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Editorial

Allergic Bronchopulmonary Aspergillosis: Lessons Learnt from Genetics

Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction, most often encountered in patients with bronchial asthma or cystic fibrosis (CF), as a consequence of colonisation of the tracheobronchial tree by *Aspergillus fumigatus*.[1] It complicates the course of 2% to 32% of patients with bronchial asthma and 1% to 15% of patients with CF.[2,3] This disorder was first described by Hinson in 1952 from the United Kingdom,[4] whereas the first case was described from India in 1971.[5] The disease presents with varied clinical and radiographic manifestations ranging from an asymptomatic patient with or without pulmonary infiltrates to severe uncontrolled asthma with or without central bronchiectasis.[6] Bronchiectasis may be absent in the early stages of the disease (seropositive ABPA).[7-10] The major reason of interest in this entity stems from the fact that the condition responds remarkably to glucocorticoid therapy, and early diagnosis and treatment can prevent progression to end-stage lung disease.[11,12]

In ABPA, the immune responses are heavily skewed towards a Th2 CD4+ T-cell response with interleukin-4 (IL-4), IL-5 and IL-13 secretion with little or no IL-2 or interferon-gamma (IFN-γ) secretion.[13-17] *Aspergillus* hypersensitivity can be considered as the first step in the development of ABPA, and ABPA can be conceptualised as an exaggerated form of *Aspergillus* hypersensitivity. However, only a minority of patients with *Aspergillus* sensitivity go on to develop the complete clinical picture of ABPA.[18] Why does the immune response in ABPA differ from *Aspergillus* sensitive asthma patients? It was initially thought that exposure to large concentrations of *A. fumigatus* cause ABPA as in exposure to garbage dump sites, agricultural conditions, bird droppings, and smoking moldy marijuana.[4,19-22] While the exposure to the fungi is universal, ABPA is seen in only a minority of individuals demonstrating that specific host susceptibility factors may be important for the development of the disease. It has been hypothesised that ABPA develops in patients with bronchial asthma and CF who are genetically predisposed.[23] There are references to the relationship between genetic risk factors and ABPA in the published literature (Table 1).[14,15,24-41] The first insight into genetic risk factor for ABPA was made in 1978, when the association between human leukocyte antigen (HLA) alleles and the disorder was studied.[24] No consistent association between the HLA alleles and ABPA was noted. Since then, numerous studies have evaluated genetic predisposition in ABPA and have found association with numerous genetic mutations/polymorphisms. Abnormalities in the CF transmembrane conductance regulator (CFTR) gene, innate immune response and/or the adaptive immune response can predispose to ABPA.

The occurrence of ABPA in CF raises the possibility that mutations in the CFTR gene may be associated with ABPA. A key element in immunopathogenesis of ABPA may be exposure of bronchial lymphoid tissue to high levels of *Aspergillus* (and their allergens), perhaps because of abnormal mucus properties resulting from the CFTR mutations.[42] In support of this hypothesis, five small studies[26,27,29,31,41] suggest that subjects with ABPA have a higher carrier rate of CFTR mutations compared to the general population. Genetic polymorphisms in the innate immunity can lead to either persistence of *A. fumigatus* in the airways or modify the subsequent immune responses. The collectins (surfactant protein [SP]-A, SP-D, mannose binding lectin [MBL]), a family of antimicrobial peptides secreted into the airways; and, toll-like receptors (TLRs), a class of proteins that recognise structurally conserved molecules derived from microbes play an important role in innate immunity. Polymorphisms in the genes encoding these proteins (SP-A, MBL, TLR-9) have been shown to be associated with ABPA.[32,35,36,39,40] The adaptive immune system is composed of highly specialised processes that eliminate or prevent pathogenic challenges with the key player being T-cells. The polymorphic MHC class II molecules on antigen presenting cells play a critical role in restricting antigen specific T-cell activation, which is important in the induction of immune responses to extrinsic allergens. These events determine the ensuing phenotype of the responding T-cells, the nature of antibodies synthesised and the character of the resulting inflammatory response. Several authors have found association between MHC class II polymorphisms and ABPA (Table 1).[14,27,28] The T-cell receptors are another key component involved in T-cell recognition of an allergen, and T-cell receptor usage might play a significant role in the production of allergen specific antibodies. Chauhan *et al*[30] found that Vβ13 gene was associated with susceptibility to ABPA whereas the Vβ1 gene was associated with resistance. Finally, genetic polymorphisms of the cytokines (or their receptors) involved in adaptive immune response can also predispose to ABPA. Specifically polymorphisms of IL-10, IL-4Rα, and transforming growth factor-beta (TGF-β) genes have been associated with ABPA.[33,37,38]

Table 1. Studies evaluating genetic susceptibility in allergic bronchopulmonary aspergillosis complicating bronchial asthma and cystic fibrosis

