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Genetic Variation and Fungal Infection Risk: State of the Art

Michail S. Lionakis [1]

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Abstract
Purpose of Review Fungal infections cause significant mortality in patients with acquired immunodeficiencies including AIDS, hematological malignancies, transplantation, and receipt of corticosteroids, biologics or small-molecule kinase inhibitors that impair key immune pathways. The contribution of several such pathways in antifungal immunity has been uncovered by inherited immunodeficiencies featuring profound fungal susceptibility. Furthermore, the risk of fungal infection in patients with acquired immunodeficiencies may be modulated by single nucleotide polymorphisms (SNPs) in immune-related genes. This review outlines key features underlying human genetic fungal infection predisposition.
Recent Findings The discovery of monogenic disorders that cause fungal disease and the characterization of immune-related gene SNPs that may regulate fungal susceptibility have provided important insights into how genetic variation affects development and outcome of fungal infections in humans.
Summary Recognition of individualized genetic fungal susceptibility traits in humans should help devise precision-medicine strategies for risk assessment, prognostication, and treatment of patients with opportunistic fungal infections.

Keywords Fungal infection · Inherited immunodeficiency · Single nucleotide polymorphisms · Candidiasis · Aspergillosis · Genetic

Introduction

Despite continuous and ubiquitous exposure of humans to fungal microorganisms via the respiratory and gastrointestinal mucosal surfaces and the skin, the majority of these fungal encounters do not result in clinical disease. Endothermy and homeothermy [1], and the induction of potent innate and adaptive antifungal immune responses account for the resistance of mammals against most fungi [2, 3]. In the past few decades, advances in clinical medicine that include the wider implementation of hematopoietic stem cell or solid organ transplantation and the advent of effective chemotherapeutic and/or immunomodulatory treatments for neoplastic and autoimmune diseases have led to a significant expansion of patient populations with iatrogenic immune suppression that are at risk for developing opportunistic fungal infections [2, 3].

Despite the administration of antifungal drugs with potent activity *in vitro* and in preclinical models, such fungal infections carry unacceptably high mortality rates and represent unmet medical conditions. To improve fungal infection-associated patient outcomes, research efforts have primarily focused on the discovery of novel effective antifungal agents and the development of improved fungal-targeted diagnostic tests [4, 5]. More recently, increased research interest has been generated in identifying individualized genetic factors that may enhance the risk of developing opportunistic fungal disease and/or suffering worse outcomes from such infections. Indeed, such knowledge could aid in devising precision medicine strategies for risk stratification, prognostication, prophylaxis, vaccination, and/or treatment of patients at risk for opportunistic fungal infections.

The research field of immunogenetic risk of fungal disease in humans has been largely ignited by the discovery and study of inherited monogenic disorders that cause susceptibility to fungal infections, which has revealed important immunoregulatory pathways that are specialized for the tissue-specific

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✉ Michail S. Lionakis
lionakism@mail.nih.gov

[1] Fungal Pathogenesis Section, Laboratory of Clinical Immunology & Microbiology (LCIM), National Institute of Allergy & Infectious Diseases (NIAID), National Institutes of Health (NIH), 9000 Rockville Pike, Building 10, Room 12C103A, Bethesda, MD 20892, USA

control of fungal pathogens [6–8]. The characterization of these pathways has catalyzed the study and identification of SNPs in immune-related genes within the same or other signaling pathways that may regulate the risk of fungal disease in patients with acquired immunodeficiency states.

Herein, I briefly outline current concepts pertaining to genetic variation in immune pathways, whether monogenic or not, which regulate protective mucosal and systemic host defense against the most common human fungal pathogens such as *Candida*, *Aspergillus*, *Cryptococcus*, and endemic dimorphic fungi. This review discusses both (a) inborn errors of immunity that underlie the spontaneous development of severe human fungal disease and (b) immune-related gene SNPs that may modulate the risk of acquisition and/or outcome of fungal infections in critically ill patients in the intensive care unit (ICU) and in patients with iatrogenic immunosuppression such as recipients of allogeneic hematopoietic stem cell transplantation (HSCT).

Inherited Monogenic Disorders that Predispose to Chronic Mucocutaneous Candidiasis (CMC): the Key Role of IL-17 Receptor (IL-17R) Signaling

In 2009, Sarah Gaffen's laboratory was the first to demonstrate the critical contribution of IL-17R signaling in host defense against oropharyngeal candidiasis in mice [9••, 10, 11]. Mechanistically, IL-17 cytokines (i.e., IL-17A, IL-17F) that are produced locally at the mucosa by αβ T cells (natural Th17 cells), by γδ T cells, and, to a lesser extent, by innate lymphoid cells type 3, act on IL-17RA and IL-17RC on the surface of mucosal epithelial cells to induce the generation of potent antimicrobial peptides (e.g., β-defensin 1, β-defensin 3, S100a8, S100a9) that exert direct anti-*Candida* activity and restrict mucosal fungal invasion [9–14]. Concordantly, in 2011, seminal work led by Jean-Laurent Casanova and Anne Puel showed that genetic deficiency of IL-17R signaling in humans, in the form of either IL-17RA or IL-17F deficiencies, predisposes to CMC, which is characterized by recurrent infections of mucosal surfaces by *Candida* species [15]. Follow-up work by the same group discovered that inherited deficiencies in IL-17RC or the IL-17R adaptor ACT1 (TRAF3IP2) also drive susceptibility to CMC in humans [16–18]. Some of these monogenic disorders (i.e., IL-17RA and ACT1 deficiencies) can also manifest with staphylococcal skin disease and pulmonary bacterial infections, indicative of broader mucocutaneous host defense impairments caused by IL-17R signaling defects [15–18]. Notably, consistent with the segregation of immune factors that are required for mucosal versus systemic control of *Candida* [3, 19], the aforementioned inborn errors of IL-17R-mediated immunity do not predispose patients to systemic candidiasis despite the recurrent nature of CMC.

