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Review Article

Review Article

Genetic defects in fungal recognition and susceptibility to invasive pulmonary aspergillosis

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Abstract

The interindividual variability in the onset and clinical course of invasive pulmonary aspergillosis (IPA) raises fundamental questions about its actual pathogenesis. Clinical and epidemiological studies have reported only a few examples of monogenic defects, however an expanding number of common polymorphisms associated with IPA has been identified. Understanding how genetic variation regulates the immune response to *Aspergillus* provides critical insights into the human immunobiology of IPA by pinpointing directly relevant immune molecules and interacting pathways. Most of the genetic defects reported to increase susceptibility to infection were described or suggested to impair fungal recognition by the innate immune system. In this review, we discuss the contribution of host genetic variation in pattern recognition receptors to the development of IPA. An improved understanding of the molecular and cellular processes that regulate human susceptibility to IPA is ultimately expected to pave the way toward personalized medical interventions based on host-directed risk stratification and individualized immunotherapy.

Key words: Single nucleotide polymorphism (SNP), innate immunity, immunocompromised host, fungal recognition, pattern recognition receptor, personalized medicine.

Introduction: A genetic perspective on the host-*Aspergillus* interaction

Despite the existence of several well-known clinical risk factors, the determinism of invasive pulmonary aspergillosis (IPA) remains largely misconstrued. Because exposure to the fungus is required for infection to develop, IPA is often considered a textbook example of a disease that results from the interaction between the environment and the clinical circumstances of the patients at-risk. Like many human infectious diseases, IPA is characterized by significant interindividual variability in its development and progression. While a significant involvement might be credited to fungal virulence attributes, recent evidence has highlighted the dominant role of heritable factors in defining human susceptibility to IPA.[1–3] Mouse studies have also widely illustrated the influence of genetically-driven effects on IPA, by showing disparities between inbred strains regarding survival following experimental aspergillosis.[4]

Our current understanding of the genetic predisposition to IPA is derived from the study of individuals with rare monogenic defects and from cohort-based studies to identify common polymorphisms associated with disease.[2] By pinpointing the functional implications of these genetic variants to the cellular and molecular mechanisms that regulate the immune response, these reports have provided crucial insights into the genetic control of antifungal host defense in humans. Future studies evaluating the genetic architecture of the host-fungus interaction are therefore expected to significantly support clinical translation and personalized medical interventions in IPA.[5] In this review, we address our current knowledge on genetic variation in pattern recognition receptors (PRRs) and their role in susceptibility to IPA. Also discussed is the impact of genetic variation in these innate immunity components on the activation of antifungal immune responses and how these processes can be exploited in the personalized management of IPA based on individual host genetics.

Pattern recognition receptors and innate antifungal immunity

In 1992, Charles Janeway Jr. revolutionized our understanding of innate immunity with his concept of selective recognition of conserved microbial motifs by germline-encoded PRRs.[6] We now acknowledge that the first step required for the development of an innate immune response implies the recognition of pathogens by PRRs in an acute and conserved fashion.[7] Although there are considerable differences in the way different classes of pathogens are perceived by the immune system, the overall framework for fungal recognition typically involves the binding of conserved pathogen-associated molecular patterns (PAMPs) by PRRs.[8] Owing to its inherent dynamic composition and structural plasticity during germination and interaction with the host, the fungal cell wall is often considered the most relevant repository for PAMPs.[9]

Five major classes of PRRs have been identified to date: Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD) leucine-rich repeat containing receptors (NLRs), retinoic acid-inducible gene I protein (RIG-I) helicase receptors, and absent in melanoma 2 (AIM2)-like receptors (ALRs).[6] By inducing the secretion of proinflammatory cytokines and chemokines and activating mechanisms leading to phagocytosis and production of reactive oxygen species (ROS), PRRs not only mediate downstream intracellular events involved in pathogen clearance, but also participate in complex immunoregulatory processes and activation of adaptive immunity.[10] The efficiency of fungal recognition and interaction with phagocytes is also critically dependent on opsonization by soluble pattern recognition molecules, including collectins, pentraxins, ficolins and components of the complement pathway.[11] In addition, PRRs are also able to respond to products released from damaged host cells during fungal infection, including nucleic acids, alarmins and metabolic products, collectively known as danger-associated molecular patterns.[12]

