REVIEW 10.1111/1469-0691.12800

Host genetics and opportunistic fungal infections

Z.-D. Pana[1], E. Farmaki[2] and E. Roilides[1]

1) *Infectious Diseases Unit, 3rd Department of Paediatrics, and* 2) *Laboratory of Clinical Immunology, 1st Department of Paediatrics, Faculty of Medicine, Aristotle University School of Health Sciences, Thessaloniki, Greece*

Abstract

Current knowledge on the human pathophysiology of fungal infections highlights the crucial role of genetic pitfalls in specific immunity pathways that determine, together with other risk factors, the predisposition to and clinical outcome of fungal disease. In several studies, associations between gene polymorphisms and genetic errors have been implicated in an immunodeficiency phenotype and an increased incidence of opportunistic fungal diseases. The major challenge is to fully understand the complex interactions between genetic variations and multiple factors, and their relative contributions to the final clinical fungal disease phenotype. The aim of this review is to present updated knowledge on immunity genetics and susceptibility to medically relevant fungal diseases, such as those caused by *Candida*, *Aspergillus*, and certain other more rare fungi.

Keywords: Adaptive immunity, *Aspergillus*, *Candida*, fungi, immune markers, innate immunity
Article published online: 10 October 2014
Clin Microbiol Infect 2014; **20**: 1254–1264

Corresponding author: E. Roilides, Infectious Diseases Unit, 3rd Department of Paediatrics, Faculty of Medicine, Aristotle University School of Health Sciences, Hippokration General Hospital Konstantinoupoleos 49, Thessaloniki, 54642 Greece
E-mail: roilides@med.auth.gr

Introduction

Fungal infections remain a major cause of significant morbidity and mortality among specific patient groups and of an increased financial burden to the healthcare economics. One major priority in the field is the extended identification of all possible fungal-specific and host-specific factors for fungal disease predisposition, which is crucial knowledge that could 'refine' the future management of these patients. A large panel of well-defined clinical and laboratory parameters has been implicated in the development, severity and outcome of certain invasive fungal diseases (IFDs) in the immunocompromised host.

On the other hand, significant variability has been reported in the development and outcome of IFD among patients with the same predisposing factors, implying an individualized genetic pattern of susceptibility. Accumulating evidence has recently shown that immune system genetic variations leading to imbalances in both proinflammatory and anti-inflammatory responses may predispose to fungal infections. Hence, it is reasonable to speculate that genetic variations involved in important pathways of the innate and adaptive immune systems may represent a potential source of variability in susceptibility to IFD.

These genetic variations, known also as single-nucleotide polymorphisms (SNPs), refer to one of multiple alternative forms within a nucleic acid sequence that occurs with increased frequency (>1%) within a population and allows evolution by natural selection. SNPs are perceived as equally acceptable alternatives in a DNA sequence, and in most cases their impact on a gene may not significantly influence the activity of the encoded protein. Nevertheless, under certain circumstances, even these minor effects may significantly influence susceptibility to human disease. In contrast, mutations result from rare (<1%) genetic errors originating from unrepaired errors in the DNA replication process. These genetic errors can have an impact on the phenotype of an organism, especially if they occur within the pro-

tein-coding sequence of a gene. Mutations can be also divided into hereditary or germline mutations, when the error exists in the reproductive cells and can be passed from generation to generation, and acquired or somatic mutations, when the error occurs in the DNA of individual cells that develop throughout a person's life and is passed only to direct descendants of those cells. For many pathological conditions, there may even be different mutations in the gene, which may cause the same disease with variations in the phenotype. A few clinically relevant disorders may be the result of only a single defective gene mutation, and are called monogenetic disorders. These inherited diseases, controlled by a single pair of alleles, are passed on from one generation to another in a simple pattern according to Mendel's laws.

In recent years, variants in several immune-related SNPs and inborn genetic errors of immunity associated with monogenetic disorders have been proposed to affect immunity against *Candida* and *Aspergillus* species by influencing commensalism, symbiosis, latency and dissemination of the fungi. Selection of the appropriate candidate 'key' genes and their polymorphisms remains a great challenge, and metagenomic technologies hold promise for resolving questions regarding the functional effects of crucial genes in IFD predisposition. This review highlights the present knowledge on immunity genetics and susceptibility to IFD.

