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EDITORIAL REVIEW

Can persistent IgE responses be suppressed?

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INTRODUCTION

Since the discovery of IgE in the late 1960s (Ishizaka, Ishizaka & Hornbrook, 1966; Johansson & Bennich, 1967) several animal models have been developed to study the regulation of IgE. IgE responses in atopic people are typically long lived and can be maintained when they are no longer exposed to allergen as in hay fever patients outside the pollen season. Such responses have proved difficult to produce in most species, with the exception of mice, and after an initial burst of IgE when first immunized, the response generated is rapidly suppressed. The artificial induction of IgE responses in rodents has required the use of adjuvants such as aluminium hydroxide and *Bordatella pertussis* or concomitant nematode infection (Jarrett & Stewart, 1972).

T cells play a central role in regulating IgE responses (Okumura & Tada, 1971a; Katona, Urban & Finkelman, 1988), and as well as providing help for IgE B cells, they are capable of suppressing both primary and secondary IgE responses (Okumura & Tada, 1971b; Holt, Batty & Turner, 1981a). Thus two opposing functions for T cells in IgE regulation can be seen. These effects are mediated at least in part by T cell-derived cytokines. High levels of interleukin-4 (IL-4) were found to potentiate IgE synthesis from lipopolysaccharide (LPS) stimulated murine B cells *in vitro* (Coffman & Carty, 1986) and this effect could be antagonized with interferon-gamma (IFN-γ) (Snapper & Paul, 1987). Anti-IL-4 antibody (Finkelman *et al.*, 1986, 1988a) or IFN-γ (Finkelman *et al.*, 1988b) both suppress antigen and *Nippostrongylus braziliensis*-induced IgE responses *in vivo*. With *N. braziliensis* infestation, IgE levels spontaneously decline following worm expulsion but similar effects were also seen with anti-IL-4 and IFN-γ in *Heligmosomoides polygyrus*-infested mice, where the worm is not expelled and IgE levels do not fall (Finkelman *et al.*, 1990).

The secondary IgE response produced with antigen and $Al(OH)_3$ was largely but not completely inhibited with anti-IL-4 (Finkelman *et al.*, 1990); these investigators conclude that the role of IL-4 in the maintenance of an IgE response is to recruit new cells to secrete IgE rather than to sustain the secretion of IgE by existing IgE plasma cells. However, it is not yet clear what proportion of the human IgE response is derived from fully differentiated, and possibly radio-resistant B cells compared with newly generated IgE B cells. Until we are clear what proportion of IgE is generated through these two types of cell, it is difficult to design IgE modifying agents which would act on the persistent human IgE response.

The production of IFN-γ and IL-4 is restricted in different subpopulations of murine CD4 T cells, Th1 and Th2 (Mosmann *et al.*, 1986), although it is now clear that there are several other subpopulations of CD4 T cells which show a different spectrum of cytokine production. CD8 T cells may also be involved in the regulation of IgE responses and inhalation of allergen in rats has been shown to generate IgE-specific suppressor T cells that are of the CD8 phenotype (Sedgwick & Holt, 1985). Cloned murine CD8 T cells have been shown to produce large amounts of IFN-γ (Fong & Mosmann, 1990) that could suppress IgE, and some rat CD8 T cells are a rich source of IFN-γ (unpublished observation).

PERSISTENT IgE RESPONSES: ANIMAL MODELS

In assessing the ability of vaccines or other drugs to manipulate the IgE response it is essential to distinguish the normal rise and fall in IgE following immunization from a persistent IgE response. Most mouse strains (Holt *et al.*, 1981c) and some strains of rat (Jarrett, 1978), when immunized with antigen alone or with an adjuvant such as $Al(OH)_3$ or *B. pertussis*, produce a transient IgE response; as do non-atopic humans immunized with ragweed antigen and $Al(OH)_3$ (Marsh, Lichtenstein & Norman, 1972). Furthermore, exposure to food antigens in early life causes a transient IgE response to milk or egg in some infants (Hattevig *et al.*, 1984).