The role of TLRs in antimicrobial defense was first reported in the 1990s following the observation that fruit flies lacking the hematocyte receptor Toll were remarkably susceptible to infection with fungi and Gram-negative bacteria.[13] Shortly thereafter, TLRs expressed on cells of the mammalian immune system were discovered. The extracellular domains of these receptors contain leucine-rich repeats involved in the recognition of PAMPs, whereas the amino acid sequence of the cytoplasmic domain is highly homologous to the sequences in the interleukin (IL)-1 and IL-18 receptors.[14] After engagement of TLRs by their cognate ligands, kinase cascades are activated, promoting the translocation of transcription factors to the nucleus, where they induce gene expression and downstream production of inflammatory mediators.[7,15]

The large family of CLRs includes members such as dectin-1, dectin-2, mannose receptor, dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN), macrophage inducible C-type lectin (Mincle), macrophage C-type lectin (MCL), and the recently identified MelLec.[16] These receptors have carbohydrate recognition domains and bind microbial polysaccharides commonly present in fungi and bacteria.[16] Dectin-1 was the first CLR to be identified and is currently the best described non-TLR receptor able to coordinate activation of adaptive immunity.[17] Following recognition of β-1,3-glucans, dectin-1 triggers different intracellular signaling pathways that, synergistically and through cross-regulatory mechanisms, regulate and fine-tune nuclear factor (NF)-κB activation and cytokine gene expression.[18] More recently, a novel CLR named MelLec (encoded by the *CLEC1A* gene) was demonstrated to specifically recognize 1,8-dihydroxynaphthalene (DHN)-melanin and to activate protective immunity to *A. fumigatus*.[19]

In addition to the mainly membrane-bound TLRs and CLRs, there are cytoplasmic receptors—NLRs and the DNA-sensing RIG-I helicase receptors—that are activated when pathogens invade a cell or release PAMPs into the cytoplasm. Although the exact fungal ligands that are recognized by NLRs are not known, their activation during infection results in the assembly of multimeric protein complexes named inflammasomes that convert inactive pro-IL-1β and pro-IL-18 into bioactive cytokines.[20] Specifically, the NLR family pyrin domain containing 3 (NLRP3) and AIM2 inflammasomes were shown to form a dual cytoplasmic surveillance system that orchestrates protective immune responses against *A. fumigatus*.[21] The contribution of NLRs to the immune response against *A. fumigatus* has nonetheless been recently found to extend beyond inflammasome formation. Strikingly, studies *in vitro* and in animal models have revealed that the NOD-containing receptor 1 (NOD1) plays an inhibitory role in the host defense against *A. fumigatus* by suppressing dectin-1 expression and cytokine responses responsible for optimal fungal killing.[22] These observations support the existence of highly dynamic regulatory mechanisms activated by intracellular fungal recognition with important consequences to the overall antifungal immune response.

Whatever the PRRs or soluble molecules implicated in fungal recognition or opsonization, the coordinated regulation of the immune response depends not only on the relative degree of stimulation of the individual receptors (e.g., specific PAMP exposure during fungal germination) but also on the level of receptor cooperation and cellular localization. For example, and despite this has not been exploited in detail in the context of aspergillosis, the cross-talk between TLRs and CLRs is needed for optimal antifungal immune responses.[8]

Genetic defects in pattern recognition receptors and susceptibility to infection

Genetic variants in the genes encoding PRRs can affect susceptibility to different fungal diseases, including IPA.[23] Currently,

