

Coffee Anyone? Are You at Risk of Allergy?

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It has been estimated that approximately 1.4 billion cups of coffee are consumed worldwide every day. Global average consumption is 4.6 kg per head per year; this figure is 5.6 kg in the European Union. In fact, coffee has become ingrained into many cultures and countries around the world, where it is regarded as an institution, with the best quality coffee being served around the clock. Records show that in Istanbul alone, there were at least 500 cafes towards the end of the 16th century, with the first cafes being opened in Europe by immigrants from Asia in around 1650. As coffee is enjoyed by many around the globe on a daily basis, it is appropriate to ask the question ‘Am I at risk of coffee allergy?’ This editorial explores coffee-bean allergy and the people at risk, in the light of recent original research findings presented in this issue of the *International Archives of Allergy and Immunology* [1].

When one examines the literature on coffee allergy, the first report on occupational asthma among workers of a coffee production plant was described back in 1950 by Figley and Rawling [2]. However, in this study, contamination by castor beans was implicated in the occupational allergic response. In 1961, Freedman et al. [3] reported in *Nature* that chlorogenic acid was the major allergen of coffee and castor beans. This work was later challenged and disputed by Layton et al. [4] in 1965, with a report published in the *International Archives of Allergy*

and *Applied Immunology*, which later resulted in the general rejection of chlorogenic acid’s role in allergic disease. It was not until 1978 that Lehrer et al. [5] reported on the extraction and analysis of coffee-bean allergens, demonstrating that coffee-bean allergens differ from the allergen of castor beans. This was followed by a number of important serological and clinical studies establishing the importance of green coffee beans in the trigger of allergic responses among coffee workers, with varied prevalence [6–11]. Almost two decades after their first report in 1978, the same group [5] reported that coffee workers could be sensitized by roasted coffee beans, suggesting that green coffee allergens may survive the roasting process [12], but occur in a lower concentration. With this in mind, it can be argued that the general coffee-consuming public may be at risk of allergy. This does not appear to be the case, however; the problem is among workers at coffee manufacturing plants, where sensitization occurs with green coffee-bean dust, which can be released throughout the entire plant, through inhalation or contact with the skin. In fact, recently it was shown that orally administered coffee in an allergic mouse model prevented allergy development [13]. So the consumption of coffee continues, with potential health benefits due it being a rich source of antioxidants [14].

Allergic reactions occur when a genetically predisposed individual comes in contact with the fine dust gen-

erated from green coffee beans, which is characteristic of coffee manufacturing plants. Despite extensive serological and clinical studies establishing the importance of green coffee-bean allergens in the triggering of occupational allergy among workers at coffee production plants, until now there has been no attempt to clone and characterize recombinant coffee allergens. In this issue of the *International Archives of Allergy and Immunology*, the seminal work of Manavski et al. [1] shows the successful identification, cloning, expression and immunological characterization of the first coffee allergen, Cof a 1. This study is significant as it is likely to contribute to the preparation of highly purified and standardized novel recombinant reagents for the specific and accurate diagnosis of coffee allergy in the very near future. Before embarking on the cloning work, they screened a population of 17 symptomatic coffee-industry workers for the presence of serum IgE to natural green coffee-bean extracts, using the commercially available ImmunoCAP system. It is important to note here that none of the subjects reported symptoms after drinking coffee, which is a further indication that observed symptoms were in response to the occupational exposure of the green coffee-bean dust. Two sera were identified for use in the screening of the green coffee-bean cDNA library to identify IgE-binding clones for further investigations. The authors chose the innovative phage display technique as a cloning strategy. This technique employs the display of heterologous recombinant proteins, encoded by the cDNA cloned into the phage, on the surface of an infectious phage. These recombinant proteins are repeatedly selected against the serum IgE and amplified, through a process known as biopanning, resulting in the enrichment and identification of those that possess a high affinity and binding to serum IgE. Indeed, after 3 rounds of affinity selection (biopanning), more than 60 IgE-binding phage clones had been successfully identified. Subsequent DNA sequencing and sequence database searches revealed the identification of a new coffee allergen, which was named Cof a 1 by the WHO/IUIS Allergen Nomenclature Subcommittee. A highly interesting finding of Cof a 1 is its 47% amino acid identity with coffee class III acidic endochitinase and other class III plant chitinases including concavalin B and hevamine. Hevamine, in particular, is a major latex allergen and is therefore an important source of allergy among health care workers; it further establishes the allergenic importance of Cof a 1 and the possible implication of these allergens as a new form of plant panallergens. However, before Cof a 1 and latex hevamine can be referred to as panallergens, it is

pivotal to perform essential allergenic cross-reactivity immunoassays between the two.

Once cloning and sequencing had been performed, Manavski et al. [1] set out to express and purify recombinant Cof a 1 (rCof a 1) to enable the completion of the final aim of their study of immunological characterization. They expressed soluble GST-Cof a 1-His fusion protein successfully and readily purified the recombinant protein (with the expected size of 55 kDa) using GST, followed by Ni-NTA and affinity chromatography under nondenaturing conditions. Although the authors should be congratulated for their fine efforts with the cloning and expression of rCof a 1, extreme caution needs to be exercised with regard to what effect the fusion partner of the recombinant allergen will have to its downstream allergenic activity. This is particularly important in their study, as there were 2 fusion partners, namely GST and His. One needs to question what effect such fusion partners will have on protein folding, and, more importantly, on the conformational IgE-binding epitopes. If such a recombinant allergen is to be used in diagnostics, it is highly desirable that it has an identical IgE reactivity to the natural allergen equivalent. A recombinant allergen with reduced IgE-reactivity, although not useful for diagnostics, may be useful in allergen-specific immunotherapy, as long as it maintains its T cell reactivity. Having said this, the removal of fusion partners from recombinant proteins is now readily achievable following purification. Indeed, the authors successfully demonstrated specific IgE reactivity to rCof a 1 from 3/17 (18%) of the sera, which included the 2 sera that reacted to the natural coffee-bean extract originally, suggesting that natural IgE-binding epitopes were maintained. As further confirmation, inhibition immunoassays for IgE-binding between rCof a 1 and green coffee-bean extract can be performed. Although the GST fusion partner can effect protein folding due to its rather large size (22 kDa) – and therefore compromise conformational IgE-binding epitopes – it can also be argued that the GST protein itself can be responsible for IgE-binding. The authors showed clearly that this was not the case because none of the 17 sera reacted with a purified recombinant GST. Moreover, none of the 8 control sera indicated IgE-binding to rCof a 1. Finally, they showed that Cof a 1-binding IgE was detected in a pool of sera from patients with latex allergy, providing preliminary evidence for cross-reactivity with latex chitinases and perhaps the involvement of a novel group of plant panallergens. However, such cross-reactivity assays need to be performed with purified latex chitinases before definitive conclusions can be drawn.

In conclusion, Manavski et al. [1] should be congratulated on their pioneering work on the cloning, expression and immunological characterization of the first coffee allergen, Cof a 1. Without a doubt, this publication will be of great interest to the readership of the *International Archives of Allergy and Immunology* and promises to open up new and exciting ways for further research, in the quest for more effective and standardized reagents for the diagnosis, and perhaps treatment, of occupational allergy to green coffee beans.

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