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The pathogenesis of fungal-related diseases and allergies in the African population: the state of the evidence and knowledge gaps

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Short title: **Pathogenesis of immune-mediated fungal diseases in Africa**

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Abstract

The prevalence of allergic diseases in the African continent has received limited attention with the allergic diseases due to fungal allergens being among the least studied. This lead to the opinion being that the prevalence of allergic disease is low in Africa. Recent reports from different African countries indicate that this is not the case as allergic conditions are common and some; particularly those due to fungal allergens are increasing in prevalence. Thus there is need to understand both the aetiology and pathogenies of these diseases, particularly the neglected fungal allergic diseases. This review addresses currently available knowledge of fungal-induced allergy, disease pathogenesis comparing findings from human vs. experimental mouse studies of fungal allergy. The review discusses the potential role of the gut mycobiome and the extent to which this is relevant to fungal allergy, diagnosis and human health.

Introduction

Fungi are eukaryotic, filamentous and mostly spore forming organisms that are ubiquitous in nature [1-3]. They are important disease-causing agents either directly as exemplified by cryptococcal meningitis [4], pneumocystis pneumonia [5], pulmonary aspergillosis [6-8] or indirectly as allergens that can induce or exacerbate respiratory diseases such as asthma [9].

Fungi are responsible for considerable morbidity as they cause a wide variety of diseases ranging from superficial skin mycoses [10-12] to potentially fatal systemic mycoses [13,14]. Annual global mortality due to fungal diseases is estimated to be over 1.6 million [15,16]. In Africa, tinea capitis dominates the overall burden with an estimated 8.6 million [17] affected in Ethiopia, Ghana [18] and South Africa [17,19]. Despite this, the association between fungal pathogenesis and the adverse health sequelae remains poorly characterised partly because it frequently develops in patients with multiple morbidities including immunodeficiencies [20,21].

In the last decade, there has been an increase in the incidence of fungal diseases [22,23]. The increase has partly been attributed to climate change with global warming believed to favour the propagation of fungal spores [22,24]. Although fungi are a common and integral part of ecosystems, the impact of fungal diseases on the entire ecosystem can be devastating [7,25-27]. Thus, fungi are considered a current and future public health problem that should not be underestimated [28].

Public health burden of fungal-related diseases

The global prevalence of skin infections due to fungal infestation is estimated to be over a billion [7,29] with an age-standardised disability-adjusted life year (DALY) rate of 48.9 per 100 000 sixteen times less than that of malaria (794.7 per 100 000) [30]. More than 100 million people are said to be affected with mucosal fungal infections [16], whilst more than 10 million people succumb to severe allergies and a million die due to fungal infections [6]. As of 2017, global mortality owing to fungal infections was greater than that for malaria [31] and was equivalent to that for tuberculosis (TB) [16,32]. The public health impact of this relatively silent cause of morbidity and mortality has not been adequately addressed.

In Africa, the precise prevalence of fungal diseases is currently unknown; however, the very large number of HIV [33] and pulmonary TB cases in most African countries leads to a large number of cases of opportunistic fungal infections [17]. These fungal infections have been observed in most African countries in studies carried out by the Global Action Fund for

Fungal Infections (GAFFI) [17,34]. In Senegal, Nigeria, Malawi and South Africa, 12.5%, 11.8%, 7.54% and 7.1% [19,35-37] of the populations respectively are estimated to suffer from serious fungal diseases each year. These infections include chronic pulmonary aspergillosis [18,19,35], pneumocystis pneumonia [18,36,38], cryptococcal meningitis [19,39,40], allergic bronchopulmonary aspergillosis [35,40,41] and recurrent vulvovaginal candidiasis [40-42]. However, the epidemiology of allergic diseases due to fungi exposure such as asthma and allergic rhinitis have not been fully elucidated [43]. This review focuses on immune-mediated fungal diseases.

