The Editors' Choice

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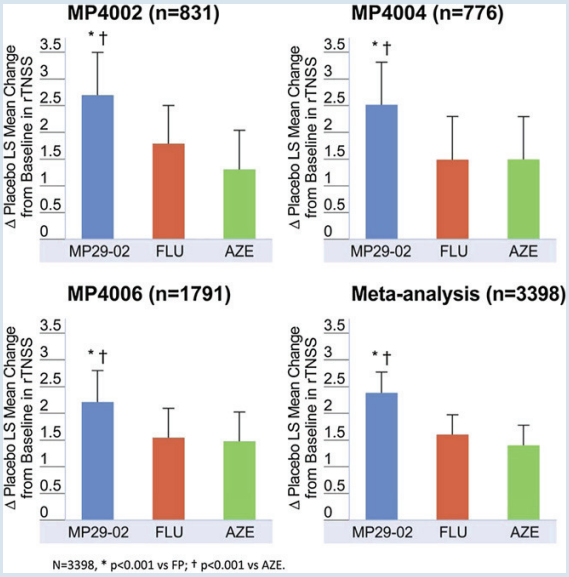
MP29-02: A major advancement in the treatment of allergic rhinitis

Intranasal corticosteroids (INSs) are the most effective therapy for the treatment of allergic rhinitis (AR). Little evidence exists to support the benefit of one INS over another. Furthermore, there is a paucity of head-to-head data involving INS therapy, with most studies focusing on patient preference and not on efficacy and safety. In the current issue of the *Journal*, Carr et al (p 1282) compare, for the first time, the efficacy of MP29-02 (a novel azelastine/fluticasone propionate formulation) with fluticasone propionate, azelastine, and placebo using the same formulation in 3398 patients with moderate-to-severe seasonal AR in 3 multicenter, randomized, double-blind, placebo-controlled, 14-day, parallel-group trials. In these 3 head-to-head comparisons, they reproducibly demonstrate that MP29-02 is significantly more effective than intranasal fluticasone or azelastine (see Figure). The improvement of MP29-02 over standard therapy was substantial, occurred faster (up to 5 days faster than fluticasone and up to 7 days faster than azelastine), and was more complete, with 1 of 8 MP29-02–treated patients exhibiting complete/near-complete symptom resolution. With this improved efficacy, there were no new safety concerns beyond those of currently marketed fluticasone and azelastine. Given these findings, MP29-02 can be considered the drug of choice for the treatment of AR.



Effect of MP29-02, fluticasone propionate *(FP),* and azelastine *(AZE)* on the overall reflective total nasal symptom score *(rTNSS; AM + PM)* in patients with moderate-to-severe seasonal AR.

Allergen-specific immunotherapy reduced to 3 injections

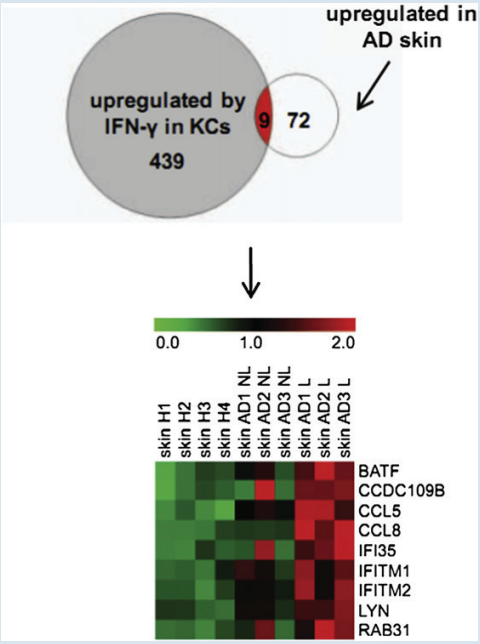
Allergen-specific immunotherapy is the only disease-modifying treatment of allergies, but it requires numerous allergen administrations over 3 to 5 years, so that less than 5% of patients with allergies choose immunotherapy. Senti et al (p 1290) could reduce the number of allergen injections to 3 by enhancing antigen presentation. First, allergen was injected directly into lymph nodes. Second, the allergen, recombinant cat dander allergen Fel d 1, was fused with an intracellular translocation sequence and with an invariant chain to enhance presentation through MHC class II to CD4 T cells. Such rapid intracellular translocation of the allergen has the additional advantage of reducing IgE cross-linking on mast cells, reducing skin test reactivity approximately 100-fold. In this double blind, placebo-controlled trial, patients with cat dander allergy received 3 intralymphatic injections within 2 months, either with modified Fel d 1 or placebo. Injections were practically painless and safe. Induction of regulatory T cells correlating to IgG_4 responses was observed, and nasal tolerance increased 74-fold ($P < .001$, vs placebo). In summary, intralymphatic immunotherapy with modified recombinant Fel d 1 elicited no adverse events, and 3 injections were sufficient to render patients with cat allergy tolerant. Reduced treatment duration might make immunotherapy more attractive for today's busy patient.