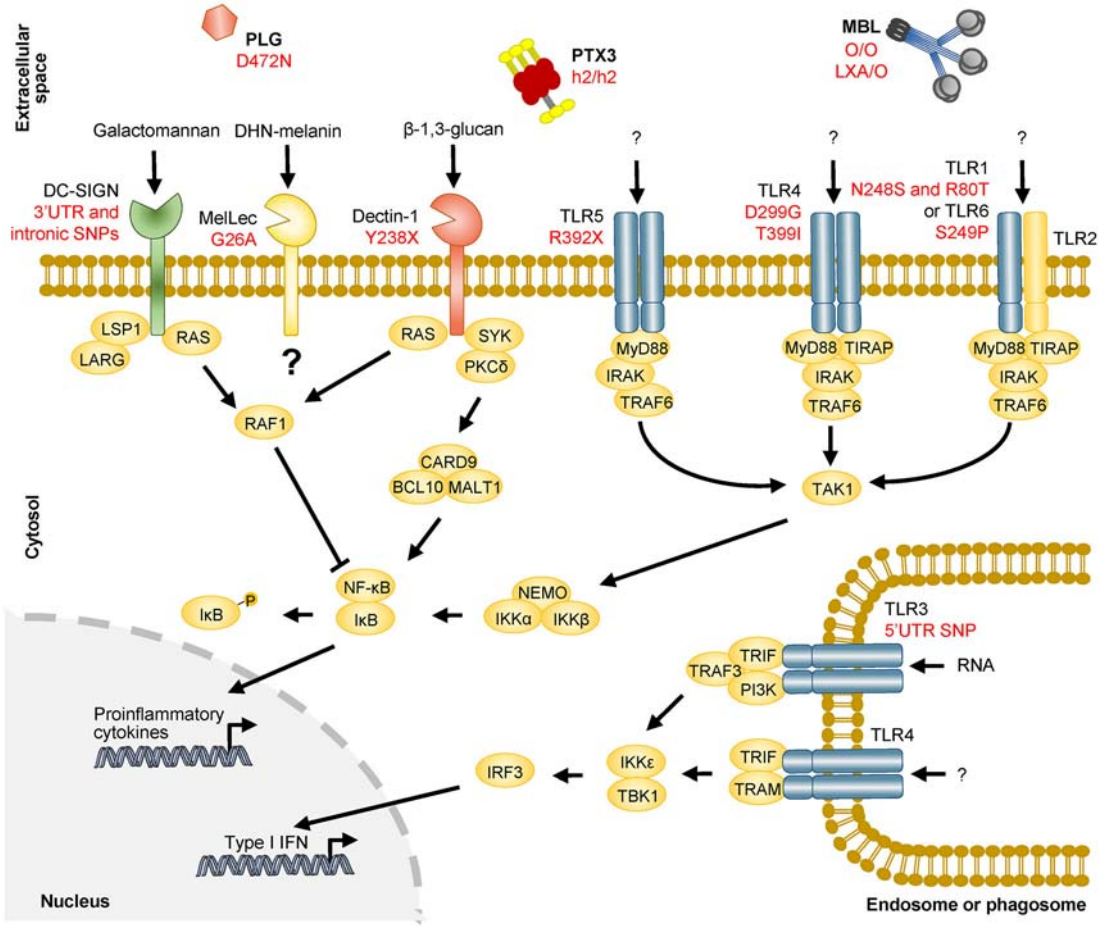

Figure 1. Genetic defects in PRRs and their role in susceptibility to IPA. PRRs are expressed on the cell surface and endosomes or are present in the cytosol, where they detect PAMPs, including fungal cell wall components such as β-1,3-glucans, DHN-melanin, or nucleic acids. The activation of downstream signaling pathways triggers different cellular processes, including the transcription of proinflammatory cytokines and chemokines, production of reactive oxygen species, phagocytosis and fungal killing. The genetic variants in PRRs that have been implicated in IPA as well as the amino acid changes underlined by non-synonymous variants or their localization in the gene region are indicated in red. h2/h2 denotes a diplotype in *PTX3* consisting of the GG and AA genotypes at rs2305619 and rs3816527, respectively. O/O and LXA/O represent low-producing genotype combinations of promoter and structural variations in *MBL2*. MyD88, myeloid differentiation primary response protein 88; TIRAP, Toll-interleukin-1 receptor (TIR) domain-containing adaptor protein; TRAM, TRIF-related adaptor molecule; IRAK, IL-1 receptor-associated kinase; TRAF, tumor necrosis factor receptor-associated factor; TAK1, transforming growth factor-β-activated kinase 1; NEMO, NF-κB essential modulator; IKK, inhibitor of NF-κB kinase; IκB, inhibitor of NF-κB; TBK1, TANK-binding kinase 1; PI3K, phosphoinositide 3-kinase; IFN, interferon; IRF, IFN regulatory factor; LSP1, leukocyte-specific protein 1; LARG, Rho guanine nucleotide-exchange factor; RAF1, RAF proto-oncogene serine/threonine-protein kinase; SYK, spleen tyrosine kinase; PKCδ, protein kinase C-δ; CARD9, caspase recruitment domain-containing protein 9; BCL10, B cell CLL/lymphoma 10; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1. This Figure is reproduced in color in the online version of *Medical Mycology*.

