The gut as target organ for oral immunovaccination with allergen DNA: new hope for patients with anaphylactic reactions to food?


Abstract
Food allergy is a common and often fatal disease with no effective treatment. We describe here a new immunoprophylactic strategy using oral allergen-gene immunization to modulate peanut antigen-induced murine anaphylactic responses. Oral administration of DNA nanoparticles synthesized by complexing plasmid DNA with chitosan, a natural biocompatible polysaccharide, resulted in transduced gene expression in the intestinal epithelium. Mice receiving nanoparticles containing a dominant peanut allergen gene (pCMVArAh2) produced secretory IgA and serum IgG2a. Compared with non-immunized mice or mice treated with ‘naked’ DNA, mice immunized with nanoparticles showed a substantial reduction in allergen-induced anaphylaxis associated with reduced levels of IgE, plasma histamine and vascular leakage. These results demonstrate that oral allergen-gene immunization with chitosan–DNA nanoparticles is effective in modulating murine anaphylactic responses, and indicate its prophylactic utility in treating food allergy.

Comment
The management of patients with food allergy is unsatisfactory as the mechanisms underlying these reactions are not well understood and the diagnostic means to confirm food allergy on an objective basis are limited. Consequently, the clinical relevance of food allergy in the pathogenesis of gastrointestinal diseases is largely unclear. However, epidemiological studies suggest that food allergy is common, particularly in children, and often causes fatal reactions. The treatment options are often not successful as avoiding relevant food allergens may be extremely difficult, even if they could be clearly identified, and standard immunotherapy lacks efficacy. Because of the reported severe or even fatal reactions, which seem to be mostly IgE mediated, effective prophylactic and therapeutic strategies are urgently needed.

Roy et al report a new approach to the modulation of anaphylactic responses to food allergens using a murine model of peanut allergy. Susceptible strains of mice were treated orally with nanoparticles containing DNA coding for a major peanut allergen (ArAh2) complexed with chitosan, a natural polysaccharide derived from crustacean shells. Chitosan served as an delivery vehicle promoting adhesion to the mucosa and transport through the epithelial layer. Control animals received ‘naked ArAh2 DNA’ or were not immunised. The authors showed that oral delivery of chitosan–DNA nanoparticles resulted in gene expression in the intestinal epithelium. Subsequently, after pretreatment, mice were sensitised three times with crude peanut extract via oral and intraperitoneal administration, followed by intraperitoneal challenge with recombinant ArAh2 protein. In control animals, intraperitoneal challenge with ArAh2 protein caused a severe anaphylactic reaction with typical symptoms accompanied by increased plasma histamine concentrations, raised peanut specific serum IgE, and increased vascular permeability. In animals pretreated with chitosan–DNA nanoparticles, this reaction was substantially diminished. The authors provide evidence that the nanoparticles may act by improving local defence mechanisms, such as production of IgA, and by directing the immune response to a T helper cell type 1 response as indicated by increased IgG2a production. The data clearly show that oral immunisation with chitosan–DNA nanoparticles is effective in modulating murine anaphylactic responses. The authors claim that these findings may be of use as prophylactic treatment for food allergy.

DNA vaccination has been looked at as a possible treatment for allergic airway diseases, but was only effective if DNA was administered through parenteral routes (intramuscular, intradermal, subcutaneous). Here, Roy and colleagues show for the first time that oral DNA vaccination is also effective, provided that DNA is complexed with an appropriate delivery system such as chitosan; oral vaccination with naked DNA has been shown to be mostly ineffective. Oral vaccination is preferable to parenteral routes because of ease of administration and high patient compliance. Moreover, it generates both systemic and mucosal immunity. Finally, chitosan is a non-toxic, natural delivery system with lower risk potential when compared with viral and other vectors. Thus, Roy et al’s results seem to justify clinical studies to test the therapeutic potential of this approach. However, enthusiasm may be dampened by the fact that all of the available data are derived from animal studies, and that many important questions have still to be answered before clinical trials can be undertaken—for example, dose response and kinetic studies are lacking, long term effects have not been examined, and the results of repeated booster challenges with ArAh2-DNA nanoparticles were inconclusive. These limitations were also highlighted by Roy and colleagues. Their assumption, however, that a preventive vaccine model (as presented here) is preferable to a treatment model, is questionable because we have yet to clarify who should receive preventive immunovaccination, how ‘risk of food allergy’ should be defined, which potential allergens should be targeted, and when and how often the DNA complexes should be administered. Considering these open questions, oral immunovaccination with allergen DNA for the treatment of allergic reactions to food is some way off. In the meantime studies such
as Roy et al’s afford a tantalising view of a possible future and improve our understanding of the mechanisms under-
lying gastrointestinal disease.

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