Additional inherited immunodeficiencies that are caused by mutations in other genes beyond the IL-17R signaling cascade manifest with CMC by directly or indirectly affecting IL-17R-dependent immune responses [8]. Such examples include (but are not limited to) *RORC* mutations that impair Th17 cell development [20], autosomal-dominant hyper-IgE (Job's) syndrome caused by dominant-negative *STAT3* mutations that abrogate STAT3-dependent RORγt-mediated generation of Th17 cells [21], DOCK8 and CARD9 deficiencies that lead to defective Th17 cell differentiation [22, 23], *STAT1* gain-of-function mutations that impair Th17 cell development indirectly via the induction of Th17 cell-inhibitory cytokine circuits [24], and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) caused by *AIRE* mutations that feature neutralizing autoantibodies against Th17 cell-derived cytokines [25, 26], similar to patients with thymoma [27], who also develop mucosal candidiasis (reviewed in detail elsewhere [3, 6–8]).

Of interest, the introduction of IL-17R signaling-targeted biologics in the treatment of inflammatory and autoimmune disorders, primarily psoriasis and inflammatory bowel disease, has provided an additional layer of clinical evidence for the crucial role of this immunoregulatory pathway in mucosal host defense against *Candida* in humans. Indeed, patients who receive biologics that inhibit IL-12p40 (ustekinumab), IL-23p19 (guselkumab, tildrakizumab), IL-17RA (brodalumab), IL-17A (secukinumab, ixekizumab), or IL-17A/IL-17F (bimekizumab) occasionally develop refractory mucocutaneous, but not systemic, candidiasis [28].

Inherited Monogenic Disorders That Predispose to Invasive Fungal Infections: Fungal Infection-Specific Differential Contribution of Neutrophils, Mononuclear Phagocytes, and T Cells to Effective Host Defense

The identification and characterization of a plethora of inherited monogenic disorders in recent years has highlighted the critical contribution of certain immunoregulatory pathways and immune cell subsets in host defense against invasive infections by *Candida*, *Aspergillus*, endemic dimorphic fungi, and *Cryptococcus* [7].

Invasive Candidiasis

Effective immunity against invasive candidiasis depends on myeloid phagocyte recruitment and effector function [19, 29]. The role of oxidative burst-dependent phagocyte fungal killing in mediating control of invasive candidiasis has been long-recognized given that a proportion of patients with complete myeloperoxidase deficiency or chronic granulomatous disease

(CGD), caused by mutations in the NADPH oxidase complex, can spontaneously develop invasive *Candida* infections without an associated breach in mucocutaneous barriers by central intravenous catheters, abdominal surgery or chemotherapy-induced mucositis [30, 31]. However, the majority of myeloperoxidase-deficient and CGD patients do not develop invasive candidiasis indicating that an intact mucocutaneous barrier, which as mentioned earlier depends on functional IL-17R signaling, and non-oxidative burst-dependent mechanisms of phagocyte fungal killing can compensate for the lack of reactive oxygen species-mediated phagocyte functions.

In recent years, CARD9 deficiency has emerged as an important inherited immunodeficiency that predisposes to both mucosal and invasive candidiasis, being the only monogenic disorder known to date to combine enhanced mucosal and systemic *Candida* infection risk [32–34, 35•, 36]. Of interest, patients with CARD9 deficiency only develop fungal disease without infection susceptibility to non-fungal microorganisms or predisposition to non-infectious complications [22]. Importantly, CARD9-deficient individuals develop invasive *Candida* infections with a predilection for certain anatomical sites, namely the central nervous system (CNS), the eyes, the bone, and the gut, without reported hepatosplenic or renal candidiasis thus far.

The CNS-targeted fungal susceptibility of CARD9-deficient patients has recently been elucidated. Specifically, CARD9 deficiency is associated with a significant defect in mobilizing neutrophils to the *Candida*-infected CNS tissue in mice and humans [32, 37]. This defect lies at the level of production of key mediators of neutrophil recruitment in the infected CNS tissue rather than at the level of neutrophil-intrinsic chemotaxis. Indeed, we recently showed that sequential production of IL-1β and CXCL1 by CARD9-expressing CNS-resident microglia, upon their stimulation by the *Candida albicans* secreted peptide toxin candidalysin [38, 39] and subsequent activation of p38 and c-Fos signaling, is fundamental for the trafficking of protective CXCR2-expressing neutrophils from the blood into the *Candida*-infected CNS [37]. This axis is impaired in CARD9 deficiency and results in CNS-specific neutropenia during fungal disease that contributes to the CNS infection susceptibility of CARD9-deficient patients. Moreover, the limited number of neutrophils that accumulate in the infected CNS are defective in their ability to non-oxidatively kill unopsonized *Candida* yeast cells [32, 40], which contributes to the collective impairment of effector function of neutrophils in the setting of CARD9 deficiency during CNS fungal disease. Given the refractory nature of fungal disease in these patients, adjunct GM-CSF treatment has been successfully used in some CARD9-deficient patients [41•, 42, 43•], while others have required allogeneic HSCT for infection control [44•].