Author (year)[reference]	Number of Patients with Disease	Control Population	Genetic Risk Evaluated	Results
Flaherty (1978)[24]	22 ABPA	69	HLA alleles	No consistent association with HLA
Morris (1980)[25]	21 ABPA; 82 asthma	100	HLA alleles	HLA B12 associated with production of IgE antibodies
Chauhan (1996)[14]	3 ABPA	–	HLA alleles	HLA DR2 and DR5 restriction noted in ABPA. Specific HLA DR2 (DRB1*1501, DRB1*1503 and DRB1*1601 and DR5 alleles (DRB1*1101, DRB1*1104 and DRB1*1202) were prevalent in ABPA vs controls
Miller (1996)[26]	11 ABPA	53	6 CFTR mutations	1 patient carried 2 CF (ΔF508; R347H) and 5 carried 1 CF (4 ΔF508; 1 R117H). Mutations seen in 6/11 ABPA vs 1/53 controls
Chauhan (1997)[15]	18 ABPA	Historical	HLA alleles	HLA DR2/DR5 restriction: 88.8% ABPA vs 42.1% controls. Frequency of HLA DR2 (44.4 vs. 19.9%) and DR5 (38.8 vs. 19%) significantly increased in ABPA. Same allele subtypes as described previously
Aron (1999)[27]	16 ABPA, 56 allergy, 98 CF	39	HLA alleles, 31 CFTR mutations	HLA DR4/DR7 increased in ABPA/allergy/CF vs controls. DR7 association highest in ABPA, DR5 non-significantly increased in ABPA. CFTR mutation (1 R1162X; 1 N1303K, 2 ΔF508) in 4/14 (28%) vs 4% general population
Chauhan (2000)[28]	35 asthma/CF associated ABPA, 50 Af asthma	98	HLA alleles	HLA DR2/DR5: 74.3% ABPA vs 36% Af asthma vs 34.7% controls. Specific HLA DR2 (DRB1*1503) allele almost exclusively seen in ABPA (20%)
Marchand (2001)[29]	21 ABPA, 43 Af negative asthma	142	13 CFTR mutations	CFTR mutations encountered in 6/21 (2 ΔF508; 1 G542X; 1 R1162X; 1 R117H; 1 717-1 G >A) ABPA vs 2/43 Af negative asthma vs 6/142 controls
Chauhan (2002)[30]	14 ABPA (12 asthma/2 CF), 12 Af asthma	–	T-cell receptors	86% of ABPA expressed Vβ13 gene indicating its role in susceptibility; Vβ1 seen in non-ABPA in dicating its role in resistance
Eaton (2002)[31]	31 ABPA, 23 Af asthma, 21 Af-asthma	34	16 CFTR mutations	4/31 patients with ABPA showed CFTR mutations (3 ÄF508; 1 R117H) vs. 1 of 23, 21 and 34 in Af-asthma, Af-asthma and controls, respectively
Saxena (2003)[32]	22 ABPA	23	SP A polymorphisms	2 intronic polymorphism SPA-1 (C1416T, T1492C) and 2 exonic polymorphism SPA-2 (G1649C, A1660G) increased in ABPA vs controls. SPA-2 A1660G and G1649C showed stronger association with ABPA and were associated with clinical markers of severity
Brouard (2005)[33]	27 ABPA, 119 Af colonisation	–	IL-10 polymorphisms	1L-10 -1082GG genotype non-significantly high in ABPA whereas the same genotype significantly high in those with Af colonisation
Kurup (2005)[34]	Murine ABPA model	–	Numerous gene expression profile	Of the 12000 genes studied, 1300 genes showed enhanced expression and represent chemokine, cytokine, growth factor, signal transduction and transmembrane receptor genes as well as gens related to arginine metabolism
Madan (2005)[35]	11 ABPA	20	SP A and MBL polymorphisms	Frequency of the 'A' allele of the intronic SNP G1011A of MBL significantly higher in ABPA than controls. ABPA patients with G1649C, A1660G alleles of SP-A2 and G1011A of MBL showed sig nificantly high IgE levels and eosinophilia
Kaur (2006)[36]	11 ABPA, 49 asthma with allergic rhinitis	84	MBL polymorphisms	G1011A intronic SNP of MBL significantly increased in asthma and ABPA compared to controls but not in ABPA vs asthma
Knutsen (2006)[37]	14 CF and 26 asthmatic ABPA, 56 non-ABPA CF (33) and asthmatic (23) controls	–	IL-4Rα polymorphisms	Any IL-4Rα polymorphisms seen in 38/40 (95%) ABPA vs 34/56 (61%) non-ABPA patients. The ile75val IL-4Rα SNP seen in 80% ABPA vs 54% non-ABPA. The ile75val IL-4Rα homozygous SNP seen in 43% ABPA vs 11% non-ABPA
Sambatakou (2006)[38]	9 ABPA, 2 SAFS, 1 AFS,	65-330	IL-10, IL-15, IFN-γ, TNF-α and TGF-β polymorphisms	ABPA associated with IL-10-1082*G and G/G, TGF-β +869*T allele. No association with IL-15, IFN-γ or TNF-α alleles
Vaid (2007)[39]	7 ABPA	47	SPA-1, SPA-2 and MBL polymorphisms	Intronic polymorphism at T1492C and codon polymorphism at G1649C of SP-A2 in ABPA. T allele at position 868 of MBL seen with increased frequency in ABPA
Carvalho (2008)[40]	22 ABPA, 14 SAFS	80	TLR polymorphisms	Susceptibility to ABPA seen with allele Con T-1237 C (TLR9). However, importance not known whether it is due to coexistent asthma or ABPA as all patients also had asthma
Lebecque (2011)[41]	18 ABPA		> 1300 CFTR mutations	12/18 ABPA patients showed CFTR mutation. No asthma control group

