

Cross reactivity of moulds

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Mould allergic individuals are often sensitive to several mould species. This clinical observation has led to the assumption that the degree of so called »cross-reactivity» is high among different mould species – much in analogy with grass pollen cross-reactivity. Among allergologists cross-reactivity is seldom well defined, but the term is commonly used to express similarities of different species with respect to sensitization and reactions in the human IgE-system. Immunologists, on the other hand, are usually more precise, by talking of antigenic identity or partial identity on the molecular level, i.e. as demonstrated by gel precipitation techniques. The molecules may share similar or identical antigenic determinants.

The present paper will employ the term »IgE cross-reactivity» which will be restricted to reactions in the human IgE-system. Assume that an antigen (allergen) in one fungal species is capable of sensitizing an individual to produce specific IgE antibodies to this antigen. If an antigen (allergen) in another fungal species is capable of binding specifically to these IgE antibodies, the two antigens, and the two fungal species, are said to cross-react.

The degree of IgE cross-reactivity between the two species will depend on the number and the relative importance of the individual allergens that cross-react. It will also depend on the patient sera used to study the cross-reactivity. The »degree of cross-reactivity» is thus a very vague term and should always be related to the experimental conditions used. Inhibition experiments, such as RAST-inhibition and CRIE-

inhibition, are probably best suited for such studies.

From this it should be clear that common clinical observations of simultaneous parallel mold sensitivities in several patients is no proof of real IgE cross-reactivity on the molecular level. On the contrary, there are reasons to believe that the IgE cross-reactivity between moulds are much less important than in the case of pollens (11). It may be more appropriate to explain the clinical observations by thinking in terms of multiple, parallel, but independent mould allergies. The question of cross-reactivity of fungi is important since it has implications for our attitude to immunotherapy in the treatment of mould allergies.

We may compare different fungi by their appearance in a microscope which is the tool of the taxonomist. We may also compare them immunologically by their antigenic and allergenic composition. This is clearly more relevant for the patients sensitivities. A third, and more ideal, alternative would be to compare the fungi on the genotype level, such as by DNA hybridization techniques. Depending on what approach is chosen one may end up with different conclusion as to the degree of cross-reactivity.

A further complicating factor is that fungi have an extraordinary tendency to vary in composition. There is no guaranty that the conditions used to grow a particular strain gives a final preparation that is adequately representing all potential allergens in that strain (2, 11, 12, 13). This limits the value of all studies of IgE cross-reactivity unless

they are based on a number of preparations of the strain grown under different conditions. To our knowledge, in the limited literature on IgE cross-reactivity of moulds, little or no attention has been paid to this fact.

The limitations of taxonomy of fungi is an important problem that has been largely ignored by allergologists. There is a tendency to regard the various taxonomic categories as concrete and stable, and more or less sacred (10). Living organisms are constantly evolving. Any attempts to pigeon-hole them into a system of classification are nothing more than the artificial attempts of biologists to organize their knowledge of the moment (1). Even when our knowledge of fungi becomes much greater than it is at present, any attempts to draw hard and fast lines between taxonomic categories will be futile because the categories themselves are only human concepts and intermediate forms are bound to exist and to rise by hybridization and mutation.

It is as a humorous paradox that the concept of cross-reactivity between two fungal variants is only put into consideration if they are given different names. Otherwise one would speak of strain difference rather than uncomplete cross-reactivities.

Most fungal species important in human allergology belong to the fungi imperfecti in the form class Deuteromycetes. Generally these fungi are considered as asexual states of Ascomycetes or, in a few cases, as Basidiomycetes where sexual states either do not exist or have not yet been discovered (10). The fungi imperfecti is not a true botanical system of classification which take into account the whole fungus in all its facets, forms and potentialities, latent or expressed. Rather the fungi imperfecti are an artificial classification system which is largely based on the appearance and characteristics of the spores, such as size, shape, colour and surface ornamentation. The spores of the fungi imperfecti are called conidia. It goes without saying that the mycologists description of the conidia, based

on the use of a microscope, does not necessarily reflect the biochemical and immunological properties of the fungi important for the patients. Such a rough basis for taxonomy will also necessarily lead to faulty classification in some cases. There has also been indications that different mycology experts may tend to disagree in certain cases.

