

ORIGINAL ARTICLE

The role of IgG antibodies in allergy and immunotherapy

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Abstract

In specific immunotherapy (SIT), a beneficial response is associated with an increase in allergen-specific IgG₄. This does not indicate that IgE-producing B cells have switched to IgG₄ production, because in human DNA, IgE is downstream from IgG₄. Thus, by conventional switching, B cells should produce IgG₄ before IgE. This presentation discusses three possible hypotheses explaining the favourable association between IgG₄ and SIT, including that SIT causes B cells to become regulatory. Regulatory B cells may produce cytokines like IL-10 that promote IgG₄ production. IgG₄ can undergo *in vitro* switching to create bispecific antibodies that recognize more than one antigen, which has important consequences for reducing IgE–allergen complexes in immunotherapy.

High levels of specific IgG₄ are, in general, considered favourable in specific immunotherapy (SIT). However, some confusion exists about the basis for the production of IgG₄ in SIT (1). Some believe it is because of a B cell switch from IgE to IgG₄ production. However, this cannot happen in B cells because conventional Ig-switching mechanisms allow switching from IgG₄ to IgE, but not vice versa. Therefore, IgG₄ production does not imply loss of IgE production. In fact, B cells may switch from IgG₄ to IgE production as part of a short-lived postseasonal increase in allergen-specific IgE. The airway mucosa contains everything needed to generate IgE-producing plasma B cells, including precursor B cells that produce either IgG₁ or IgG₄ (2, 3). In this context, generating IgG₄-producing B cells may be undesirable. Therefore, if IgG₄ is associated favourably with SIT, we must explore explanations other than IgE to IgG₄ switching in B cells.

Three major hypotheses may explain the association of IgG₄ with favourable SIT. The first is that IgG₄ production is an epiphenomenon, so IgG₄ is helpful, but its production mainly reflects conditions favourable for tolerance such as activation of T-regulatory cells to produce anti-inflammatory factors like interleukin (IL)-10 and transforming growth factor (TGF)- β . IL-10 increases IgG₄ production and affects regulatory T cells. Therefore, IgG₄ may not be protective, but might be a sign that regulatory T cells are producing protective IL-10.

A second hypothesis is that IgG₄ antibodies act as blocking antibodies. This classical explanation states that IgG₄ antibodies protect by blocking IgE-dependent allergen-

induced activation of mast cells. Blocking antibodies are thought to neutralize allergen so it no longer activates IgE-sensitized mast cells. This may be a part of the protective effect of IgG₄, but another more likely explanation is interference with the activation of T cells. IgE enhances allergen-induced activation of T-helper (Th)2 cells, whose major role may be inducing inflammation. In this case, the pro-inflammatory activities of Th2 cells are promoted by IgE. If blocking antibodies interfere with allergen–IgE interaction, this may lead to reduced activation of proinflammatory Th2 cells.

The third hypothesis is that B cells both make antibodies and are good cytokine producers. IL-10-producing B cells have been found in mice and in humans. IgG₄-producing B cells may or may not be the same cells that produce IL-10, so IL-10 may be acting in an autocrine fashion. If a B cell is induced by some mechanism to switch to producing IL-10, then IL-10 induces that cell or similar cells in the environment to switch to making IgG₄. As mentioned above, IL-10 is also an anti-inflammatory agent. Whether an IgG₄-switched B cell might be a good producer of IL-10 is not yet clear. The relationship between the production of IL-10 and allergen-specific IgG₄ and the suppression of allergen-induced symptoms is still poorly defined (4).

IgG₄

IgG₄ is highly unusual immunoglobulin. It is a nonprecipitating antibody, so in double-diffusion assays, even at high

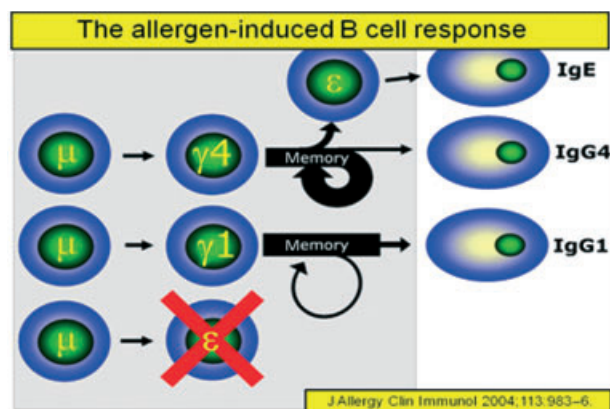


Figure 1 The allergen-induced B-cell response. Reprinted from Journal of Allergy and Clinical Immunology, 113/5, Rob C. Aalberse, Thomas A.E. Platts-Mills, How do we avoid developing allergy: Modifications of the Th2 response from a B-cell perspective, 983–986, Copyright (2004), with permission from Elsevier.