Prevalence of the immune mediated fungal diseases in African populations

Allergy was thought to be rare in Africa in line with the hygiene hypothesis [44,45] until the results of the International Study of Asthma and Allergies in Childhood (ISAAC) which showed an increase in the prevalence of allergic asthma, rhinitis and eczema in African countries [46-49]. Reports from different African countries indicate that allergic conditions are common [50-52]. However, there has been limited reports of allergy due to fungal allergens in the continent due to inadequate reporting, limited awareness and diagnostics [53,54].

Recently, Kwizera *et al.*,[55] carried out a systematic review and meta-analysis to estimate the burden of fungal asthma in Africa using data from cross-sectional studies and review articles. The data was obtained from 13 African countries and this showed the average prevalence of fungal asthma as 28%. These results show that fungal asthma is a significant problem in Africa but there is still a dearth of epidemiological data in most countries [55].

From previous studies in parts of sub-Saharan Africa, the prevalence of fungal sensitisation was high, being 14.9% [50] ,53% [56] and 28% [57] amongst referral patients in Zimbabwe, South Africa and Botswana respectively. The patients included in these studies were secondary referrals, so only those with severe symptoms that warranted specialist consultation and had the financial capacity to afford specialist care were included. Consequently, it is likely that the cost barriers meant only a small proportion of affected individuals were captured in the studies.

The optimum conditions for fungal spore growth is in the range of 12°C to 30°C [58] but some fungi species can tolerate lower or higher temperatures [22]. This climatic criteria encompasses the majority of the African countries located in the subtropical zone, providing an optimum environment for fungal survival and growth [59,60]. Hence, the data presented in these studies are likely to be an underestimation of the true extent of fungal sensitisation in sub-Saharan Africa.

Types of immune-mediated fungal diseases

The spectrum of immune-mediated fungal diseases is huge and a number of these diseases have been widely studied [61,62]. The main diseases that affect individuals are allergic rhinitis [63], allergic conjunctivitis, allergic fungal sinusitis [64], atopic dermatitis [65] and asthma [66]. Other less common immune-mediated diseases are allergic bronchopulmonary mycoses (ABPM) [67] and hypersensitivity pneumonitis (HP) [68]. These are briefly discussed.

Allergic rhinitis

Allergic rhinitis is a common inflammatory disease of the nose [62,69,70]. It affects up to 40% of the population in Europe and the States [71]. Exposure to fungi/ dampness has been associated with allergic rhinitis in epidemiological studies [63,72]. In a longitudinal population-based study, Shaaban et al [73] found that the presence of allergic rhinitis significantly increases the probability of adult-onset asthma [74].

Allergic conjuctivitis

Allergic conjunctivitis is an inflammatory disease of the conjunctiva [75,76]. It affects 15-40% of the population [75] and maybe associated with allergic rhinitis [72]. Symptoms of allergic conjunctivitis are usually aggravated by exposure to dry and windy climates [77].

Atopic dermatitis

Atopic dermatitis is a chronic inflammatory skin disease characterised by pruritic skin lesion [78,79]. Atopic dermatitis usually starts in early childhood and is frequently associated with allergic rhinoconjuctivitis and allergic asthma [65]. Most atopic dermatitis patients have been shown to be sensitised to the fungi *Malassezia* [80].

The small size of fungal spores (less than 10μm) [81,82] enable fungi to penetrate the bronchi, which may lead to allergic reactions of the lower respiratory tract resulting in allergic asthma, ABPM and allergic alveolitis [82].

Allergic bronchopulmonary mycoses (ABPM)

ABPM is a rare hypersensitivity disease of the lower airways characterised by sensitisation to fungi [83]. ABPM occurs in susceptible individuals with asthma and cystic fibrosis [84]. The most frequent ABPM is caused by *Aspergillus fumigatus* antigens and is commonly known as

Allergic bronchopulmonary aspergillosis (ABPA) [85]. The pathogenesis of ABPA is characterised by colonisation of fungi in the lower airways and combines elements of Type I, III and IV hypersensitivity reactions [86].