Taxonomically, fungi are given Latin double names, the first expressing the genus, the second giving the species within the genus. Examples are *Cladosporium* (genus) herbarum (species) and *Alternaria* (genus) alternata (species). There is little mentioned of the high number of different strains (or isolates) that are known within each species. From centres such as ATCC (American Type Culture Centre) and CBS (Centraalbureau voor Schimmel cultures) a high number of strains of each species can be obtained. There is no information as to which strain is clinically most important or most suited for allergen extract preparation. The choice of strain for cross-reactivity studies may have great impact on the outcome of the study.

From a theoretical point of view one would expect the least cross-reactivity between different genera, some cross-reactivity between different species, and a high degree of similarities between different strains of the same species. However, the real life situation is not as clearcut as this.

1. In some cases there are little or no cross-reaction between different genera. Karr and coworkers found no cross reactivity between *Aspergillus fumigatus* and *Alternaria alternata* (7). Salvaggio and Aukrust found a single antigen (but no allergens) common in *Alternaria alternata* and *Cladosporium herbarum* (11). No cross-reactivity was found between the two Basidiomycetes *Cantharellus cibarius* and *Coprinus comatus* or between the two Basidiomycetes themselves (11).

2. In other cases, however, there are significant IgE cross-reactivity between different genera. Hoffman and Kozak (6) demonstrated cross-reaction between *Al-*

ternaria, *Stemphylium* and *Curvularia* and sometimes between *Spondylocladium* and *Dresclera*. Another important example was recently presented by Gravesen and Nyholm (4). They demonstrated great similarities between *Ulocladium* and *Alternaria*. The *Ulocladium* strain studied contained higher amounts of the major allergen Alt-1, (first isolated from *Alternaria alternata* (16)) than the *Alternaria alternata* strain studied.

3. Different species of the same genus may show similarities, but also significant differences. This has been shown by Hoffman and Aukrust with respect to *Cladosporium herbarum* and *Cladosporium cladosporioides* (5). It has been demonstrated by Karr and coworkers with *Aspergillus fumigatus* and *Aspergillus flavus* (7) and by Kim and Chaparas studying several *Aspergilli* (8). Similar results were also obtained by Vijay and coworkers studying *Alternaria alternata* and *Alternaria solani* (14).

4. Different strains of each species show similarities, but also considerable differences. Aukrust and coworkers demonstrated that 10 different strains of *Cladosporium herbarum* showed pronounced immunological and biochemical differences (2, 13). Aukrust and coworkers (3) and Schumacher and coworkers (12) have demonstrated differences among different *Alternaria alternata* strains and isolates. The same conclusions were reached by Wallenbeck and coworkers (15) when studying 10 strains of *Aspergillus fumigatus* and by Malo and coworkers studying this species (9).

It is disturbing that in some cases immunological differences may be greater between strains of the same species than between genera (such as *Alternaria* and *Ulocladium*).

In conclusion, an endless series of fungal variants exists in nature. Some show extensive similarities whereas other clearly represent completely different allergen populations. The taxonomical names and categories of genus, species and strain does not in a simple way express the true im-

munological relationship between the variants. More research is needed to establish the allergological importance of the individual variants and the degree of IgE cross-reactivity between them. Assume, however, that a selected panel of extracts are available which fully represent the allergologically most important fungi such as *Cladosporium*, *Alternaria*, *Aspergillus*, *Penicillium*, *Fusarium* and *Mucor*. Each extract could be made from a pool of closely related variants (strains or species). The degree of IgE cross-reactivity between these extracts must be expected to be minimal or negligible. Clinical observations of multiple sensitivities to several of these extracts may frequently occur. This observation is probably best explained as multiple, independent and parallel mould allergies.

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