genetic defects have been identified across the different classes of PRRs, although in some cases (e.g., the NLR family), these have yet to be definitively linked with susceptibility to infection. The variety of implicated PRRs highlights the complexity of the host genetic signatures influencing antifungal host defenses and that regulate human susceptibility to IPA (Fig. 1). Although the focus of this review lies primarily on PRRs, several reports have also linked genetic variation in adaptive immunity components and IPA. For example, earlier studies have shown that genetic variation restraining the activation of the T helper (Th)17 pathway conferred resistance to IPA.[24] More recently, genetic variants in interferon (IFN)-γ, the hallmark cytokine of Th1 type of responses, were implicated in the risk of IPA.[25] Altogether, these observations highlight the central role that genetic variation in adaptive immunity may play in regulating overall susceptibility to IPA, particularly in patients without any obvious innate immune defects.

Genetic variation in Toll-like receptors

Soon after the initial description of TLRs, genetic variation in these genes was proposed to account substantially for interindividual differences in susceptibility to infectious and inflammatory diseases.[26] Although the monogenic deficiency of TLR pathways promotes large effect sizes, this is typically a rare (or very rare) event on the general population. Instead, the genes

encoding TLRs are remarkably polymorphic and encode many variant amino acid sites as the result of strong selective pressures during their evolution.[27] For this reason, and before the dawn of genome-wide association studies, polymorphisms in TLRs were considered biologically plausible candidates for involvement in susceptibility to infectious diseases, including fungal infections.[28]

A TLR4 haplotype underlying the concurrent D299G and T399I amino acid substitutions was reported to decrease the interaction of the receptor with its cognate ligand, lipopolysaccharide.[29] Importantly, the presence of these variants in donors of allogeneic hematopoietic stem-cell transplantation (HSCT) was associated with the development of IPA in the corresponding patients,[30] an association that has been validated in independent HSCT cohorts[31,32] and in immunocompetent individuals suffering from chronic aspergillosis.[33] Of note, the TLR4 haplotype was reported to delay the reconstitution of specific immune cell populations after transplant,[32] and this could be a critical mechanism explaining the described associations. Other studies have however failed to replicate the same associations.[34–36] In addition, the exact mechanism by which TLR4 variants may influence the immune response to *A. fumigatus* remains debated, particularly since the fungal ligand (or the endogenous molecule released during infection) is currently not known.

Genetic variation in other TLRs has also been deemed relevant to the risk of IPA, although no validation studies have been provided thus far. Earlier studies have reported associations between the non-synonymous polymorphisms N248S in TLR1 and S249P in TLR6,[36] but only TLR6 has been shown to be required for the human immune response to *A. fumigatus*.[37] Another interesting example regards TLR5, the receptor for flagellin, the PAMP present in the flagellum of flagellated bacteria.[38] The presence of a polymorphism leading to an early stop codon in TLR5 (R392X) abrogates recognition of flagellin.[39] Importantly, the presence of this polymorphism in the recipient was associated with an increased risk of IPA following HSCT,[40] thereby suggesting a likely important antifungal function of TLR5 in the nonhematopoietic compartment. However, functional data are not available, and further studies are warranted to identify the so far unsuspected mechanisms (and the ligand) by which TLR5 might influence susceptibility to IPA. In any case, the common frequency of this polymorphism, without driving a severe primary immunodeficiency phenotype, suggests that it has a redundant role in host defense.[41]