Allergic fungal sinusitis

Allergic fungal sinusitis is a severe form of chronic rhinosinutis in which individuals develop an intense inflammatory reaction to airborne fungi [87]. The pathogenesis is characterised by eosinophil –predominant Type I hypersensitivity reaction sustained by fungal antigens in the mucosa of the sinonasal tract in atopic individuals [64,88].

Hypersensitivity pneumonitis (HP)

HP also known as extrinsic allergic alveolitis [89] is an immunologically mediated lung disease which predominantly occurs as an occupational disease [90]. The pathogenesis of HP is characterised by Type III and IV hypersensitivity reactions [68].

Allergic asthma

Allergic asthma is an inflammatory disease of the airways characterised by bronchial hyperresponsiveness and airflow limitations [91,92]. Fungal sensitisation maybe associated with severe asthma attacks requiring hospital admission [93]. Although the evidence that fungi can act as an asthma trigger is widely accepted, the mechanisms by which this occurs is still not clear [94,95] , nor has it been conclusively proven that fungi exposure is responsible for these clinical manifestations [96].

While effective therapies for controlling allergic reactions are available, none are curative. Consequently, allergic diseases such as asthma often persists from early childhood through to adulthood [97,98]. Such allergies usually have a detrimental effect on the quality of life of the affected individual and have been known to affect their sleep, competencies at work or school as well as their social interaction [99].

Auto-allergic and autoimmune conditions

Fungi contribute to auto-reactivity against self-antigens due to shared epitopes between fungal and human proteins [61] such as Manganese superoxide dismutase (MnSODs) [100], thioredoxin, cyclophins and acid ribosomal proteins. The underlying mechanism is thought to be molecular mimicry [61,101] maintaining severe chronic allergic diseases such as atopic dermatitis[102].

Currently, the evidence for fungal exposure being linked to the induction of autoimmune diseases is controversial. Studies by Miyoshi *et al*., and Myllykangas-Luosujarvi *et al*., [103,104] all suggest that fungal proteins have a role to play in autoimmune diseases. However, further studies are needed to establish the role of fungi in the immunopathology of autoimmune diseases.

Fungal allergens

The most common fungi species implicated in allergic reactions are *Alternaria*, *Cladosporium*, *Aspergillus*, and *Penicillium* [105,106], which can be established by the use of a skin prick testing or allergen specific IgE antibody detection [107,108]. The allergenic proteins of these fungi [109] can induce sensitisation and result in immune-mediated diseases such as asthma [110,111], allergic bronchopulmonary diseases [112-114] and/or hypersensitivity pneumonitis [115,116].

Although progress is being made in identifying and characterising the fungal allergens involved in eliciting allergic immune responses, fungal allergens are thought to be still neglected and underestimated, compared to other aeroallergens [117,118] such as pollen or house dust mites.

Fungi polysensitisation (sensitisation to multiple fungi) or cross-reactivity is frequently observed in clinical cases. This makes the precise identification of a given fungal allergen challenging. This is further complicated by the fact that fungi share several potentially allergenic epitopes, making a precise diagnosis of a specific fungal allergy difficult [119]. The use of component-resolved diagnostic techniques [120] that involve mapping the allergen sensitisation of a patient at a molecular level using purified natural or recombinant allergenic molecules instead of allergenic extracts [121] has enabled progress in attributing fungal allergen sources to allergic manifestations.

Progress has also been made in the characterisation and identification of clinically relevant allergens. Nonetheless, to improve molecular diagnosis both the cross-reactive and the species-specific allergens need to be identified [118]. From the relevant literature, some of the following allergens have been identified from *Alternaria alternata*, *Aspergillus fumigatus* and *Cladosporium herbarum*. These are presented in **Table 1** and **Table 2**.

