved by the use, or the specific targeting and functional modulation, of antigen-presenting cells such as dendritic cells, leading to the ability to specifically induce immunity or tolerance to any given antigen.

Thus, I presume that vaccination for allergies will become as normal as vaccination for infectious agents. However, once a pathological immune response was established and the more polarized it has become (e.g. by continuous antigenic stimulation), the more difficult it is to therapeutically modulate the type of immunity that is elicited upon additional contact with antigen.

Therefore, the future of immunotherapy will not be to vaccinate in order to shift or reverse existing pathological immune responses, but to prevent the development of such a pathological immune deviation. In this respect we might see preventive (tolerogenic) vaccination against common allergens to become as normal as (immunogenic) vaccination against bacterial or viral pathogens.

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Commentary 2

If ever one type of cell had to be blamed for the existence of allergies, anaphylactic type-1-reactions that is, it would have to be the mast cell (MC) (19). Cum grano salis, the activation of MC, resulting in the degranulation and de novo synthesis of an impressive plethora of proinflammatory mediators, may be held responsible for all symptoms of allergic reactions.

So far, unfortunately, antiallergic pharmacological therapies aimed at making MC degranulation impossible have had only limited success. However, considerable progress has been made over the past few years regarding our understanding of how MC activation may be inhibited, reviving the elusive concept of “MC releasability” (11).

It now appears feasible that several recently identified negative regulatory mechanisms of MC activation may be exploited for the development of new and better ways of treating allergies. Some of these mechanisms (summarized in Table 1) have been shown to virtually eliminate subsequent MC degranulation and/or MC production of proinflammatory cytokines.

While the development of therapeutic agents based on these findings may see us succeed in being able to shut down MC activation, this may not be what we were looking for.

Firstly, targeting inhibitory receptors will not be MC specific and other cell types will be affected also. Secondly (and more importantly), is the elimination of functional MC really what we want, considering that MC may operate as important physiological modulators of tissue remodelling connective tissue turnover and angiogenesis (14, 15) and in the light of recent findings showing that MC may be beneficial to the host in the context of innate immune responses in bacterial infections (8)? Indeed, we know that the pharmacologically induced increase of MC numbers significantly improves survival in a murine model of acute septic peritonitis (13).

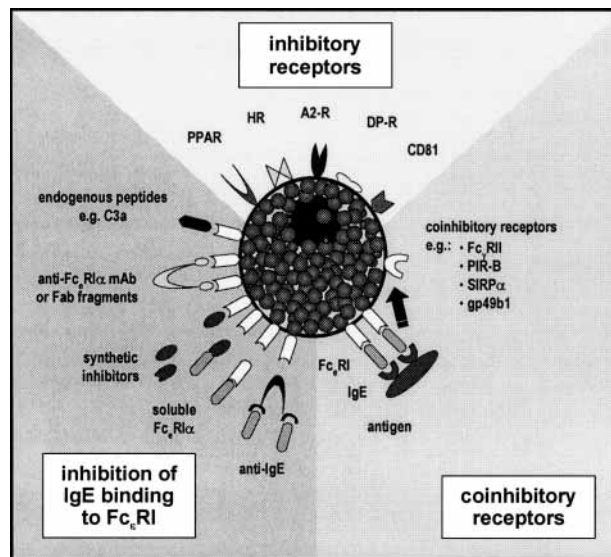


Figure 1. Selected inhibitory mechanisms of MC activation for abbreviations and references see text.

Therefore, it appears even more promising to work exclusively with mechanisms inhibiting Fc_εRI-mediated MC degranulation, leaving other ways of MC activation untouched (Fig. 1). This may be achieved by making use of the ever growing families of coinhibitory receptors of Fc_εRI activation identified over the past few years. Fc_εRI-mediated activation of MC has been shown to be inhibited by coligation of Fc_γRII (5, 25), gp49b1 (9), the paired Ig-like receptor PIR-B (3), and signal regulatory proteins of the alpha subtype SIRP α (10) among others (for review see 20).

Alternatively, and first examples of this approach are being tested in clinical settings already, we ought to try to shut down Fc_εRI/IgE-mediated MC activation by interfering with the binding of specific IgE and/or antigen. Several candidates appear to be promising in this respect. Takai et al.

Table 1. Selection of recently described inhibitory mechanisms of MC-activation

| Receptor | System | Inhibition of | Reference |
|--|---------------|-----------------------------------|-----------|
| peroxisome proliferator-activated receptors (PPAR) | HCMC | cytokine production degranulation | 21 |
| prostanoid DP-receptor (DP-R) | Rat PMC | degranulation | 4 |
| histamine receptors (HR) | Rat PMC HMC-1 | cytokine production | 2, 12 |
| high affinity binding sites for benzodiazepines | MMC | cytokine production degranulation | 1 |
| CD81 | RBL PCA | degranulation PCA | 7 |
| adenosine A2 receptor (A2-R) | HCMC | degranulation | 22 |

Abbreviations: HCMC=human cultured MC, PMC=peritoneal MC, HMC-1=human leukemic MC, MMC=mouse MC, RBL=rat basophilic leukemia cells, PCA=passive cutaneous anaphylaxis.

have reported that pretreatment of human basophils with Fab fragments that recognize the Fc_εRIα chain inhibits subsequent MC degranulation by cross-linking Fc_εRI. Likewise, Fc_εRI-mediated degranulation is inhibited by high-affinity oligonucleotide ligands to IgE (26) or designer peptides modeled to compete with IgE binding to Fc_εRI (16). Interestingly, endogenous peptides (like C3a) have also been reported to inhibit MC degranulation by binding to Fc_εRI (6).

Let us lastly not forget the possibility to inhibit MC activation at the level of signal transduction. We know that targeting receptor-associated protein kinases like Syk that are activated by cross-linking Fc_εRI will effectively inhibit MC degranulation (17, 18). Yet, this affects signal transduction pathways in lots of other cell types. The goal is again to provide Fc_εRI-selective, MC-specific inhibition of activation, and (just maybe) MC themselves could help us do it. Exciting new data from Henry Metzger's group suggests, that keeping Fc_εRI busy with excess low affinity ligands inhibits signaling from Fc_εRI binding high-affinity ligands and subsequent MC degranulation by using up critical kinases involved in Fc_εRI-mediated signaling (24).

While none of these leads are likely to result in new immunomodulatory therapeutic agents within the immediate future, in the long run, they may be the key to potently, selectively and specifically shutting down MC in allergic reactions. After all – isn't taking out the bad guys what we are really looking for...?

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