Despite better known for recognizing viral double stranded RNA,[42] TLR3 function is also important for antifungal immunity, particularly in the sensing of fungal nucleic acids by cross-presenting dendritic cells.[43] Of note, a regulatory variant in the 5′-untranslated region of human TLR3 leading to decreased expression of the receptor was found to compromise the efficient priming of protective memory $CD8^+$ T-cell responses to *A. fumigatus*, and to render HSCT recipients more prone to develop IPA.[43] This study provides a critical example of how genetic variation affecting fungal recognition may also have substantial implications in the activation of adaptive antifungal immunity, a notion that was strengthened by the recent implication of the same variant in the development of severe asthma with fungal sensitization.[44] As such, an improved understanding of how interindividual variation coordinates the activation of adaptive immunity might be helpful beyond disease stratification approaches. Indeed, the diagnostic performance of immunodiagnostic strategies based on the evaluation of *A. fumigatus*-specific adaptive immune responses[45] may benefit from an expanded knowledge of the genetic background of the patient. Further supporting this hypothesis, a promoter variant in the gene encoding the immunoregulatory cytokine IL-10 that underlined an increased risk of IPA was found to control the expression of the cytokine and to coordinate the activation of proinflammatory responses to the fungus.[46] Taken together, these observations imply that the success of novel diagnostic and immunotherapeutic approaches for IPA is conditioned to personalization based on the interindividual variability in immune function.[47]

Genetic variation in C-type lectin receptor signaling

Genetic variation in CLRs has also been implicated in susceptibility to IPA (Fig. 1). The genetic variability of dectin-1, the major PRR for β-1,3-glucan in the fungal cell wall, and its contribution to the risk of fungal infection has been extensively investigated. Genetic analysis of a family with recurrent vulvovaginal candidiasis and onychomycosis resulted in the identification of the early stop codon polymorphism Y238X.[48] This truncated form of dectin-1 was not appropriately expressed at the surface of myeloid cells and its ability to bind β-1,3-glucan was compromised, leading to defective production of cytokines, especially IL-17. Because the ability of cells to ingest and kill *Candida albicans* yeasts remained intact,[48] the contribution of dectin-1 deficiency to mucosal candidiasis was established to critically depend on the defective activation of Th17-mediated immunity. Whether the Y238X polymorphism also influences the isoform localization of dectin-1, a process known to regulate the signaling quality of the antifungal immune response,[49,50] remains to be assessed.

Although the clinical phenotype of patients with dectin-1 deficiency is relatively mild and less severe than that of patients with classic chronic mucocutaneous candidiasis,[51] heterozygous carriers of the dectin-1 stop codon were found to be more prone to develop IPA[52,53] and to be colonized with *C. albicans*[54] when undergoing HSCT. Additional variants in dectin-1, dectin-2, and DC-SIGN (CD209) were also implicated in the development of IPA in hematological patients.[55,56] Of note, genetic deficiency of dectin-1 in both transplant donors and recipients synergizes towards risk of infection,[53] a finding that was recently validated in the largest HSCT cohort at-risk of IPA collected to date,[35] and that highlights the pivotal contribution of dectin-1 expression in

multiple cell types to antifungal immunity. In addition, given that β-1,3-glucan recognition by dectin-1 has been demonstrated to confer innate immune memory to infection by regulating multiple processes of cellular metabolism,[57–59] it will be interesting to evaluate the extent to which the Y238X polymorphism contributes to the risk of IPA by impairing immunometabolic responses and induction of trained immunity.

Several members of a family with mutations in caspase recruitment domain-containing protein 9 (*CARD9*), the adaptor molecule that mediates signaling induced by dectin-1 and other CLRs, have also been found to display increased susceptibility to mucocutaneous fungal infections.[60] Strikingly, patients with rare mutations in CARD9 were also found to develop extrapulmonary aspergillosis with sparing of the lungs.[61] These mutations were found to compromise CARD9 expression and cytokine release, while retaining normal numbers of monocytes, neutrophils and Th17 cells. Although neutrophil phagocytosis, killing, and oxidative burst were intact, neutrophils failed to accumulate in the infected tissue as the result of a defective production of neutrophil chemoattractants in extrapulmonary tissue. It is currently not known whether common polymorphisms with smaller effect sizes on CARD9 function may also be important risk factors for aspergillosis in immunocompromised hosts, regardless of the affected site. Of note, multiple CLRs signal through CARD9, and the more severe phenotypes of CARD9 deficiency are most likely due to antifungal immunity mechanisms that are independent of dectin-1,[62–64] bringing to light the plausible hypothesis that genetic variation in CLRs other than dectin-1 might also regulate the risk of IPA.