CARD9 is an intracellular adaptor molecule that relays C-type lectin receptor-dependent fungal sensing signals downstream of the spleen tyrosine kinase Syk [45, 46]. Of note, the Syk inhibitor fostamatinib is currently administered in > 40 clinical trials (www.clinicaltrials.gov) in patients with various acquired conditions such as rheumatoid arthritis, acute leukemia, lymphoma, graft-versus-host disease, solid tumors that themselves alone predispose patients to develop invasive candidiasis, and other fungal infections [47]. In addition, fostamatinib was recently approved by the US Food and Drug Administration (FDA) for the treatment of patients with refractory chronic immune thrombocytopenia. Therefore, based on the profound susceptibility of CARD9-deficient patients to fungal disease, fostamatinib-treated individuals should be closely monitored clinically for the development of invasive candidiasis or other fungal infections that can also affect CARD9-deficient patients such as mucosal candidiasis, extrapulmonary aspergillosis, deep-seated dermatophytosis, and subcutaneous or CNS phaeohyphomycosis [34, 48, 49, 50•, 51•].

Invasive Aspergillosis

Effective immunity against invasive pulmonary aspergillosis relies on neutrophils and recruited monocytes [52]. CGD is the prototypic inherited immunodeficiency to predispose humans to invasive aspergillosis, with an associated lifetime infection risk of ~ 40–50% [53]. CGD patients display an enrichment of invasive aspergillosis caused by cryptic *Aspergillus* species that exhibit different clinical behavior compared to *Aspergillus fumigatus*, which typically causes infection in patients with iatrogenic immunosuppression [54]. The exception to the rule of CGD-associated invasive aspergillosis is deficiency in the p40phox subunit of the NADPH oxidase complex, which does not impair oxidative burst-dependent neutrophil fungal killing and, as a result, does not predispose to invasive aspergillosis in stark contrast to the deficiencies in the p22phox, p47phox, p67phox, and gp91 subunits of the NADPH oxidase complex [55••]. This observation is consistent with the previously reported finding that the degree of residual reactive oxygen species generation by CGD neutrophils directly correlates with favorable patient outcomes (including resistance to invasive infections) [56].

Besides CGD, other inherited monogenic disorders that predispose to invasive aspergillosis include GATA2 haploinsufficiency and *STAT1* gain-of-function mutations, yet, the underlying immunological mechanisms of impaired phagocyte functions remain unknown in these patients [7]. Moreover, patients with autosomal-dominant hyper-IgE (Job's) syndrome can develop invasive aspergillosis secondary to pre-existing structural lung disease, not because of neutrophil recruitment or effector function defects [57]. Recently, deep intronic *STAT3* mutations that exert dominant-negative effects were reported, which would have been missed by Sanger sequencing of coding regions and essential splice sites

[58•], as well as splice site *STAT3* mutations that lead to STAT3 haploinsufficiency [59], which may predispose to invasive aspergillosis that involves extrapulmonary tissues with sparing of the lungs.

Two inherited immunodeficiencies which lead to bacterial infection susceptibility but have not been known to predispose to invasive aspergillosis are X-linked agammaglobulinemia due to *BTK* mutations and genetic C5 deficiency. Strikingly, and unexpectedly based on the absence of invasive aspergillosis susceptibility in the corresponding monogenic disorders, administration of ibrutinib, a small-molecule kinase inhibitor of BTK, and of eculizumab, a humanized monoclonal antibody targeting C5a, has been associated with the emergence of invasive aspergillosis, including cases of disseminated disease involving the CNS. Ibrutinib treatment confers varying degrees of invasive aspergillosis risk ranging from ~ 3 to ~ 40% depending on the underlying malignancy and co-administration of corticosteroids and/or other immunosuppressive therapies [60••, 61–64]. BTK is expressed on myeloid phagocytes and ibrutinib-mediated inhibition of BTK on phagocytes impairs their anti-*Aspergillus* activity [65••]. Notably, eculizumab-associated invasive aspergillosis was recently recognized in post-marketing surveillance of eculizumab-treated patients, which prompted the FDA to update the package insert with a warning for this infection, besides the well-recognized risk for infections due to encapsulated bacteria [66, 67]. The reasons for the discrepancy in the phenotypes between the aforementioned two monogenic disorders and the corresponding pharmacological inhibitors remain elusive and require investigation but may reflect the detrimental nature of acute blockade of the corresponding immune pathways relative to genetic defects, which manifest from birth and may allow for developing efficient compensatory immune mechanisms. Clinical awareness will be required to determine whether acute inhibition of other immune pathways by small-molecule kinase inhibitors or biologics may unexpectedly lead to invasive fungal infection susceptibility despite the absence of observed aspergillosis risk in the corresponding inherited monogenic disorders.

Invasive Infections by Endemic Dimorphic Fungi or Cryptococcus

Effective immunity against endemic dimorphic fungi (i.e., histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, talaromycosis) and cryptococcosis relies on the cross-talk between Th1-polarized lymphocytes and activated monocytes/macrophages, which engulf fungal elements for intracellular destruction [3].

Genetic defects across the IL-12/IFN-γ signaling pathway such as mutations in IL-12 or its receptors, mutations in IFN-γ receptors, loss-of-function *STAT1*, *STAT3*, or *STAT4* mutations, GATA2 haploinsufficiency, and *STAT1* gain-of-function mutations are well-recognized to predispose to varying degrees of susceptibility to invasive infections by the aforementioned intracellular fungi, but also by other intracellular pathogens such as nontuberculous mycobacteria of low virulence potential [3, 7]. These patients develop fungal infections that are disseminated, frequently involving the CNS and bone, and are typically refractory despite intensive antifungal therapy (reviewed in detail elsewhere [3, 7]).