levels, it does not precipitate antigen. Even if SIT induces high levels of IgG₄, the antibodies produced are nonprecipitating. We explained this phenomenon in humans with experiments that generated recombinant IgG₄ antibodies, using antibodies against grass and cat allergens. We injected mice with a mixture of these two antibodies and found that the antibodies recombined within the mice, posttranslationally, to generate antibodies with affinity to both antigens (5). After only a few hours in mice, antibodies had switched partners and often became bispecific, meaning in the same antibody, one side had affinity to grass allergen and the other to cat allergen. The antibodies began as regular, symmetrical antibodies with two identical binding sites. Antibodies with one binding site to one antigen and another to a different antigen are monovalent towards a single antigen, making them nonprecipitating. The recombination does not happen spontaneously if the antibodies are mixed *in vitro*. This explains the nonprecipitation of the IgG₄ antibodies, and as far as we know, IgG₄ is the only antibody with this capacity.

This IgG₄ phenomenon is relevant to SIT because IgG₄ antibodies are quite inefficient at clearing allergens. Although the importance of allergen clearance is still debatable, effective allergen clearance requires antibodies other than IgG₄. However, IgG₄ may be more effective as an inhibitor of allergen presentation because it reduces complex size and hence reduces B-cell activation. In contrast, IgG₁ antibody, for example, can cross-link several allergens in a large, new complex that binds IgE to B cells much more efficiently than a small complex of IgG₄. In this sense, IgG₄ is a better blocking antibody than IgG₁, which might have more complex effects, including making IgE more potent.

In mice and humans, IgE memory cells are rare. IgE-producing cells circulating in the blood are preplasma cells that produce and secrete IgE spontaneously but lack B-cell markers. These cells are on their way from lymph nodes where they are produced to the bone marrow where they persist.

Therefore, the long-lived IgE response is not based on IgE memory cells, but occurs because plasma cells in the bone marrow can survive for many years. If we want to eliminate IgE production, we must eliminate these plasma cells, but this is almost impossible. IgE-switched B cells are killed in the lymph nodes because they lack surface IgE. Nonetheless, a booster effect exists, for example in allergy, reflected in the postseasonal increase described above. This is a natural, indirect switching and does not produce IgE from real IgE memory cells but from an allergen-specific, IgE-negative precursor, e.g. an IgG₄-switched B cell (Fig. 1).

IgE-producing plasma cells have two origins: they may go almost straight from early IgM-producing B cells to IgE secreting plasma cells. These cells have very little time for affinity maturation. They are likely to have a different specificity than IgE-producing cells that originate from the second path, which involves indirect switching, e.g. via an IgG₄ intermediate. These cells largely have different specificities.

These findings about IgG₄ show that SIT is not a single type of therapy because it addresses several types of allergic symptoms from allergic rhinoconjunctivitis to anaphylaxis. The same mechanism cannot be expected for all systems. Anaphylaxis is a rapid process that cannot be prevented through the relatively slow process of T-cell activation. Therefore, protection from anaphylaxis probably depends on fast-acting blocking antibodies. In contrast, reducing inflammation in the airways is much more likely to involve regulatory T cells. Multiple mechanisms are operative in SIT, so SIT is much more complex than introducing a single allergen and getting a single response. For example, treatment with a peptide might favourably affect a single T-cell clone, but T-cell clones with reactivity to other allergen-derived peptides are unaffected. In this situation, SIT will not give complete protection. That SIT is highly effective supports a complex regulatory system involving IL-10, but this is also nonspecific and not restricted to a single antigen. Thus, if we accept that IL-10 is important for immunotherapy, we must assert that the therapy is not completely allergen specific. Also, if blocking antibodies are important, we must use properly folded allergens. Denatured allergens or peptides will not be optimally effective in SIT.

Finally, recent additions to the field include the finding that IL-21 is to some degree the B-cell equivalent of IL-2. As IL-2 activates T-cell expansion, IL-21 helps B-cell development. IL-21 is mostly produced by T cells that are still helper cells. Another recent advance is that we now have a central factor, cMAF, that is involved in the upregulation of IL-10 in many cell types, including Th1 and Th2 cells, dendritic cells and macrophages. These cells have a common pathway in which overstimulation with allergen causes them to turn on the cMAF transcription factor-regulated pathway that is essential for IL-10 production. We also know that CD1 from Langerhans and other dendritic cells is important, at least in mice, for B-regulatory cells. CD1 is important for the immune system to react to glycolipids. Therefore, if we want to activate B cells, particularly B-10 cells, we may need to include glycolipids in activating cocktails.

Conflict of interest

Rob Aalberse has received consultancy fees from Indoor Bio-technologies and lecture fees from ALK-Abelló.

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