Table 1: Species-specific Allergens

Allergen source (Species)	Allergen	Molecular weight range(kDa)	Protein family	References
	Alt a 15*	50-58	Serine proteases	[122]

Alternaria alternata	Alt a 10*; Alt a 8*	28-53	Dehydrogenases	[123,124]
	Alt a 4*	57	Disulfide isomerases	[81,123]
	Alt a 7*	22	Flavodoxins	[81,123]
	Alt a1*	11-45	Unknown	[123,125]
Aspergillus fumigatus	Asp f 23*	44	Ribosomal proteins	[126]
	Asp f 17*	19.42	Galactomanno proteins	[126]
	Asp f 34*	19-20	Cellwall proteins	[127]
	Asp f 10*	34-35	Aspartic proteases	[126,128]
	Asp f 15*	15-16	Cerato platanins	[126]
	Asp f 9*	33.7	Glycosyl hydrolases	[126,129]
	Asp f 5*	42-43	Metallo proteases	[126]
	Asp f 2*	34-37	Fibrinogen binding proteins	[126]
	Asp f 1*	16-18	Ribonucleases	[81]
	Asp f 4*; Asp f 7*	11-45	Unknown	[126]
	Cla h 9*	50-58	Serine proteases	[122]

Cladosporium herbarum	Cla h 8*; Cla h 10*	28-53	Dehydrogenases	[123,124,130]
	Cla h 7*	22	Flavodoxins	[123]
	Cla h HCh1	10.5	Hydrophobins	[131]
	Cla h2*	11-45	Unknown	[125]

*These allergens have been approved by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Committee [132]. All the other allergens can also be found in the Allergome database[133].

Table 2: Cross-reactive Allergens

Allergen source (Species)	Allergen	Molecular weight range(kDa)	Protein family	References
Alternaria alternata	Alt a 6*	45-48	Enolases	[81,123]
	Alt a 12*;Alt a 5*	11-12	Ribosomal proteins	[81,123]
	Alt a 3*	65-90	Heat shock proteins	[123,125]
	Alt a TCTP	18-22	Translationally Controlled Tumour proteins	[134]
	Alt a NTF2	13-14	Nuclear transport factors	[135]
	Asp f 22*	45-48	Enolases	[136]

Aspergillus fumigatus	Asp f 11*; Asp f 27*	16-20	Cyclophins	[137,138]
	Asp f 6*	22-25	Manganese superoxide dismutases	[126,139,140]
	Asp f 8*	11-12	Ribosomal proteins	[141]
	Asp f 12*	65-90	Heat shock proteins	[123]
	Asp f 3*	17-19	Peroxisomal proteins	[142]
	Asp f 13*;Asp f 18*	32-34	Serine proteases	[143,144]
	Asp f 28*;Asp f 29*	10-12	Thioredoxins	[119,145]
	Asp f GST	26	Glutathione-S-transferases	[146]
Cladosporium herbarum	Cla h 6*	45-48	Enolases	[123,147]
	Cla h 12*;Cla h 5*	11-12	Ribosomal proteins	[119,141]
	Cla h TCTP	18-22	Translationally Controlled Tumour Proteins	[148]
	Cla h NTF2	13-14	Nuclear transport factors	[135]

*These allergens have been approved by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Committee[132]. All the other allergens can also be found in the Allergome database[133].

Exposure to fungi and fungal species in Africa

The mid and hot tropical climates [149] in Africa provide favourable growth conditions for fungi species and as such it is possibly the most exposed of all continents [150]. In addition to the climatic conditions, factors such as poverty make it highly plausible for people in Africa to consume mycotoxin-contaminated food. These mycotoxins are produced by some fungal species as secondary metabolites [151]. Majority of the food crops [152] contaminated are part of the main ingredients in weaning porridge [153] and due to this, it has been suggested that exposure to the mycotoxins maybe a causative factor for child stunting and underweight [154,155] observed in some African children.

Pathogenesis in fungal allergic diseases

In this review, we are looking at the pathogenesis of fungal allergic diseases in a wider study to understand allergic reactivity in Africa. The allergic diseases can result from immune-mediated inflammatory responses to fungal allergen sources causing tissue damage [156]. The fungal allergens can elicit hypersensitivity reactions including of type I (IgE mediated), type III (IgG/IgM-mediated) and type IV (delayed type hypersensitivity) and these, may act together to mediate the pathogenesis of different allergic diseases. A schematic illustration of these reactions are shown in **figure 1**, but the specific allergens responsible for symptoms remain poorly characterised [95,117,157]. Additionally it is not known why fungal allergens produce more severe airway diseases than other common aeroallergens [67]. One possible explanation could be that colonisation with fungi as well as their ability to actively germinate in the host predisposes the host to immune-related diseases and severe disease course [82,158].