Of interest, some of the infections by endemic dimorphic fungi are enriched in individuals of certain ethnic backgrounds, further attesting to the genetic risk modulation of host susceptibility to these infections [3]; it is unknown whether impaired responses of the IL-12/IFN-γ pathway underlie this susceptibility. Recently, whole genome sequencing analysis revealed that susceptibility to blastomycosis in individuals of Hmong ancestry is associated with genetic variants surrounding the *IL6* locus [68•]; whether patients treated with tocilizumab that inhibits IL-6 receptor signaling may be at risk for blastomycosis or other dimorphic fungal infections at endemic geographic areas warrants clinical surveillance. Importantly, concordant with the aforementioned inherited infection susceptibility of patients with mutations in the IL-12/IFN-γ signaling pathway, development of adult-onset severe invasive infections by endemic dimorphic fungi and *Cryptococcus* (particularly *Cryptococcus gattii*) has been attributed to neutralizing autoantibodies against IFN-γ and/or GM-CSF [69, 70]; notably, some of these autoantibodies are often enriched among Asian-born Asian patients and may be amenable to rituximab-mediated depletion.

Non-monogenic Immune-Related Gene Variation and the Risk of Invasive Fungal Disease

Besides the aforementioned monogenic disorders that confer marked susceptibility to spontaneous fungal disease in humans, significant interest has been generated recently in identifying immune-related gene SNPs that may influence the risk of developing fungal disease and/or suffering worse outcome after fungal infection in patients with acquired immunodeficiency states. These SNPs alone do not confer susceptibility to spontaneous fungal infection like monogenic defects do, but they may augment the risk of fungal infection in the setting of hospitalization together with other associated iatrogenic pressures in acutely, critically ill patients.

Two such clinical examples are worthwhile highlighting. Approximately 3–5% of critically ill patients in the ICU develop invasive candidiasis despite the fact that the vast majority of ICU patients have similar iatrogenic risk factors for the infection such as central intravenous catheters, abdominal surgery, broad-spectrum antibiotics, total parenteral nutrition, or immunosuppressive treatment [71]. Similarly, approximately

5–10% of allogeneic HSCT recipients develop invasive aspergillosis despite the fact that the vast majority of allogeneic HSCT recipients have ubiquitous exposure to inhaled *Aspergillus* conidia and similar iatrogenic risk factors for the infection such as neutropenia or corticosteroid use [72, 73]. Therefore, genetic variation may influence the risk of invasive candidiasis in ICU patients and of invasive aspergillosis in allogeneic HSCT recipients beyond that ascribed to conventional clinical or microbiological risk factors.

Several studies have revealed genetic associations that show promise for leading to improved risk assessment of patients at risk for these fungal infections, personalized antifungal prophylaxis, and/or optimized donor selection in the context of allogeneic HSCT. Although some of these studies have limitations that relate to population stratification biases, findings that may be in linkage disequilibrium with genetic variants in nearby genes that could themselves drive the observed phenotype, lack of multivariate analysis of the observed outcomes, and/or lack of validation studies in large patient cohorts, they provide important information on potential genetic factors that may predispose to invasive candidiasis in the ICU or to invasive aspergillosis following allogeneic HSCT. A few representative examples of such SNPs are briefly presented below; however, a detailed description of immune-related gene SNPs is beyond the scope of this review and has been discussed in detail elsewhere [6, 74–76].

Invasive Candidiasis

Genetic variation in cytokines (*IL10*, *IL12B*, *TNFA*), chemokines (*CCL8*), chemokine receptors (*CXCR1*, *CX3CR1*), pattern recognition receptors (*TLR1*), type I interferon-dependent signaling molecules (*STAT1*, *PSMB8*, *SP110*), and other genetic loci (*VAV3*, *CD58*, *TAGAP*, LCE4A-C1orf68) has been associated with enhanced risk of developing invasive candidiasis in medical and/or surgical ICU patients and/or increased risk of suffering worse outcome following infection, namely greater mortality, persistent fungemia, and/or disseminated infection beyond the bloodstream [77–84].

We previously showed that in a mouse model of invasive candidiasis, the monocyte/macrophage-targeted chemokine receptor Cx3cr1 is critical for host survival and control of tissue fungal proliferation [79]. Cx3cr1 promotes macrophage accumulation in the infected tissue, which is important for early macrophage-fungal interactions *in vivo* and fungal killing. Mechanistically, Cx3cr1 drives macrophage accumulation via regulating their survival by preventing caspase-3-dependent apoptosis, not by modulating their trafficking, differentiation, or proliferation. In humans, we identified the dysfunctional allele *CX3CR1-M280* to be associated in multivariate analysis of two independent patient cohorts with increased risk of both developing invasive candidiasis and suffering worse outcome following infection [79]. Mechanistically, consonant with the mouse data, primary human monocytes from individuals carrying *CX3CR1-M280* in homozygosity had impaired survival attributed to their inability to induce cell survival–promoting ERK and AKT activation upon CX3CL1 stimulation [85]. Importantly, individuals carrying the homozygous *CX3CR1-M280* allele had decreased monocyte counts in peripheral blood [85]. Collectively, these mouse and human studies reveal the critical contribution of CX3CR1 in host defense against invasive (but not mucosal [86]) candidiasis and show that variation at the *CX3CR1* locus is a novel population-based genetic factor that regulates monocyte signaling and influences the risk of invasive candidiasis in humans.