The discovery of MelLec and its functional characterization as the receptor for DHN-melanin from *A. fumigatus* prompted the identification of the nonsynonymous polymorphism G26A driving an amino acid substitution in the cytoplasmic tail of MelLec.[19] The presence of G26A in HSCT donors was found to strongly increase the risk of IPA as the result of a general defect in cytokine production by PBMCs and human macrophages, likely due to deficient intracellular signal transduction and not fungal recognition. Although contrasting with data showing that MelLec expression in mice is restricted to a specific population of endothelial cells,[19] this finding highlighted the importance of MelLec expression in myeloid cells to human immunity to *A. fumigatus*.

Defects of soluble pattern recognition receptors

Some components of the complement system have the capacity to interact with and bind to microbial polysaccharides without transducing intracellular signals, thereby functioning as soluble PRRs. One critical example is mannose-binding lectin (MBL), which binds carbohydrate structures of microorganisms and activates the complement system.[65] A number of studies has established that genetic variation drives a strong effect on the levels and function of MBL in as much as 8% of individuals in a given population, and yet these do not display any obvious clinical consequences.[66] Although not presenting as an outright immunodeficiency, MBL deficiency is acknowledged as an important risk factor for infection, particularly in immunocompromised hosts. For example, low circulating concentrations of MBL were detected in patients suffering from IPA,[67] although the extent to which genetic variation regulated this phenotype was not assessed.

The long pentraxin-3 (PTX3) has been shown to bind microbial moieties from a vast range of pathogens, including bacteria, viruses and fungi, particularly *A. fumigatus*.[65] Although no classic immunodeficiency phenotype related to PTX3 has been disclosed to date, common polymorphisms have been proposed as risk factors for multiple infectious diseases, namely, *Pseudomonas aeruginosa* colonization in cystic fibrosis patients[68] and urinary tract infections.[69] Remarkably, and in line with its nonredundant role in immunity to *A. fumigatus* in mouse models of infection,[70] genetic variation in the human gene encoding PTX3 was revealed as a critical risk factor for IPA following HSCT.[71] This association was validated in a large, independent study[35] and extended across different clinical settings, including solid organ transplant recipients[72,73] and patients with chronic obstructive pulmonary disease.[74,75] Taken together, these studies disclose genetic variants in PTX3 as the most robust genetic markers for IPA identified to date. Mechanistically, PTX3 deficiency was found to hamper the normal alveolar expression of the protein, and, at a cellular level, it impaired the antifungal effector mechanisms of neutrophils.[71] In fact, neutrophil function appears to be critically relevant to the observed association since the association signal was lost in patients that developed IPA in the context of severe neutropenia.[71,76] In addition, because PTX3 binding to myeloid differentiation protein 2—an adapter of the TLR4 signaling complex[15]—is critically required for immune protection in experimental aspergillosis,[77] it is tempting to speculate that the concurrent genetic deficiency of PTX3 and TLR4 might underlie an enhanced risk of IPA than the individual defects alone, something that has yet to be documented.

Alveolar levels of PTX3 have been endowed with significant diagnostic potential in the discrimination of microbiologically confirmed pneumonia in mechanically ventilated patients.[78] Given that these vary according to individual PTX3 genotypes,[71] the quantification of PTX3 in bronchoalveolar lavage fluids may be regarded as a potentially useful complementary surveillance measure to the current mycological diagnostic workup. Perhaps more importantly, genetic variation in PTX3 has also been shown to profoundly influence the levels of proinflammatory cytokines in the lung of patients suffering from IPA as well as their performance in diagnostic approaches.[79] Finally, the fact that restoring normal levels of PTX3 reverts the functional defect of neutrophils *in vitro*[71] further highlights the potential of PTX3-based immunotherapies to treat (or prevent) IPA in patients

at-risk.[80] Indeed, the supplementation of antifungal therapy with recombinant PTX3 treatment has been found to surpass the efficacy of the drug alone in animal models of IPA.[81,82]

Other relevant examples of genetic defects in soluble PRRs include the identification of a deleterious variant (D472N) in plasminogen (PLG)—a regulatory molecule with opsonic properties—as an important modulator of susceptibility to IPA in humans.[83] Strikingly, the contribution of D472N to IPA was identified by resorting to a pioneering strategy based on the genetic mapping of survival data of mice subjected to experimental infection. This highlights the potential for similar preclinical-driven approaches in the discovery of additional genetic risk signatures for fungal infection by testing different models of infection and evaluating readouts other than survival alone (e.g. specific immune function traits).