Allergic sensitisation involves the development of allergen-specific Th2 responses and IgE production. IgE binds to the high-affinity IgE receptor (FcεRI) present on mast cells. Re-exposure to the specific allergen results in cross-linking of IgE on the mast cell surface, activation and rapid degranulation of the mast cells, with the secretion of active mediators such as histamine. The late phase response involves an influx of Th2 lymphocytes and eosinophils leading to a more prolonged response with tissue damage [159,160]. Significant progress is currently being made into understanding the mechanistic pathways by which fungi cause or exacerbate allergic diseases such as asthma. It has been reported that fungal cell wall components such as β-glucans, chitin and proteases are the main source of pathogen-associated molecular patterns (PAMPs) recognized by pattern recognition receptors (PRRs) (PRRs) as well as protease activated receptors (PARs) on the host cells [161]. These cell wall components have been suggested to be widely conserved across the fungal kingdom and absent in humans, hence ideal targets for immune recognition [162]. When exposed to β-glucans, chitin and proteases, the epithelial cells mount an immune against these components by releasing chemokines, cytokines and antimicrobial peptides [163]. Repeated exposures to fungi allergens lead to the induction of Th1, Th2 and Th17 reactions, and chronic airway inflammation [164-166] as shown in **figure 2**.

Fungal proteases induce inflammatory responses by compromising mucociliary clearance , altering the permeability of epithelial barrier, and activating innate immune responses leading to asthma development [167,168]. The β-glucans induce IL-6, IL-8, and CCL-20 from airway epithelial cells through Dectin-1 receptor [169,170]. Chitin induces inflammatory responses characterized by IL-17, IL-23 and TNFα [171] as well induce the expression of IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which activate innate lymphoid cells (ILC2s) [172] to express IL-5 and IL-13, leading to eosinophilia [173] and accumulation of alternatively activated macrophages.

ILC2s have been shown to contribute to the initiation and persistence of fungus-mediated allergic immune responses in mice [174,175], suggesting that they have a role to play in fungal allergy. However, the mechanism that explains how airway exposure to fungal allergens results in increased production and secretion of pro-type 2 cytokines, such as IL-33, leads to activation of ILC2s and other inflammatory cells in airway mucosa, are only partly understood [174]. Therefore, further studies are required to have a better understanding of the mechanistic pathways involved in the pathogenesis of fungal allergy.

Gut microbiome and fungal allergy

There is increasing evidence that resident microbial communities in the gastrointestinal tract, airways and on the skin contribute to health and disease [176]. Several studies have highlighted that gut microbiome dysbiosis can influence susceptibility to non-infectious diseases [177] such as atopic dermatitis, allergy, cancer, obesity and diabetes [178,179].

In context of the entire microbiota, fungi are considered a minor component [180] and hence rarely focused on when discussing microbiome which mainly refers to bacteria. The role of gut mycobiome in immune regulation and asthma development has been documented in murine experimental model studies. In particular, Wheeler *et al.,* investigated the importance of a 'healthy mycobiota' in the gut in modulating immune function [181] using mice. In this study they found that prolonged oral treatment of mice with anti-fungal drugs increased the abundance of *Aspergillus*, *Epicoccum* and *Wallemia spp* in the gut and exacerbated the development of allergic airway diseases [181]. The authors also reported that inducing alterations in the existing mycobiome could change the course of house dust mite (HDM)-induced allergic diseases.

In addition, studies by Noverr *et al*., [182,183] demonstrated that mice develop allergic airway responses if their endogenous microbiota is altered as compared to those with normal microbiota. All these studies suggest that there is a connection between the gut microbiome and allergy at least in animal models. The challenge remains how to interpret these sorts of results from experimental studies in terms of human patients.

