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Plasmid DNA (pDNA) encoding an antigen or allergen and injected intramuscularly or intradermally is taken up by various somatic cells including antigen-presenting cells (APC). These cells synthesize the antigen, resulting in the induction of an immune response (1, 2). Both in experimental animals and in man (2, 3), pDNA vaccination results in relatively strongly cytotoxic T-cell responses, presumably because the intracellular antigen is processed and presented on MHC class I molecules. The antibody response, especially in man in early clinical trials, is less pronounced, presumably because only very small amounts of antigen are secreted, processed, and presented on MHC class II molecules by the transfected cells, as compared with exogenous antigens. Interestingly, pDNA encoding not only bacterial and viral antigens but also allergens, which normally induce a Th2 response, induces a Th1 response in mice and rats (4–6).

Furthermore, the pDNA-induced Th1 response is dominant over the Th2 response. Mice primed with pDNA failed to produce IgE antibodies after boosting with allergen in alum. Boosting with pDNA of mice having a pre-existing Th2 response resulted in a decrease of the IgE titre and interferon- γ (IFN- γ)-secreting Th cells. Ovalbumin pDNA immunization also inhibited the eosinophilic infiltration in the lung after OVA inhalation. Analysis of the mechanism of the pDNA-induced Th1 response showed that noncoding immunostimulatory DNA sequences (ISS) having the motif 5'-purine-purine-CG-pyrimidine-pyrimidine-3' in the plasmid backbone were mainly responsible for the induction of the Th1 response (7). The ISS induce the secretion of IFN- γ , IFN- α , IFN- β , Interleukin-12 (IL-12), and IL-18 (6, 8) from APC, all of which are cytokines that cause the differentiation of naive T helper cells into Th1 cells. Oligodeoxynucleotides (ODN) having the CG motif also

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induce Th1 responses when mixed with allergen (8) and injected.

To take advantage of the Th1-inducing ISS-ODN and the high titre antibody-inducing ability of protein antigens such as allergens, we chemically conjugated the short ragweed allergen Amb a 1 (Amb a 1) to a 22-mer ISS-ODN at a mean ratio of 1:4 and investigated the immune response to such conjugates in BALB/c mice (H. Tighe, H. Spiegelberg, E. Raz, in preparation). The conjugates induced an earlier and stronger Th1 response to Amb a 1 than the mixture and at a 25-fold lower ISS-ODN dose. Amb a 1-ISS-ODN conjugates were also compared with Amb a 1 in an immunotherapy model of mice first primed with Amb a 1 in alum. When the sensitized mice were treated with conjugates or Amb a 1 and subsequently challenged with Amb a 1, the conjugates had a much stronger Th1-inducing

effect during the treatment period and prevented a rise in the IgE titre, reduced the IL-5 secretion by Amb a 1-specific Th cells, and induced higher IFN- γ secretion by T cells after Amb a 1 challenge. Furthermore, a 30-fold higher concentration of conjugate was necessary to induce the same amount of histamine release from basophils of ragweed-sensitive donors than Amb a 1, suggesting that the conjugates may induce less anaphylactic reactions in man than classical immunotherapy. Although allergen pDNA immunization has not yet been tested in man for efficacy, the preclinical data of immunotherapy with allergen-ISS-ODN conjugates suggests that they may be superior in induction of high titre "blocking" antiallergen IgG antibodies and downregulation of a pre-existing allergic Th2 response to allergen pDNA or classical immunotherapy in man.

References

1. Ulmer JB, Donnelly JJ, Parker SE, et al. Heterologous protection against influenza by injection of DNA encoding a viral protein. *Science* 1993;259:1745-1749.
2. Raz E, Carson DA, Parker SE, et al. Intradermal gene immunization: the possible role of DNA uptake in the induction of cellular immunity to viruses. *Proc Natl Acad Sci U S A* 1994;91:9519-9523.
3. Wang R, Doolan DL, Thong PL, et al. Induction of antigen-specific cytotoxic T lymphocytes in humans by a malaria DNA vaccine. *Science* 1998;282:476-480.
4. Raz E, Tighe H, Sato Y, et al. Preferential induction of a Th1 response and inhibition of specific IgE antibody formation by plasmid DNA immunization. *Proc Natl Acad Sci U S A* 1996;93:5141-5145.
5. Hsu CH, Chua KY, Tao MH, et al. Immunoprophylaxis of allergen-induced immunoglobulin E synthesis and airway hyperresponsiveness *in vivo* by genetic immunization. *Nat Med* 1996;2:540-544.
6. Spiegelberg HL, Tighe H, Roman M, Beck L, Raz E. Downregulation of IgE antibody formation by allergen gene immunization. *ACI Int* 1998;10:52-58.
7. Sato Y, Roman M, Tighe H, et al. Immunostimulatory DNA sequences necessary for effective intradermal gene immunization. *Science* 1996;273:352-354.
8. Roman M, Martin-Orozco E, Goodman J, et al. Immunostimulatory DNA sequences function as Th1 inducing adjuvants. *Nat Med* 1997;3:849-854.