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NEWS AND COMMENTARY

Allergy

Immunotherapy of allergic diseases by bacterial products

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Allergic diseases are characterized by excessive immunoglobulin E (IgE) production, mast cell degranulation, tissue eosinophilia and mucus hypersecretion. These responses also take place during infection with multicellular parasites, and are linked to the production of a characteristic set of cytokines by T helper (Th)2 cells. By contrast, many other microbial infections are associated with cytokine production by Th1 or Th17 cells. There have been extensive efforts to subvert the Th2 responses of allergic diseases by treatment with microbial products.

The paper by Fonseca *et al.* (e-pub ahead of print: *Immunology and Cell Biology* (15 March 2011); doi:1038/icb.2011.9) reports the effect of two microbial products on a mouse model of asthma.[1] The authors found that treatment with the combination of CpG-oligodeoxynucloeotides (CpG) and mycobacterial proteins reduced inflammation and airway hyperresponsiveness. The combination of CpG and mycobacterial proteins was significantly more effective than CpG alone on several parameters of airway inflammation, and the mycobacterial proteins alone had little effect. The beneficial effect of CpG and mycobacterial proteins depended on the Th1 cytokine interferon (IFN)-γ. CpG and mycobacteria have separately been the subject of extensive research for their potential to inhibit allergic diseases, and both types of agent have been tested (separately) in clinical trials of immunotherapy. The paper by Fonseca *et al.* is significant because it demonstrates improved efficacy when the two different agents are combined.[1]

The incidence of asthma and other allergic diseases has increased in developed countries over the past several decades. A popular explanation for this increase is the hygiene hypothesis, which states that reduced exposure to bacterial infections favours the development of Th2 responses. Therefore, therapy with bacterial products has been investigated as a possible mechanism to skew the immune system away from Th2-associated allergic responses.[2] However, not all observations fit neatly into a simple presentation of the hygiene hypothesis. There is evidence that bacterial infection may be associated with allergic diseases. For example, bacterial colonization of the airways at the age of 1 month was significantly associated with the subsequent development of wheeze, asthma and elevated total IgE.[3]

Immunotherapy is the only known way to treat the cause of allergic disease rather than ameliorate the symptoms. The many controlled trials of immunotherapy show that for subjects who respond, the result is as efficacious as pharmacological treatment.[4] The catch is that at least 3 years of treatment with 20–30 injections per year are required for an approximately 50% improvement. Furthermore, immunotherapy carries a risk of systemic allergic reactions. Adjuvants that can increase the efficacy and safety and reduce the treatment regimen of immunotherapy would be very useful. The strategy used in the paper of Fonseca *et al.*[1] has the potential to be adapted for clinical trials in the immunotherapy of allergic diseases.

There is extensive evidence in mouse models of asthma that therapy with CpG inhibits allergic responses,[2] but most clinical trials of CpG to date have had limited success. It is possible that the use of type A CpG (containing phosphodiester bonds) may be more effective than the more commonly used type B CpG, which have a phosphorothioate backbone, and which were used in the Fonseca *et al.* article.[1] While both type A and type B CpG bind to TLR-9, they have different effects on their target cells, which in humans are plasmacytoid dendritic cells and B cells. Type A CpG induce more type 1 IFN than type B ODNs, and do not upregulate major histocompatibility complex and costimulatory molecules. Type A CpG have the drawback of containing DNase-sensitive sites, but they can be protected by inclusion in virus-like particles.[5] A small trial for grass pollen allergy using a type A adjuvant with such protection produced extremely promising results that clearly warrant follow-up in a double-blind placebo-controlled trial.[6]

There has been extensive research on the possible protective effect of mycobacterial infection against allergic diseases. The impact of BCG vaccination on allergic diseases has been very controversial. A recent meta-analysis indicates that on balance BCG probably confers some degree of protection against subsequent development of asthma.[7] However, a trial on the use of BCG as an adjuvant for subcutaneous immunotherapy in established allergic disease did not find efficacy.[8] The paper by Fonseca *et al.* used a preparation of culture filtrate proteins, secreted by cultures of *M. tuberculosis*, which are highly immunogenic, and are being studied for use in tuberculosis vaccines.[1] It is possible that this preparation might contain adjuvants in addition to the mycobacterial proteins.

Although the results of Fonseca *et al.* seem promising, there are many important differences between model systems of mouse pulmonary eosinophilia and human asthma, only a few of which are described here.[1] A

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critical difference with respect to Th1-inducing adjuvants is that clinical asthma is characterized by increases in Th1 as well as Th2 cytokines.[9] Th1 cytokines are found in allergen-stimulated lungs and in peripheral blood mononuclear cells in asthma patients, and there is evidence that they are important for disease. Attention should be paid to the possibility that Th1-inducing adjuvants could increase the pathogenic process in the human hypersensitivity reaction. An encouraging feature of the Fonseca *et al*. paper is that although the therapy increased IFN-γ production, it was not associated with Th1-type inflammation in the lung.[1] Furthermore, humans have preexisting Th1 responses, while the mouse models usually have negligible Th1 elements. It is also apparent that Th17 cells have a role in human disease, especially in the neutrophilic component found in severe, steroid-resistant asthma.[10] Finally, there are also important differences between mice and humans in the mechanism of Th subset regulation. Mouse Th2 cells are very sensitive to inhibitory effects of the Th1-associated cytokines interleukin-12 and IFN-γ, while human Th2 cells are refractory to the direct effect of these cytokines and instead are downregulated by type 1 IFNs that do not directly promote human Th1 and Th17 responses.[11]

Thus, although the application of Th1 adjuvants for immunotherapy along with the hygiene hypothesis may need further distilling, we are in a golden age for the development of new adjuvants, with derivatives of natural microbial products and study of the innate immune system being at the forefront. It remains intriguing that understanding the interaction between infectious disease and susceptibility to allergic disease could lead to new therapeutics.

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