It has been observed both in human and experimental models that allergic diseases correlate with widespread use of antibiotics [182-186] and alteration in faecal microbiome, which lead to overgrowth of yeast such as *Candida albicans*, which can secrete potent prostaglandin-like immune response modulators, involved in inflammation. Given the widespread use of antibiotics in African countries [187,188] and the increasing prevalence of allergic diseases in this continent, there is a likelihood that gut mycobiome are involved in allergic diseases, though studies are needed to investigate this association.

The mycobiome has also been implicated in other diseases such as Inflammatory bowel disease [189-191], Crohn's disease [192], Autism [193] as well as Rett syndrome[194]. Benito-Leon *et al*, [195] hypothesised that the gut mycobiome has a role to play in Multiple sclerosis (MS) and this was observed in a case-control study [196]. However further studies are necessary to comprehensively understand the role of the mycobiome in the pathophysiology of these diseases.

Limitations of mouse models

Studies of fungal exposure and allergy have benefited greatly from the use of murine models to evaluate fungal pathology [174,197-200]. However, little is known about how these specific cell types translate to human patients who have asthma and other allergic diseases [174].

Murine research has contributed to defining the immunological mechanisms underlying allergic asthma and has provided some understanding of the disease [201]. Although mouse models are widely used, it is important to be cognizant of the fact that mouse airways differ significantly from human airways, in terms of the anatomy, development and physiology as well as in the nature of allergen exposure [201,202]. These differences underlies some of the challenges in translating findings from experimental models to human disease [203].

Mice do not have asthma and do not exhibit spontaneous "symptoms" consistent with asthma [204] and hence, are usually manipulated to develop allergic/Th2-type immune responses. This results in sensitisation of the animal by systemic administration of the allergen, whereas, in humans there is no systemic administration of allergen. The allergic diseases in mice are acute and transient, so it is difficult to establish chronic allergic diseases in mice [205]. Furthermore, experimental mice are inbred strains whereas humans are not, hence other environmental factors might also influence how humans respond to the allergens [202]. Overall this leads to difficulties in transposing mice immunological responses into useful human data [206].

Knowledge gaps relevant to improve fungal allergy and human health

Although fungal-related diseases are now recognised as a growing problem globally [6], there continues to be a paucity of epidemiological data in Africa as majority of the published data is from Europe and the States [16]. Additionally, in Africa, there are diagnostic challenges as most people have limited healthcare access due to cost barriers, poor healthcare infrastructures as well as lack of expertise [207].

In general, there is paucity of studies in relevant model systems for human fungal disease; hence, mechanism of pathogenesis remains unclear despite all the research progress made in experimental models. It has been suggested that human microbiome (ensemble of microbes that reside in and on and interact with the human body) [208] has a crucial role in the development and severity of allergic disorders and are involved in their resolution or chronicity. Currently, there is still a limited understanding of the interactions between the human microbiome, immune system and allergic disorders [209].

Allergic sensitisation and inflammation studies of human populations and experimental studies in animal models point to interactions between the external environment, the microbiome, and immune function in early life as causing an underlying predisposition to allergic sensitisation [98]. The majority of the studies report that an alteration in the microbiome [210] is associated with development or exacerbation of allergic conditions such as asthma [181-183,211]. Only a limited number of studies have been carried out in human populations, highlighting the need to further extend present knowledge regarding the relationship between the human microbiome and fungal allergy, which would give insight on the pathogenesis of fungal-induced allergies.

Thus, we will be investigating the role of human microbiome in fungal allergy. Of particular interest, is the association of gut mycobiome in the development of sensitivity or tolerance to fungal allergens.

Conclusion

Although progress has been made on identification and characterisation of fungal allergens, the pathogenesis of fungal allergic diseases still remains elusive because of the complexity of the immunological response to fungi exposure especially in African populations. Understanding this will impact on the way allergic diseases are diagnosed and managed in these populations.