Immune Genetic Profile and Aspergillosis

Innate immunity plays a significant role in the initial phase of ingestion, killing and elimination of *Aspergillus* conidia. Furthermore, the local production of cytokines by activated macrophages and neutrophils seems to regulate proinflammatory (Th1) and anti-inflammatory (Th2) immune reactions. Several cytokine gene polymorphisms are considered to be candidate prognostic biomarkers for *Aspergillus* infection (Table 1). Cytokine functional gene polymorphisms (interleukin (IL)-10, IL-15, transforming growth factor (TGF)-β1, tumour necrosis factor (TNF)-α, and interferon (IFN)-γ) have been evaluated in patients with chronic cavitary pulmonary aspergillosis (CCPA) and allergic bronchopulmonary aspergillosis (ABPA) [1]. Specific alleles have been more frequently detected in patients suffering from invasive aspergillosis (IA), such as the IL-15 +13689A allele [1]. The presence of the IFN-γ 874T>A polymorphism as a single SNP or as a combined deficiency with an SNP in Toll-the like receptor (TLR)-4 gene (1063A>G) has shown a trend to cause increased susceptibility to IA [1,2]. CCPA patients have been genetically determined produce less IL-10 and TGF-β1, owing to the frequent presence of the IL-10 −1082G and TGF-β1 +869T alleles [1]. In patients undergoing allogeneic stem cell transplantation (SCT), SNPs in the promoter region of the IL-10 gene and an ACC haplotype are independent protective markers for invasive pulmonary aspergillosis (IPA), suggesting that the genotypic variability of the IL-10 gene promoter region modulates the production of IL-10 and indirectly influences the risk of developing IPA [3,4]. In particular, for the IL-10 −1082(AA) genotype, the results are rather controversial. According to Sainz *et al.*, the IL-10 −1082(AA) genotype is associated with resistance to the development of IPA, whereas in another study the genotype was associated with an increased risk of ABPA in patients with cystic fibrosis [5].

A polymorphism in the IL-4 receptor gene plays a role in the occurrence of ABPA [6]. Sainz *et al.* [7] evaluated the role of IL-1 gene cluster polymorphisms in the pathogenesis of, susceptibility to and resistance to IPA, and found that specific haplotypes (VNTR2/–889C/–511T) were significantly associated with the development of IPA, whereas others (VNTR2/–889C/–511C) were associated with resistance. In a recent study by Carvalho *et al.* [8], a prognostic role of IL-23 receptor gene polymorphism was found in patients undergoing SCT, implying that donors with the R381Q haplotype gave a protective effect against IA. In evaluation of the genetic risk for developing IPA, IL-6 gene polymorphisms (promoter at positions −174 (C/G) and −634 (G/C)) were not significantly associated with an increased predisposition to develop IPA [9].

As well as SNPs in other cytokine receptor genes, SNPs in the TNF receptor 1 and TNF receptor 2 genes have been associated with IPA predisposition in two studies, owing to decreased TNF expression [10,11]. SNPs in the gene encoding chemokine ligand 10, which enhances chemokine secretion after *Aspergillus* stimulation, seemed to influence susceptibility to IPA in alloSCT patients [12]. A non-synonymous SNP in the gene encoding plasminogen, a factor that binds to fungal cell wall of *Aspergillus fumigatus*, affected the risk of developing IA in patients after SCT [13]. An SNP in the gene encoding dectin-1 receptor, a major receptor for fungal β-glucans on myeloid cells, leads to a decreased Th17 response and seems to influence the presence of IA in non-SCT patients but not the clinical course of IA in SCT recipients [14]. However, in another study, this SNP increased the risk of IA, with the risk being highest when the SNP was detected simultaneously in both donor and recipient [15]. Finally, the carriage of several alleles of dectin-1 and DC-SIGN polymorphisms increases the risk of IPA [16].

The role of genetic variations of TLR genes in IA predisposition has been extensively evaluated, with partially contradictory results. TLR-2 gene polymorphism has not been associated with CCPA and IA in haematological patients after SCT [17,18].