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Genomics of Fungal Allergens

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Allergy, also known as hypersensitivity type I, represents a major health problem worldwide. It is a disease caused by IgE–mediated reactions to otherwise innocuous substances, referred to as allergens. These are usually proteins, glycoproteins or metalloproteins from various sources. Allergy often has a genetic origin, described as atopy and an atopic individual usually becomes sensitized in early childhood or adolescence by allergens [1]. Fungi are uncommon allergens in the human affecting 3-12% of the population depending on geographical location. However, when it occurs, fungal allergy is associated with ~40% of the most severe forms of asthma including Allergic BronchopulmonaryAspergillosis (ABPA) and Severe Asthma with Fungal Sensitisation (SAFS) [2]. These conditions alone are thought to affect millions of people worldwide. There are three fungal phyla that contain all of the species that cause allergic responses in humans. These include Ascomycota (*Aspergillus*, *Alternaria*, *Candida*, *Cladosporium*, *Fusarium* and *Penicillium*), Basidiomycota (*Malassezia*, *Calvatia* and *Coprinus*) and Zygomycota (*Rhizopus* and *Mucor*) [3]. Although a lot of effort has been made to fully understand the mechanism of action of allergens, little is known why some proteins cause strong allergic responses in some individuals but others do not. It is also unknown why some organisms produce several different allergens but others are rarely associated with allergy. Genome sequencing and RNAseq databases can be useful in providing answers to several troubling questions but to date only a small number of fungal species have been studied in greater detail.

Although the mechanism of allergic responses and the source of allergens are moderately well understood, the repertoire of allergens and their molecular structures are still poorly characterised. An essential step in characterisation of allergens and their epitopes is to identify their encoding genes [4] and in the recent years several new species of fungal genomes have been sequenced. A number of laboratories worldwide have attempted to clone and produce hundreds of recombinant allergens using various available techniques with great success. It has been demonstrated that the fungi play a very important role in triggering allergic reactions in humans. According to the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Subcommittee (www.allergen.org) currently there are 765 approved allergens and 105 (13.7%) are of fungal origin. However, based on the BLAST search and structural similarity methods it is predicted that from over 100 000 protein entries deposited in the Swiss-Prot database, there are over 4000 (~4-5%) proteins with allergen motifs [5]. On average, fungi contain between 6000 and 10000 genes and some may produce approximately 20 well characterised allergens and up to 60 less characterised IgE binding proteins [6]. Further analysis shows that another 20 proteins may be homologues to known allergens in other species. *Aspergillus fumigatus*, possibly the most important human pathogenic mould, contains 23 approved by the Allergen Nomenclature Subcommittee allergen proteins, although Asp f 9 and Asp f 16 are possibly the same proteins [4]. It also produces over 80 IgE binding proteins that may be involved in pathophysiology of allergic diseases by this fungus [7]. The high-throughput screening technology shows that other fungal species show a similar pattern, such as for example *Cladosporium herbarum* (8 approved allergens and 28 IgE-binding proteins), *Coprinus comatus* (5 approved allergens and 37 IgE-binding proteins) and *Malassezia furfur* (3 approved allergens and 27 IgE-binding proteins) [8]. This suggests that the number of known fungal allergens is far from being complete and the better we study fungal genomes and proteomes the higher the chance to discover more molecules responsible for triggering allergic responses. Although many of the allergen encoding genes is present in fungal genomes, their expression may be highly dependent on the environmental condition in which the fungus grows [9], therefore thorough genomic analysis combined with RNAseq, proteomics and clinical studies may reveal the true repertoire of fungal allergens.

The sequence availability for many fungal genomes allows us to analyse allergen homologues in various species. Many of the known allergens are specific to some fungi, such as Asp f 1 (*Aspergillus fumigatus*), Alt a 1 (*Alternaria alternata*) or Cla h 1 (*Cladosporium herbarum*) but many have close orthologues across the fungal kingdom. Given that *Cladosporium*, *Aspergillus* and *Alternaria* account for the majority of known fungal allergens it is possible to speculate that they are the most important fungi in sensitising individuals to allergens. However, these are also the most frequently studied organisms and it is likely that other fungi that carry very similar complements of allergen proteins will also yield approximately 20 allergens per species. Thus the prime sensitising agent in fungal allergy remains obscure. Therefore, careful analysis of sensitisation to these species specific allergens may yield useful information.

Several proteins show cross-reactivity with other homologous proteins found in other fungal species which has been confirmed by either genome analysis or experimental procedures. Cross-reactivity is a known phenomenon and arises from the structural similarity of two proteins, however it has been shown that only a single amino acid change in the protein is able to change the reactivity of a protein [10]. One startling observation is that human orthologues of allergen proteins provoke strong allergic reactions in fungus sensitised individuals raising the possibility of auto allergic interactions [11]. Cross-reactivity can be tested in various ways including bioinformatics analyses of potential candidate proteins or cloning and expressing them and comparing with sera of known reactivity. Although the bioinformatics approach provides very useful data, the experimental proceduresare far from being perfect. This is due to the lack of standardisation of production of allergens that greatly affects their better understanding and reliable evaluation of immunodiagnosis of allergic disorders.

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Genome sequencing has helped us to improve our knowledge of fungal allergens, discover their real and complete coding sequences, create better *in silico* 3-D structures, predict the cross-reactivity and allowed us to better understand their role in allergic responses. Although a huge leap has been made in recent years in terms of studying fungal genomes, there is still a vast amount of work to be done before we uncover the full repertoire of fungal allergic molecules and understand their functions.

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