Innate antiviral responses at birth can predict the future

Viral respiratory tract infections are perhaps the most common cause of acute illness and a major factor in chronic sinusitis and asthma in childhood and later life, but why one patient might be more or less susceptible to infection is uncertain in almost all cases. In this issue Sumino et al (p 1267) studied cord blood monocytes obtained from a high-risk cohort of children with at least 1 parent with allergy or asthma and found that a decrease in the usual induction of *IFNG* mRNA in response to a common virus (respiratory syncytial virus) was predictive of an increase in upper respiratory tract infections (nose, ear, and sinus), pneumonias, and respiratory hospitalizations during the first year of life. Because the investigators studied the innate immune system, the findings challenge the previous dogma that the adaptive immune system (particularly a skewed T-cell response) is the primary determinant for susceptibility to viral and perhaps postviral illness. The findings also revise the conventional view that the *IFNG* gene is only active in lymphoid cells. Moreover, because the investigators studied the response present at birth, the observations also challenge the proposal that microbial hygiene in the childhood environment is the primary influence on viral sequelae.

IFN-γ–induced apoptosis of keratinocytes in patients with atopic dermatitis

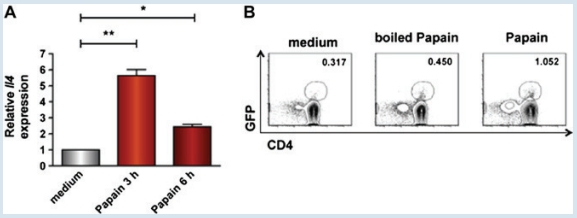
Atopic dermatitis is a common chronically relapsing skin disease. T_H2 bias with increased IgE levels are widely recognized hallmarks of extrinsic atopic dermatitis. However, it is less well known that in the chronic phase of skin inflammation, IFN-γ as a characteristic cytokine for T_H1 cells plays a role as a dominant factor and causes enhanced apoptosis of keratinocytes in the eczematous lesions of patients with atopic dermatitis. In this issue Rebane et al (p 1297) demonstrate that keratinocytes from patients with atopic dermatitis exhibit increased IFN-γ–induced apoptosis compared with keratinocytes from healthy subjects. Further expression analysis demonstrated differences in apoptosis-related genes (*ADM*, *NOD2*, *PCSK9*, *ANXA5*, and *INNP5D*) and upregulation of IFN-γ–inducible genes in keratinocytes and skin from patients with atopic dermatitis. *In silico* analysis based on genome-wide single nucleotide polymorphism data supported the findings and showed evidence of an association between atopic dermatitis and single nucleotide polymorphisms from the *IFITM* cluster: the *RAB31*, *DUSP1*, and *ADM* genes. It is possible that altered expression of multiple apoptosis-related and IFN-γ–inducible genes is responsible for apoptosis of keratinocytes, leading to eczema, and influences the development of chronic skin inflammation in patients with atopic dermatitis. The study outlines the complexity of atopic dermatitis as a heterogeneous and multifactorial disease and proposes several potential novel genes that might play a role in the pathogenesis and can be used to develop novel treatment modalities in patients with atopic dermatitis.



Nine genes that are upregulated in the skin from patients with atopic dermatitis *(AD)* can be induced by IFN-γ in keratinocytes *(KCs)*.

Naive T lymphocytes jump-start allergic responses

The earliest steps of allergen recognition leading to differentiation of naive T lymphocytes into T_H2 cells are still a matter of debate. Allergic responses to protease allergens, such as the papaya-derived food allergen papain or parasitic infection, are associated with basophil recruitment to draining lymph nodes. Basophils have the capacity to present antigen to naive T cells and promote T_H2 differentiation directly or indirectly through production of the cytokine IL-4. How papain induces basophil migration to lymph nodes is unknown. In this issue Liang et al (p 1377) elucidate a pathway in mice in which naive T lymphocytes first encounter and recognize papain through protease-activated receptor 2 (PAR2) and initiate T_H2 differentiation. When mice were injected subcutaneously with papain, naive T cells produced basophil-attracting chemoattractant cytokines and IL-4 (see Figure), leading to basophil accumulation in the lymph nodes. A subset of naive human peripheral blood T lymphocytes



Papain stimulates *Il4* gene expression *(left)* and IL-4 production (represented by green fluorescent protein, *right*) in naive CD4 T lymphocytes.

expressed PAR2 and responded to papain in a manner similar to their murine counterparts. These results suggest that there is an allergen recognition pathway mediated by naive T lymphocytes that express PAR2, which provide an early source of IL-4 upstream of basophils and antigen-restricted T_H2 differentiation. Furthermore, PAR2 antagonism can be explored for the treatment of allergic disease.

Cytomegalovirus and common variable immunodeficiency: An emerging relationship

Patients with common variable immunodeficiency (CVID) experience a spectrum of alterations in cellular immunity. Marashi et al (p 1349) profiled the global effect of cytomegalovirus (CMV) infection on immune effector cells in patients with CVID and implicated CMV as the driving force behind the CD4/CD8 ratio inversion characteristic of these patients. A subset of patients with CVID experience debilitating inflammatory disease, and the study focused on these patients to show that expansions of CMV-specific late effector $CD8^+$ cells correlated with the presence of inflammatory disease. Remarkably, these $CD8^+$ cells proliferated *ex vivo* in response to CMV antigen without exogenous costimulation, and supernatants from proliferating cells conferred proliferative capacity on CMV-specific $CD8^+$ T cells from healthy control subjects. IFN-γ and TNF-α were important for this proliferation. The authors previously detected CMV antigens at inflammatory sites in these patients, providing a plausible explanation for the persistent antigenic stimulation that is presumably required to drive this proliferative phenotype. Infliximab and ganciclovir have been used to manage CVID-related inflammatory disease, and this study provides a compelling rationale for a controlled clinical trial. More broadly, it emphasizes the global effect of CMV infection on cellular immunity and defines a novel system for studies of $CD8^+$ T-cell regulation.