ABPA=Allergic bronchopulmonary aspergillosis, CF=Cystic fibrosis; Af=Aspergillus fumigatus; SAFS=Severe asthma with fungal sensitisation; AFS=Allergic fungal sinusitis; HLA=Human leukocyte antigen; CFTR=CF transmembrane conductance regulator; SP=Surfactant protein; IL=Interleukin; MBL=Mannose binding lectin; IFN=Interferon; TNF=Tumour necrosis factor; TGF=Transforming growth factor; TLR=Toll-like receptor; vs=Versus; IgE=Immunoglobulin E; SNP=Single nucleotide polymorphism

The caveat associated with the above studies is not only that they have studied different aspects of pathogenetic susceptibility factors in ABPA but also the numbers of patients are quite small. However, one thing which is clear is that ABPA represents the classic example of genetic hterogeneity, wherein mutations in different genes can result in the same phenotype. Thus, it can be hypothesised that on a background of genetic susceptibility[14,23,26-29,31-33,37-40] (Figure), inhaled conidia of *A. fumigatus* (and occasionally other *Aspergillus* species) are able to persist and germinate, leading to the growth of hyphae in mucus plugs. This leads to the release of *A. fumigatus* antigens and exoproteases that can compromise mucociliary clearance, stimulate and breach the airway epithelial barrier. This causes activation of the innate and adaptive immune system responses of the lung, including the epithelial and the alveolar production of several Th2 cytokines leading to total and *A. fumigatus* specific immunoglobulin E (IgE) synthesis, mast cell degranulation and promotion of a strong eosinophilic response.[43-46]

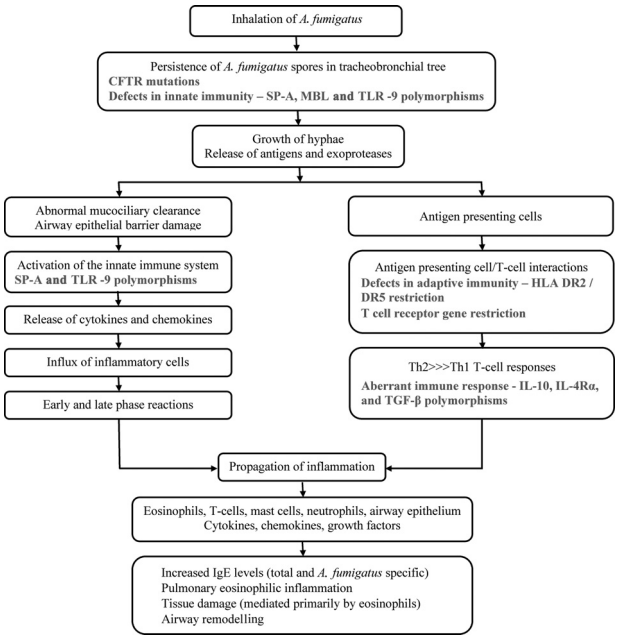

Figure. A hypothesised model of immunopathogenesis of ABPA. The role of specific genetic polymorphisms at various steps of pathogenesis have been highlighted.
CFTR=Cystic fibrosis transmembrane conductance regulator; MBL=Mannose binding lectin; SP=Surfactant protein; TLR=Toll-like receptor; HLA=Human leuckocyte antigen; IL=Interleukin; TGF-β=Transforming growth factor-beta; IgE=Immunoglobulin E

In conclusion, the ubiquitous presence of *A. fumigatus*, and its ability to infect the lung makes it an important fungal pathogen, which requires better mechanisms of diagnosis and effective treatment strategies. Recent advances in the understanding of the immune responses and developments in molecular biology have led to considerable insight in understanding of this entity. Further studis should characterise how genetic defects in CFTR, innate and adaptive immunity interact to predispose to ABPA. This understanding will enable the researchers/ clinicians to develop agents that can modulate the immune response for the benefit of the patient.

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