Opportunities for clinical translation of IPA genetics

Recent studies have thoroughly implicated genetic variation in PRRs and downstream signaling pathways in the susceptibility to IPA. Nevertheless, additional efforts are required in many cases to identify the actual causative alleles, their functional consequences and the biological mechanisms through which they influence the pathogenesis of IPA. Despite the undeniable evidence gathered so far, the development of strategies translating insights on the genetic basis of IPA into improved patient outcomes is a major challenge. This has mostly been attributed to the effect size of the identified variants, which is typically not discriminatory enough to inform clinical decision making, as many patients carrying the implicated variants will not develop infection. To enhance the predictive performance of the genetic information, future studies are expected to integrate this and other host and pathogen factors into combined stratification models for evaluation of risk and progression of disease, including treatment responses and durations, and adverse events. Although the use of genetic information to predict the risk of IPA is unlikely to alter clinical practice in the near future, a recent study has nonetheless demonstrated that combining a set of genetic and clinical factors into a predictive model could be used to guide preemptive therapy in hematological patients.[84]

In addition to risk stratification approaches, genetic variation in PRR signaling is also expected to strongly influence the success of immunotherapeutic strategies, particularly if aiming at the manipulation of these and other related pathways. Several clinical trials performed to date have failed to account for genetic variation and its relevant consequences on subgroups of individuals, and this may partly explain the disappointing outcomes of trials involving anti-inflammatory agents for the treatment of sepsis.[85] There is therefore an urgent need to pinpoint the interindividual genetic variation that may be potentially relevant in the stratification of clinical trials of immunomodulatory agents by host genotypes.

The application of systems biology and next-generation sequencing technologies now provide an exciting way to identify essential genes and pathways in the host-fungus interaction at a level of complexity that was previously impossible.[86] Several genome-wide studies exploring susceptibility to IPA are underway and are expected to provide novel and unbiased insights into the genetic defects contributing to the development of disease. Similar functional genomics approaches have already been used to identify new important players controlling susceptibility to candidemia in critically ill patients.[87,88] These studies however did not account for the dynamic contribution of genetic variants to the regulation of gene expression during fungal infection, a process that varies robustly between individuals and influences phenotypes such as cytokine production, immune cell morphology and function, and ultimately immunity to infection. The genetic analysis of gene expression represents therefore a powerful approach to generate maps of the human genomic architecture that will become pivotal for the functional interpretation of variants likely to arise from the ongoing genome-wide initiatives.[89]

The many studies addressing polygenic susceptibility to IPA have provided significant advances to our current understanding of its immunobiology. The degree to which the host genetic background impacts the antifungal host defense depends on adding effects of single genetic factors with modest effect sizes and their complex interactions with clinical predisposing factors. Approaches targeting interindividual genetic variation may provide important clinical tools for the identification of patients that might benefit from enhanced diagnostic surveillance or alternative prophylaxis and treatment strategies. More importantly, the improved understanding of the multiple targets and pathways that are directly affected by genetic variation may also contribute to innovative and personalized immunotherapeutics. The identification of genetically determined immune defects may open new avenues for innovative therapies based on the restoration of lacking or underproduced immunoregulatory molecules. The genetic deficiency of PTX3 impairing neutrophil function represents a critical example of a condition that may targeted in such a manner.[76]

The first steps uncovering the genetic signatures of IPA and how these may improve diagnosis and therapy have been taken.[90] However, there is still much to be learned about the genetic regulation of the human immune response to *Aspergillus* and the mechanisms through which genetic variants contribute to IPA. Establishment of larger and carefully controlled patient cohorts, as well as functional studies to fine-map the biological mechanisms of association with infection, are ultimately required. These approaches will support the integration of genetic testing into clinically valid processes aimed at the stratification of risk and progression of IPA and will provide pivotal information for the identification of novel therapeutic targets.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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