Year-long high levels of serum IgE antibody to grass pollen are maintained without constant exposure to allergen. It is likely to be this persistent IgE response that needs to be modified. Any animal model that is used to test potential IgE-suppressive treatment must distinguish between these two patterns of IgE response. Ongoing human IgE responses can be boosted and it is a feature of hay fever that IgE antibody levels to grass pollen rise during the pollen season and fall afterwards. Parenteral immunization with ragweed pollen antigen prior to the pollen season can suppress this seasonal boost, indicating that at least some of the IgE response is amenable to manipulation (Levy & Osler, 1967; Yunginger & Gleich, 1973).

Infestation with nematode parasites *N. braziliensis* or *Ascaris suum* results in persistent IgE responses in most strains of mouse (Mota *et al.*, 1969) and some strains of rat (Rousseaux-

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Provost, Bazin & Capron, 1977). While these are undoubtedly useful models for studying IgE regulation, it is not clear to what extent they mimic the long-lived IgE responses seen in atopic humans.

Persistent IgE responses can be produced in some inbred strains of mouse immunized with small quantities of antigen alone (Holt *et al.*, 1981c) or together with an adjuvant such as *B. pertussis* or $Al(OH)_3$ (Vaz, Vaz & Levine, 1971). This response appears to be refractory to X-irradiation (Okudaira & Ishizaka, 1981; Holt, Leivers & Batty 1981b). Long-lived IgE responses can also be produced in rats following repeated administration of ricin and antigen in low as well as high IgE responder strains of rat (Thorpe, Murdoch & Kemeny, 1989; Diaz-Sanchez & Kemeny, 1990a). It is worth noting that ricin is preferentially toxic for some CD8 T cells (Diaz-Sanchez & Kemeny, 1990b).

What is not yet clear is whether the long-lived IgE response is solely maintained by long-lived plasma cells (Holt *et al.*, 1984) or if these cells are continually generated. Indeed, the overall IgE response may constitute a combination of these. When evaluating different materials for their ability to influence IgE responses, it is important to determine which compartment of the IgE response they are altering.

MODIFIERS OF IgE RESPONSES

Suppression of IgE responses has long been considered the ideal treatment for patients with respiratory allergy. The approaches which have been studied can be divided into immunological reagents, immunosuppressive drugs and modified allergens.

Immunological reagents

Several immunological reagents have been investigated for their ability to suppress IgE. Antigen-specific IgE responses in newborn rats were shown to be suppressed by maternal IgG antibody (Jarrett & Hall, 1979, 1983) but such antibodies did not have any effect on the generation or maintenance of IgE responses in adult animals. Anti-idiotypic antibodies, produced following immunization with antigen, were reported to suppress nascent IgE responses (Blaser, Nakagawa & de Weck, 1980) and the induction of anti-IgE autoantibodies in rats was shown to reduce primary IgE responses to ovalbumin (Marshall & Bell, 1989). Finally, IFN-γ and IFN-α have both been used to treat patients with hyper-IgE syndrome with variable results (Souillet, Rousset & de Vries, 1989; Leung *et al.*, 1989).

Immunosuppressive drugs

Cyclosporin A (CyA) has been reported to suppresses ongoing IgE responses (Okudaira *et al.*, 1986). The precise mechanism for this is not known but CyA is known to augment delayed-type hypersensitivity (DTH) reactions (Aldridge & Thompson, 1986). However, Th1 T cell clones were found to be more readily inhibited by CyA than Th2 clones (Gajewski, Schell & Fitch, 1990) and, administered during the nascent IgE response, CyA enhances IgE production (Chen *et al.*, 1989). Other cytotoxic drugs, such as cyclophosphamide (Taniguchi & Tada, 1971), also enhance rather than suppress IgE responses.

Modified allergens

Various forms of modified allergen have been identified as being capable of suppressing IgE responses in animal models. One reason why these have not been more successful is that they were originally shown to suppress IgG rather than IgE. The design of IgE-specific suppressor materials should be based on the known requirements for IgE antibody production.

The use of denatured allergens (allergoids) in animal models and in humans

Allergoids are allergens which have been chemically modified, for example with gluteraldehyde (Patterson *et al.*, 1973), formaldehyde (Marsh, 1975) or urea (Ishizaka *et al.*, 1974) so that they have a reduced ability to trigger mast cells through IgE but can still have immunological effects. It is possible to suppress IgE responses in mice with urea-denatured allergen (Takatsu & Ishizaka, 1975) and this effect can be transferred with splenic T cells (Takatsu & Ishizaka, 1976). As reported in this issue, once generated, IgE-specific suppression is long-lived (HayGlass & Stefura, 1990), but there is no evidence that allergoids are capable of suppressing ongoing IgE production and they have proved to be no more effective than native allergen in humans (Norman, Marsh & Lichtenstein, 1979). One possible advantage of allergoids is that fewer injections are required, compared with native allergen.