In addition, we demonstrated in a mouse model of invasive candidiasis that the neutrophil-targeted chemokine receptor Cxcr1 promotes host survival and fungal control [83•]. Surprisingly, Cxcr1 drives neutrophil degranulation and non-oxidative burst-dependent fungal killing and is dispensable for neutrophil trafficking from the blood into the infected tissue. In humans, we identified the dysfunctional allele *CXCR1-T276* to be associated in multivariate analysis with increased risk of suffering worse outcome after infection. Mechanistically, in agreement with the mouse data, primary human neutrophils from individuals carrying the heterozygous *CXCR1-T276* allele had impaired neutrophil degranulation and fungal killing [83•]. Taken together, these mouse and human data uncover the essential contribution of CXCR1 in systemic anti-*Candida* immunity and suggest that genetic variation at *CXCR1* may be a novel population-based factor for risk stratification and prognostication of invasive candidiasis in ICU patients.

Importantly, a genome-wide association study evaluated ~ 120,000 SNPs across 186 genetic loci pertaining to immune-related conditions in hospitalized patients with candidemia relative to healthy control individuals [78]. This unbiased genomic approach discovered three novel genetic loci that increase the risk of developing candidemia, namely CD58, TAGAP, and LCE4A-C1orf68. Notably, patients who carried two or more high-risk SNPs within these loci had a ~ 20-fold increased risk of developing candidemia, indicating that combining SNPs from different genetic loci may act synergistically to increase the risk of infection [78]. Mechanistically, CD58 was shown to colocalize with *Candida* during phagocytosis and was critical for fungal uptake and killing by macrophages, whereas TAGAP was found to be important for TNF-α production and control of fungal growth in a mouse model of invasive candidiasis [78]. Given all the aforementioned genetic findings in recent years, an important direction of future research will be to develop screening genomic strategies to distinguish ICU patients who carry heightened genetic risk traits for invasive candidiasis and to design a placebo-controlled clinical trial to examine whether targeted

echinocandin prophylaxis would prevent fungal infection in these high-risk individuals.

Invasive Aspergillosis

Similar to invasive candidiasis, emerging literature has implicated genetic variation in either donors and/or recipients of allogeneic HSCT with a heightened risk of developing invasive aspergillosis post-HSCT. Specifically, genetic variation in soluble or membrane-bound fungal sensing molecules (*TLR4*, *TLR6*, *CLEC1A*, *CLEC7A*, *NOD2*, *CD209*, *PTX3*, *PLG*), cytokines (*IFNG*), cytokine receptors (*TNFR1*), chemokines (*CXCL10*), and other molecules (*S100B*) has been associated with increased risk of invasive aspergillosis following allogeneic HSCT [87, 88••, 89–91, 92••, 93–96].

A significant gene affecting susceptibility to invasive aspergillosis post-HSCT that is worthwhile expanding on is the soluble pattern recognition receptor long pentraxin 3 (*PTX3*) that recognizes *Aspergillus* conidia among other non-fungal microbial moieties. Ptx3-deficient mice are highly susceptible to invasive aspergillosis [97] and, in agreement, receipt of a HSCT from donors carrying a homozygous PTX3 haplotype that impairs normal alveolar expression of PTX3 was associated in multivariate analysis of two independent patient cohorts with increased risk of developing invasive aspergillosis following HSCT [87]. The association between *PTX3* genetic variation and the risk of invasive aspergillosis was subsequently extended to other disease cohorts such as in patients with chronic obstructive pulmonary disease or solid organ transplant recipients [98, 99]. Mechanistically, primary human neutrophils from individuals carrying the identified PTX3 haplotype exhibited impaired uptake and killing of *Aspergillus* conidia, and *Aspergillus*-infected lung tissue from these patients had impaired induction of pro-inflammatory cytokines [87, 100]. Importantly, restoration of PTX3 in neutrophils reverses the functional defects conferred by PTX3 deficiency and administration of recombinant PTX3 in *Aspergillus*-infected mice acts in synergy with triazole-based antifungal treatment when used in combination [87, 101]. Taken together, these data suggest that *PTX3* genetic variation may serve as a novel precision medicine approach for both HSCT donor selection and for assessment of invasive aspergillosis risk, and that immunotherapies based on the delivery of PTX3 hold promise as potential adjunctive approaches in immunosuppressed patients.

Conclusions

Fungal infections cause significant morbidity and mortality in immunosuppressed patients despite antifungal treatment. Identifying patients at heightened risk for developing fungal disease and/or dismal outcome following infection has major implications in devising personalized strategies for risk stratification, prophylaxis, treatment, vaccination, monitoring, and prognostication. In recent years, a surge of studies has provided exciting new evidence of the potential contribution of variation in immune-related genes in influencing the risk of developing fungal disease and/or worse infection outcomes. Some of these immune-related genes reside within immunoregulatory pathways whose indispensable role in mammalian antifungal immunity was uncovered by the discovery of inherited monogenic disorders that cause spontaneous and profound fungal susceptibility in humans. Moving forward, the further integration of genomics into clinical practice may provide the opportunity to genetically screen high-risk immunosuppressed patients with the goal of identifying those with the highest probability of developing fungal disease, in whom precision medicine strategies for monitoring, prophylaxis, or treatment may prove valuable in improving patient outcomes.

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Compliance with Ethical Standards

Conflict of Interest Michail S. Lionakis declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Robert VA, Casadevall A. Vertebrate endothermy restricts most fungi as potential pathogens. J Infect Dis. 2009;200(10):1623–6. https://doi.org/10.1086/644642.
2. Lionakis MS, Iliev ID, Hohl TM. Immunity against fungi. JCI Insight. 2017;2(11). doi:10.1172/jci.insight.93156.
3. Lionakis MS, Levitz SM. Host control of fungal infections: lessons from basic studies and human cohorts. Annu Rev Immunol. 2018;36:157–91. https://doi.org/10.1146/annurev-immunol-042617-053318.
4. Arvanitis M, Anagnostou T, Fuchs BB, Caliendo AM, Mylonakis E. Molecular and nonmolecular diagnostic methods for invasive fungal infections. Clin Microbiol Rev. 2014;27(3):490–526. https://doi.org/10.1128/CMR.00091-13.
5. McCarthy MW, Kontoyiannis DP, Cornely OA, Perfect JR, Walsh TJ. Novel agents and drug targets to meet the challenges of resistant fungi. J Infect Dis. 2017;216(suppl_3):S474-S83. doi: 10.1093/infdis/jix130.

