Comparison of relevance of specific IgG_4 and specific IgG measurement in human plasma samples

The following paper summarizes the arguments of specific IgG4 versus specific IgG testing. It should be noted that research relating to IgG4 and its association in food-mediated diseases is still ongoing.

I Biological/Physiological Aspects

- **Regulation of IgG4 antibodies:** As the immune response progresses there is a class switch from low-affinitity antibodies to higher-affinity antibodies. The requirements for IgG_4 and IgE antibodies are similar as both require IL-4/Il-13 stimulus and both are considered part of the Th2 response. Due to the arrangement of antibody light-chains on the chromosome a B-cell can switch sequentially from a IgG4 producing B-cell to a IgE producing B-cell (references 13-15 from publication 9).
- In contrast, IgG_1,IgG_2 and IgG_3 are less likely to play a prominent role in food-induced diseases as they are part of the Th1 immune response that is more prominent in the body's attack to antimicrobial challenges.
- Many studies report that in fact IgG_1 and IgG_3 antibodies are the only subclasses detected in response to different stimuli, which not only may prevent immediate appearance of IgG_2 and IgG_4 antibodies but also delay the class switch due to prominent IgG_1 response. This also leads to other phenomena in which IgG_4 antibodies outcompete other IgG antibodies. (1,2,3). Also, during the chronic exposure to allergens the absolute level of $sIgG_4$ increases and level of relative contribution of IgG_4 to total IgG is changing from 5% to up to 75% (9). This suggests that IgG_4 could be a better marker for antigens that have a long term effect on the immune system, such as foods presented in a leaky gut scenario.

- **IgG_4 and Immunotherapy:** Recent evidence has challenged the notion that successful immunotherapy is associated with elevated IgG_4 levels. For example, the Durham group showed that increased IL-10 production preceded both the clinical improvement and production of IgG_4 antibody, suggesting that IgG_4 levels are not causative for symptoms relief. The same group showed as well that the clinical benefit of immunotherapy upon treatment withdrawal is maintained, even though the allergen-specific IgG_4 levels are dropping. (4). We could conclude that these findings are not in conflict with a role of IgG4 in mediating food intolerances.

II Pathological Aspects

There are numerous papers in various diseases suggesting a strong association or causative relation of specific IgG_4 and these pathologies.

Food elimination diets in patients with IBS/Crohns Disease: There are studies showing a positive effect for IgG_4-based food elimination diets not only for Irritative Bowel Syndrome (e.g. 8, 10, 11, 12), but also related to Crohn's disease (6,7). These papers are not summarized here as they are well known within the relevant community.

III Experimental accessibility / dynamic range of values

In an in-house study looking at the relative values of IgG and IgG_4, we tried to take literature data and our own laboratory data into account. Our study results are in line with that shown by a large study conducted in China, which suggested that food specific IgG concentrations follow more or less a normal distribution in both healthy and symptomatic adults and therefore may generate many false positive signals (5).
Identical situation can be seen in attached personal communication: in a study looking at 1674 data points measuring patient's IgG_4 and IgG specific to identical food antigens, it could be demonstrated that the dynamic range of IgG_4 is clearly superior as compared to IgG. Similar to (5), a normal distribution of IgG values can be seen, centred on Reaction Class 2 and 3,

whereas in IgG_4 values, a large body of class 0 results and a more than fourfold amount of high positives occurred. In IgG_4, distribution of classes of results do not seem to follow a normal distribution shifted to the left, but clearly distinguishable populations of negative and (highly) positive reactions are formed.

Patient specific symptoms were not correlated in this study, but taking together literature based findings and the clear indications of diagnostic opportunities in the current stories, we conclude that IgG_4 is a better marker than IgG for food intolerance testing.

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