Toward a much-needed coming of age

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Toward a much needed coming of age: diagnosis of allergic sensitization to fungi

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Fungal sensitization and allergy are complex topics with many unanswered questions in terms of pathophysiology and unmet needs in clinical and laboratory practice. In recent years, advances in taxonomy, exposome science, and fungus – host interactions at the molecular level have been achieved. Stanley Letovsky and colleagues took advantage of these in order to analyze a vast database of real-world IgE testing results[1]. The contribution of their findings to clinical practice is expected to support more accurate diagnosis of fungal sensitization and allergy, thus improving the management of an array of type 2-related chronic inflammatory diseases. Moreover, their findings bring undisputable real-world support for the clinical deployment of molecular allergen-assisted diagnosis of fungal sensitization.

Allergic sensitization to fungi, defined as the demonstration of fungi-binding specific immunoglobulin (Ig) E, is a diagnostic biomarker of fungal allergy in patients with an evocative clinical history. It is also a pathophysiological contributor to allergic inflammation in asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps, allergic bronchopulmonary mycosis, and other diseases related to chronic type 2 immune responses. Taken together, these diseases span the entire lifetime, from pediatric to elderly patients, and represent a considerable burden for health systems[2-4].

Conventional diagnosis of allergic sensitization to fungi relies on extracts obtained from fungal cultures employed for either skin or blood tests. While this strategy might seem straightforward, the interpretation of its results is hampered in clinical and laboratory practice by a range of factors:

(1) the actual species and abundance of fungi to which a subject is actually exposed are unknown;

(2) diagnostic fungal extracts are only available for a small number of fungal species, among the hundreds of thousands forming the fungal environmental exposome;

(3) fungal extracts display notorious variability as a function of culture conditions, harvesting, extraction and processing time and procedure;

(4) last but not least, fungal sensitization usually comes as IgE binding to multiple fungal extracts, leaving open the question of the true pathogenic species[3,5].

The latter two points have been addressed in recent years by the molecular allergen-assisted approach, taking advantage of commercially available recombinant fungal allergenic proteins categorized as either “marker” or “cross-reactive” to distinguish between genuine sensitization (one or more fungal species triggering IgE production) and cross-reactivity (two or more fungal species recognized by IgE induced by one of them)[6,7]. Two major limitations prevent this approach from a generalized use: the limited number of commercially available fungal molecular allergens, and variable degrees of clinical deployment of the method. Thus, fungal allergenic extracts remain the main diagnostic tool in clinical practice, despite the lack of an unequivocal interpretation.

Lotevsky and coworkers sought to combine analysis on novel phylogenetic data on fungi with the results of a large study on indoor fungi present in US homes, and a vast database of almost 8 million real-world results of IgE tests to fungi in the US. Their major finding was that cross-reactivity, rather than co-sensitization (i.e., associated genuine sensitization to two or more fungal species), underlies allergic sensitization to multiple fungi. They also confirmed that allergic sensitization to multiple fungi is closely related to their phylogenetic distance, rather than to their concomitant presence in the domestic environment, i.e. co-exposure. Finally, several fungal species that associate more often than would be expected from phylogenetic data were identified.

Although several limitations are present, such as the incomplete overlap between the *in vitro* and environmental panels of fungal species, the use of unrelated databases of environmental fungi and allergic sensitization, and the lack of information on the outdoor fungal exposome, Lotevsky and

coworkers lift an important barrier in the interpretation of allergic sensitization to fungi. Their results provide compelling evidence that allergic sensitization to one or more fungal species must be regarded as widely informative on a group of cross-reacting species, rather than on a single, well-defined fungal species. Consistently taking into account the cross-reactivity inherent to fungal extracts should help identify the true culprit species, including those lacking in the assay panel, and thus assist with the choice of an appropriate allergen immunotherapy. Sampling, characterization and quantitative assessment of indoor and outdoor fungi in a given subject's domestic, professional, or leisure environment is available, providing personalized additional clues for the interpretation of allergic sensitization to fungi [8].

Moreover, it is known from other airborne allergens, such as grass pollen or house dust mites, that the demonstration of specific IgE binding to an extended panel of cross-reactive extracts usually implies the existence of a complex sensitization profile, with multiple allergenic molecules and epitopes involved in specific IgE induction, more severe clinical expression, and suboptimal efficacy of allergen immunotherapy [6]. Similar mechanisms are apparently at play in the fungal kingdom, since serum IgE from patients with allergic bronchopulmonary aspergillosis bind to multiple *Aspergillus fumigatus* proteins [9].

The results reported by Letovsky et al are expected to apply also to fungi-specific IgG, which are important biomarkers for hypersensitivity pneumonitis, infectious fungal diseases, and allergic bronchopulmonary mycosis. IgG-binding fungal proteins outnumber IgE-binding counterparts[10], suggesting that fungal cross-reactivity should be similarly considered in laboratory assays of IgG to fungi.

In conclusion, the study by Letovsky et al marks a major step in the current global effort to characterize the elusive interaction between fungi and the human host, bringing compelling evidence for consistent inclusion of fungal cross-reactivity in the diagnostic algorithm, giving clues to do so, and supporting the much-needed deployment of molecular fungal allergens into clinical practice.

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