6. Lionakis MS. Genetic susceptibility to fungal infections in humans. Curr Fungal Infect Rep. 2012;6(1):11–22. https://doi.org/10.1007/s12281-011-0076-4.
7. Lionakis MS, Netea MG, Holland SM. Mendelian genetics of human susceptibility to fungal infection. Cold Spring Harb Perspect Med. 2014;4(6). doi:10.1101/cshperspect.a019638.
8. Puel A, Cypowyj S, Marodi L, Abel L, Picard C, Casanova JL. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. Curr Opin Allergy Clin Immunol. 2012;12(6):616–22. https://doi.org/10.1097/ACI.0b013e328358cc0b.
9.•• Conti HR, Bruno VM, Childs EE, Daugherty S, Hunter JP, Mengesha BG et al. IL-17 Receptor signaling in oral epithelial cells is critical for protection against oropharyngeal candidiasis. Cell Host Microbe. 2016;20(5):606-617. doi:https://doi.org/10.1016/j.chom.2016.10.001. **This paper describes the critical contribution of epithelial cell IL-17 receptor expression in host defense against mucosal candidiasis, via the induction of anti-*Candida* antimicrobial peptides such as beta-defensin 3**.
10. Conti HR, Peterson AC, Brane L, Huppler AR, Hernandez-Santos N, Whibley N, et al. Oral-resident natural Th17 cells and gammadelta T cells control opportunistic Candida albicans infections. J Exp Med. 2014;211(10):2075–84. https://doi.org/10.1084/jem.20130877.
11. Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, et al. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. J Exp Med. 2009;206(2):299–311. https://doi.org/10.1084/jem.20081463.
12. Sparber F, Dolowschiak T, Mertens S, Lauener L, Clausen BE, Joller N, et al. Langerin+ DCs regulate innate IL-17 production in the oral mucosa during Candida albicans-mediated infection. PLoS Pathog. 2018;14(5):e1007069. https://doi.org/10.1371/journal.ppat.1007069.
13. Trautwein-Weidner K, Gladiator A, Kirchner FR, Becattini S, Rulicke T, Sallusto F, et al. Antigen-specific Th17 cells are primed by distinct and complementary dendritic cell subsets in oropharyngeal candidiasis. PLoS Pathog. 2015;11(10):e1005164. https://doi.org/10.1371/journal.ppat.1005164.
14. Jiang L, Fang M, Tao R, Yong X, Wu T. Recombinant human interleukin 17A enhances the anti-Candida effect of human oral mucosal epithelial cells by inhibiting Candida albicans growth and inducing antimicrobial peptides secretion. J Oral Pathol Med. 2019. https://doi.org/10.1111/jop.12889.
15. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science. 2011;332(6025):65–8. https://doi.org/10.1126/science.1200439.
16. Boisson B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M, et al. An ACT1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity. 2013;39(4):676–86. https://doi.org/10.1016/j.immuni.2013.09.002.
17. Ling Y, Cypowyj S, Aytekin C, Galicchio M, Camcioglu Y, Nepesov S, et al. Inherited IL-17RC deficiency in patients with chronic mucocutaneous candidiasis. J Exp Med. 2015;212(5):619–31. https://doi.org/10.1084/jem.20141065.
18.•• Levy R, Okada S, Beziat V, Moriya K, Liu C, Chai LY, et al. Genetic, immunological, and clinical features of patients with bacterial and fungal infections due to inherited IL-17RA deficiency. Proc Natl Acad Sci U S A. 2016;113(51):E8277–E85. https://doi.org/10.1073/pnas.1618300114 **This paper provides a systematic overview of the clinical, genetic and immunological features in patients with inherited deficiency in IL-17RA.**
19. Lionakis MS. New insights into innate immune control of systemic candidiasis. Med Mycol. 2014;52(6):555–64. https://doi.org/10.1093/mmy/myu029.
20. Okada S, Markle JG, Deenick EK, Mele F, Averbuch D, Lagos M, et al. IMMUNODEFICIENCIES. Impairment of immunity to Candida and Mycobacterium in humans with bi-allelic RORC mutations. Science. 2015;349(6248):606–13. https://doi.org/10.1126/science.aaa4282.
21. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature. 2008;452(7188):773–6. https://doi.org/10.1038/nature06764.
22. Drummond RA, Franco LM, Lionakis MS. Human CARD9: a critical molecule of fungal immune surveillance. Front Immunol. 2018a;9:1836. https://doi.org/10.3389/fimmu.2018.01836.
23. Tangye SG, Pillay B, Randall KL, Avery DT, Phan TG, Gray P, et al. Dedicator of cytokinesis 8-deficient CD4(+) T cells are biased to a TH2 effector fate at the expense of TH1 and TH17 cells. J Allergy Clin Immunol. 2017;139(3):933–49. https://doi.org/10.1016/j.jaci.2016.07.016.
24. Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med. 2011;208(8):1635–48. https://doi.org/10.1084/jem.20110958.
25. Constantine GM, Lionakis MS. Lessons from primary immunodeficiencies: autoimmune regulator and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Immunol Rev. 2019;287(1):103–20. https://doi.org/10.1111/imr.12714.
26. Puel A, Doffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. J Exp Med. 2010;207(2):291–7. https://doi.org/10.1084/jem.20091983.
27. Kisand K, Boe Wolff AS, Podkrajsek KT, Tserel L, Link M, Kisand KV, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. J Exp Med. 2010;207(2):299–308. https://doi.org/10.1084/jem.20091669.
28. Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. Br J Dermatol. 2017;177(1):47–62. https://doi.org/10.1111/bjd.15015.
29. Netea MG, Joosten LA, van der Meer JW, Kullberg BJ, van de Veerdonk FL. Immune defence against Candida fungal infections. Nat Rev Immunol. 2015;15(10):630–42. https://doi.org/10.1038/nri3897.
30. Lehrer RI, Cline MJ. Leukocyte myeloperoxidase deficiency and disseminated candidiasis: the role of myeloperoxidase in resistance to Candida infection. J Clin Invest. 1969;48(8):1478–88. https://doi.org/10.1172/JCI106114.
31. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore). 2000;79(3):155–69.
32. Drummond RA, Collar AL, Swamydas M, Rodriguez CA, Lim JK, Mendez LM, et al. CARD9-dependent neutrophil recruitment protects against fungal invasion of the central nervous system. PLoS Pathog. 2015;11(12):e1005293. https://doi.org/10.1371/journal.ppat.1005293.
33. Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med. 2009;361(18):1727–35. https://doi.org/10.1056/NEJMoa0810719.
34. Lanternier F, Mahdaviani SA, Barbati E, Chaussade H, Koumar Y, Levy R, et al. Inherited CARD9 deficiency in otherwise healthy