Allergen–polymer complexes (tolerogens)

Dinitrophenyl phosphate (DNP) and benzylpenicilloyl (BPO) coupled to polymerised D-glutamic acid–lysine (D-GL) have been shown to suppress IgE and IgG antibodies to DNP in mice (Katz, Hamaoka & Benacerraf, 1973; Chiorazzi, Eshhar & Katz, 1976). Similar effects were produced with murine immunoglobulin ($M\gamma G$) coupled to DNP (Lee & Sehon, 1975). The fact that the D-GL polymers are poorly immunogenic for T cells and the observation that spleen cells, taken from mice treated with DNP–$M\gamma G$ and transferred to irradiated mice, did not secrete anti-DNP antibodies following immunization with DNP–*Ascaris* suggested that hapten-specific B cells have been inactivated. Similar results have been achieved in dogs (Tse, Kepron & Sehon, 1978) and with polyvinyl alcohol (PVA)–DNP polymers (Hubbard, Lee & Sehon, 1981).

The studies of hapten tolerogens led on to experiments with antigen–D-GL polymers. Mice treated with ovalbumin–D-GL also showed suppression of IgE responses but this effect appears to be on T rather than B cells (Liu & Katz, 1979). Pre-administration of native antigen in a form which will not induce an IgE response can also generate IgE-specific suppressor T cells (Richman *et al.*, 1978; Ngan & Kind, 1978; Sedgwick & Holt, 1983, 1985). Chemical modification of ragweed *Amb a I* with polyethylene glycol (PEG) (Lee & Sehon, 1977) or methoxy polyethylene glycol (m-PEG) (Lee & Sehon, 1978) was reported to increase its ability to suppress IgE responses. As for the allergoids, there is no evidence that these tolerogens are capable of suppressing ongoing IgE production.

Indeed, those materials which have progressed to clinical trials have been found to be poor suppressors of specific IgE and, when tested in humans, none have been found to be any more effective than conventional immunotherapy (Bjorksten & Ahlstedt, 1984). The reason for this may be that these substances are at their most effective in the early phase of the IgE response and are less effective in long-lived responses. The risks inherent in the use of such vaccines to prevent the development of allergic disease in humans are so great that they are unlikely ever to be tested in this way.

CONCLUSIONS

Despite the fact that a considerable amount of effort has gone into the development of animal models and different strategies for suppressing IgE, the mechanisms regulating IgE biosynthesis are not known. It is still unclear, for example, whether the persistent IgE response is maintained by long-lived IgE plasma cells, or if B cells are continuously activated by newly generated or long-lived IgE helper T cells. The fact that seasonal rises in IgE antibody to pollen which can be suppressed by prior immunotherapy (Yunginger & Gleich, 1973) indicates that the component of the IgE response which is stimulated with pollen allergen is susceptible to suppression. Patients receiving bee venom immunotherapy show evidence of suppression of IgE antibodies to individual allergens (Kemeny *et al.*, 1983; Kemeny *et al.*, 1988).

In assessing these models it is important to consider whether they affect a nascent or an established IgE response. Furthermore, it is clear from animal studies that the way in which hapten conjugates suppress IgE is different from suppression induced with protein antigens which may limit their application in humans. The procedures reviewed here only seem able to suppress IgE responses during the early (1° and 2°) stage of the immune response, although this suppression can be long-lived (HayGlass & Stefura, 1990). None of the strategies devised so far are capable of suppressing the persistent IgE response once established (Ishizaka, 1985). This problem has been addressed by Finkelman *et al.*, (1990) while studying the effects of IFN-γ and IL-4 in mice. They have shown that some but not all of the parasite- and the $Al(OH)_3$-potentiated IgE response require the continued presence of IL-4. The proportion of the human IgE response that is IL-4-dependent or IFN-γ-sensitive is not yet known but treatments that alter the balance of these cytokines secreted by antigen-specific T cells may hold the clue to turning off the persistent IgE response.

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