Furthermore, there is need to further investigate the association between the gut mycobiome and fungal allergies as well as mechanistic pathways of interaction if any, between the two. This will inform the development of appropriate diagnostics and interventions for fungal allergic diseases, particularly those occurring as co- or multi-morbidities. This is critical for African health systems where the growing burden of non-infectious diseases must be managed on a background of endemic and epidemic infectious diseases.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Contributions

All authors contributed to the draft manuscript editing, reviewing and approval of the final version of the manuscript.

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List of Figures

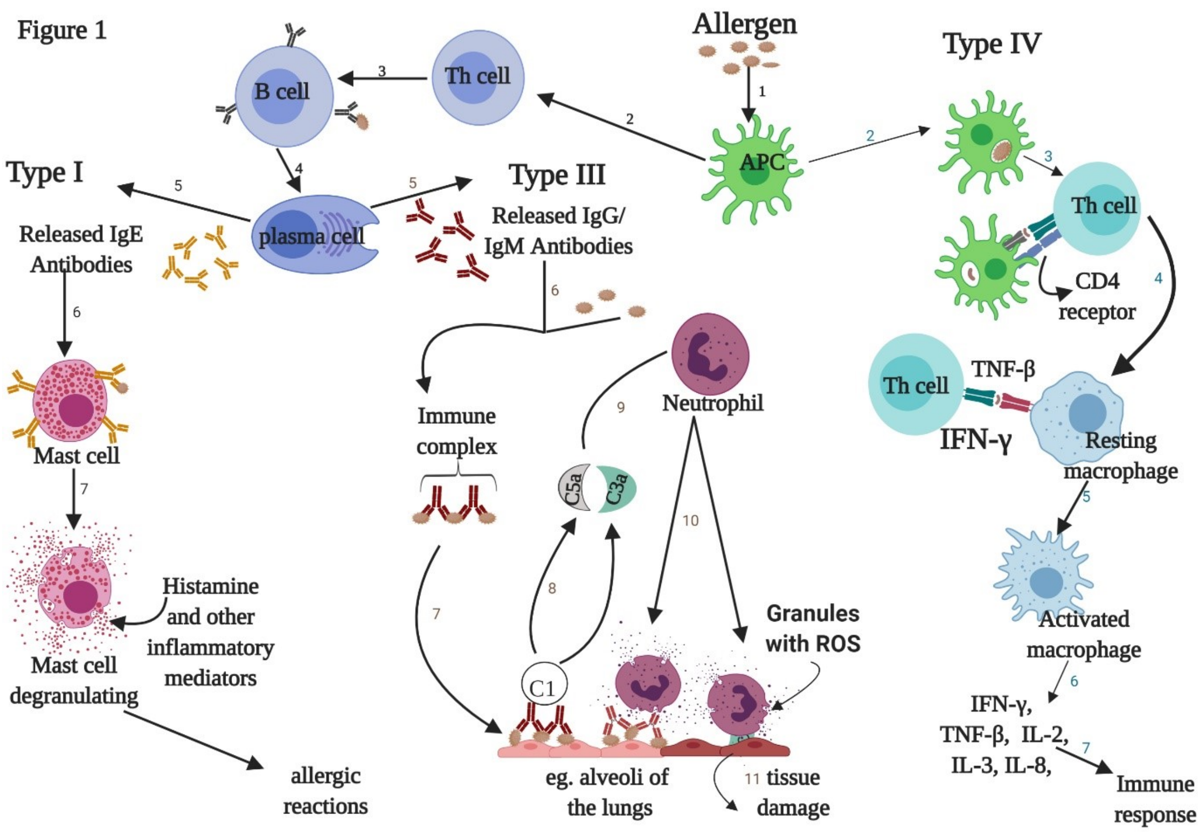

Figure 1: **Mechanisms of hypersensitivity reactions involved in fungal allergy**

In the Type I hypersensitivity reaction the mechanism of action involves preferential production of IgE (5), in response to allergens and the primary cellular component in this hypersensitivity is the mast cell (6). In Type III hypersensitivity reactions primary components are soluble immune complexes and complement (C3a and 5a) and the injury is caused by neutrophils. In Type IV hypersensitivity reactions, injury is caused by activated macrophages. Diagram adapted from Rajan et al.,[212].