children and adults with Candida species-induced meningoencephalitis, colitis, or both. J Allergy Clin Immunol. 2015a;135(6):1558–68 e2. https://doi.org/10.1016/j.jaci.2014.12.1930.

35.• Corvilain E, Casanova JL, Puel A. Inherited CARD9 deficiency: invasive disease caused by ascomycete fungi in previously healthy children and adults. J Clin Immunol. 2018;38(6):656–93. https://doi.org/10.1007/s10875-018-0539-2 **This is a thorough review related to fungal disease susceptibility in CARD9-deficient patients.**

36. Li J, Vinh DC, Casanova JL, Puel A. Inborn errors of immunity underlying fungal diseases in otherwise healthy individuals. Curr Opin Microbiol. 2017;40:46–57. https://doi.org/10.1016/j.mib.2017.10.016.

37.•• Drummond RA, Swamydas M, Oikonomou V, Zhai B, Dambuza IM, Schaefer BC, et al. CARD9(+) microglia promote antifungal immunity via IL-1beta- and CXCL1-mediated neutrophil recruitment. Nat Immunol. 2019;20(5):559–70. https://doi.org/10.1038/s41590-019-0377-2 **This paper outlines an intricate network of microglial-fungal interactions in the *Candida*-infected central nervous system that promote CARD9-dependent protective neutrophil recruitment**.

38. Moyes DL, Wilson D, Richardson JP, Mogavero S, Tang SX, Wernecke J, et al. Candidalysin is a fungal peptide toxin critical for mucosal infection. Nature. 2016;532(7597):64–8. https://doi.org/10.1038/nature17625.

39. Swidergall M, Solis NV, Wang Z, Phan QT, Marshall ME, Lionakis MS, et al. EphA2 Is a neutrophil receptor for Candida albicans that stimulates antifungal activity during oropharyngeal infection. Cell Rep. 2019;28(2):423–33 e5. https://doi.org/10.1016/j.celrep.2019.06.020.

40. Drewniak A, Gazendam RP, Tool AT, van Houdt M, Jansen MH, van Hamme JL, et al. Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency. Blood. 2013;121(13):2385–92. https://doi.org/10.1182/blood-2012-08-450551.

41.• Drummond RA, Zahra FT, Natarajan M, Swamydas M, Hsu AP, Wheat LJ, et al. GM-CSF therapy in human caspase recruitment domain-containing protein 9 deficiency. J Allergy Clin Immunol. 2018b;142(4):1334–8 e5. https://doi.org/10.1016/j.jaci.2018.05.025 **This paper along with the paper of Gavino et al outline differential outcomes of GM-CSF immunotherapy in CARD9-deficient patients with brain fungal disease.**

42. Gavino C, Cotter A, Lichtenstein D, Lejtenyi D, Fortin C, Legault C, et al. CARD9 deficiency and spontaneous central nervous system candidiasis: complete clinical remission with GM-CSF therapy. Clin Infect Dis. 2014;59(1):81–4. https://doi.org/10.1093/cid/ciu215.

43.• Gavino C, Hamel N, Zeng JB, Legault C, Guiot MC, Chankowsky J, et al. Impaired RASGRF1/ERK-mediated GM-CSF response characterizes CARD9 deficiency in French-Canadians. J Allergy Clin Immunol. 2016;137(4):1178–88 e1-7. https://doi.org/10.1016/j.jaci.2015.09.016 **This paper along with the paper of Drummond et al outline differential outcomes of GM-CSF immunotherapy in CARD9-deficient patients with brain fungal disease.**

44.• Queiroz-Telles F, Mercier T, Maertens J, Sola CBS, Bonfim C, Lortholary O, et al. Successful allogenic stem cell transplantation in patients with inherited CARD9 deficiency. J Clin Immunol. 2019. https://doi.org/10.1007/s10875-019-00662-z. **This paper describes the first successful allogeneic hematopoietic stem cell transplants in CARD9-deficient patients with refractory subcutaneous fungal disease.**

45. Drummond RA, Lionakis MS. Mechanistic insights into the role of C-type lectin receptor/CARD9 signaling in human antifungal immunity. Front Cell Infect Microbiol. 2016;6:39. https://doi.org/10.3389/fcimb.2016.00039.