Figure 2

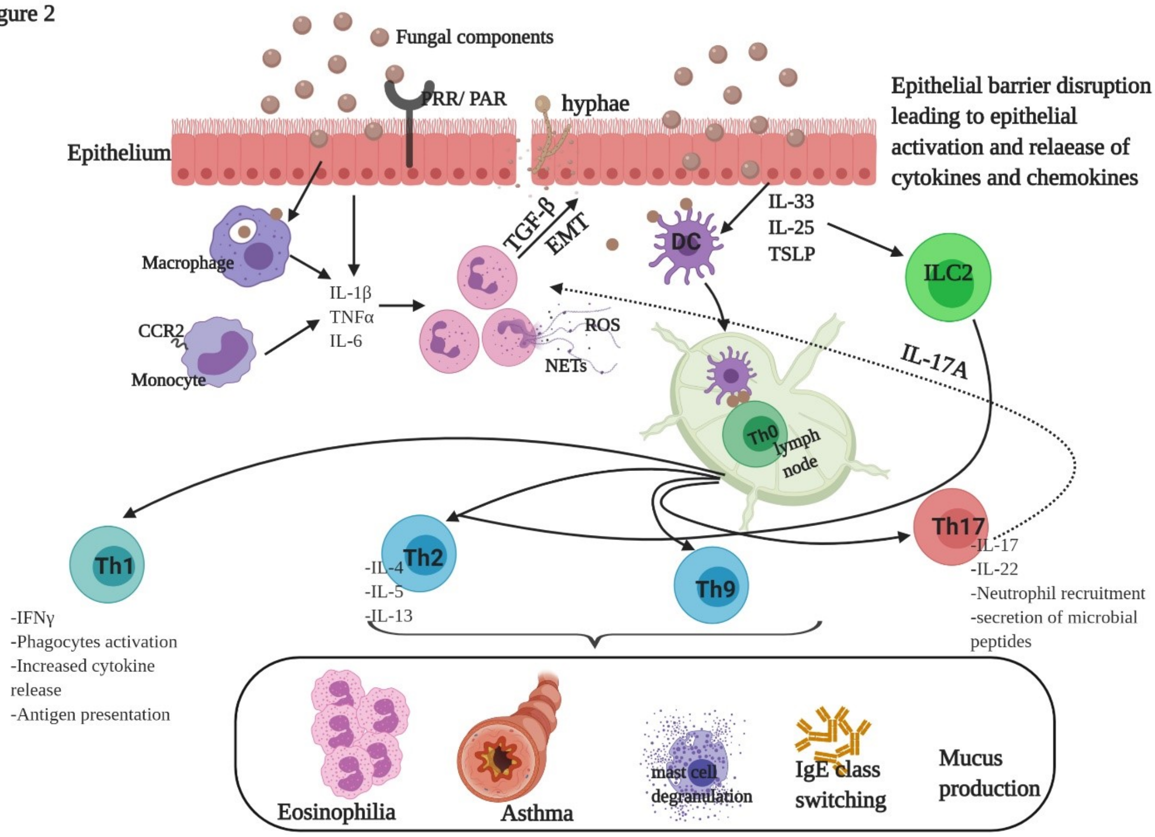

Figure 2: **Cells and cell-mediators involved in fungal allergic inflammation**

Possible effects of fungal components on the permeability of the airway epithelial and inflammatory responses. The epithelium is exposed to proteolytic enzymes from fungi, which digest proteins of the epithelial layer, making it more permeable. Exposure to fungal components induces the selective release and production of IL-33, IL-25 and TSLP by the airway epithelial cells. TSLP, IL-33 and IL-25 activate ILC2s to produce type 2 cytokines such as IL-5 and IL-13, initiating allergic inflammation. TGF-β: transforming growth factor beta; EMT: epithelial mesenchymal transition; IFN-γ: Interferon gamma. Adapted from references [173,175,209,213-218].