46. Gross O, Gewies A, Finger K, Schafer M, Sparwasser T, Peschel C, et al. Card9 controls a non-TLR signalling pathway for innate anti-fungal immunity. Nature. 2006;442(7103):651–6. https://doi.org/10.1038/nature04926.

47. Liu D, Mamorska-Dyga A. Syk inhibitors in clinical development for hematological malignancies. J Hematol Oncol. 2017;10(1):145–7. https://doi.org/10.1186/s13045-017-0512-1.

48. Lanternier F, Barbati E, Meinzer U, Liu L, Pedergnana V, Migaud M, et al. Inherited CARD9 deficiency in 2 unrelated patients with invasive Exophiala infection. J Infect Dis. 2015b;211(8):1241–50. https://doi.org/10.1093/infdis/jiu412.

49. Lanternier F, Pathan S, Vincent QB, Liu L, Cypowyj S, Prando C, et al. Deep dermatophytosis and inherited CARD9 deficiency. N Engl J Med. 2013;369(18):1704–14. https://doi.org/10.1056/NEJMoa1208487.

50.• De Bruyne M, Hoste L, Bogaert DJ, Van den Bossche L, Tavernier SJ, Parthoens E, et al. A CARD9 founder mutation disrupts NF-kappaB signaling by inhibiting BCL10 and MALT1 recruitment and signalosome formation. Front Immunol. 2018;9:2366. https://doi.org/10.3389/fimmu.2018.02366 **This paper together with that by Rieber et al showed that CARD9-deficient patients are at risk of developing extrapulmonary aspergillosis that spares the lungs**.

51.• Rieber N, Gazendam RP, Freeman AF, Hsu AP, Collar AL, Sugui JA, et al. Extrapulmonary Aspergillus infection in patients with CARD9 deficiency. JCI Insight. 2016;1(17):e89890–10.1172/jci.insight.89890 **This paper together with that by De Bruyne et al showed that CARD9-deficient patients are at risk of developing extrapulmonary aspergillosis that spares the lungs**.

52. Hohl TM. Immune responses to invasive aspergillosis: new understanding and therapeutic opportunities. Curr Opin Infect Dis. 2017. https://doi.org/10.1097/QCO.0000000000000381.

53. Segal BH, Leto TL, Gallin JI, Malech HL, Holland SM. Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine (Baltimore). 2000;79(3):170–200.

54. Seyedmousavi S, Lionakis MS, Parta M, Peterson SW, Kwon-Chung KJ. Emerging Aspergillus species almost exclusively associated with primary immunodeficiencies. Open Forum Infect Dis. 2018;5(9):ofy213. https://doi.org/10.1093/ofid/ofy213.

55.•• van de Geer A, Nieto-Patlan A, Kuhns DB, Tool AT, Arias AA, Bouaziz M, et al. Inherited p40phox deficiency differs from classic chronic granulomatous disease. J Clin Invest. 2018;128(9):3957–75. https://doi.org/10.1172/JCI97116 **This paper outlines critical clinical and immunological differences in patients with chronic granulomatous disease caused by deficiency of the p40phox subunit of the NADPH oxidase complex.**

56. Kuhns DB, Alvord WG, Heller T, Feld JJ, Pike KM, Marciano BE, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. N Engl J Med. 2010;363(27):2600–10. https://doi.org/10.1056/NEJMoa1007097.

57. Vinh DC, Sugui JA, Hsu AP, Freeman AF, Holland SM. Invasive fungal disease in autosomal-dominant hyper-IgE syndrome. J Allergy Clin Immunol. 2010;125(6):1389–90. https://doi.org/10.1016/j.jaci.2010.01.047.

58.• Khourieh J, Rao G, Habib T, Avery DT, Lefevre-Utile A, Chandesris MO, et al. A deep intronic splice mutation of STAT3 underlies hyper IgE syndrome by negative dominance. Proc Natl Acad Sci U S A. 2019. https://doi.org/10.1073/pnas.1901409116 **This paper shows that deep intronic splice mutations can exert dominant-negative effects and manifest with hyper-IgE (Job's) syndrome**.

59. Natarajan M, Hsu AP, Weinreich MA, Zhang Y, Niemela JE, Butman JA, et al. Aspergillosis, eosinophilic esophagitis, and allergic rhinitis in signal transducer and activator of transcription 3 haploinsufficiency. J Allergy Clin Immunol. 2018;142(3):993–7 e3. https://doi.org/10.1016/j.jaci.2018.05.009.

60.•• Lionakis MS, Dunleavy K, Roschewski M, Widemann BC, Butman JA, Schmitz R, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. Cancer Cell. 2017. https://doi.org/10.1016/j.ccell.2017.04.012 **This paper revealed an unexpected susceptiblity of ibrutinib-treated patients to invasive aspergillosis and showed that, surprisingly, Btk-deficient mice are also susceptible to pulmonary *Aspergillus* infection**.

61. Zarakas MADJ, Chamilos G, Lionakis MS. Fungal infections with ibrutinib and other small-molecule kinase inhibitors. Curr Fungal Infect Rep. 2019;13:86–98. https://doi.org/10.1007/s12281-019-00343-9.

62. Chamilos G, Lionakis MS, Kontoyiannis DP. Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways. Clin Infect Dis. 2018;66(1):140–8. https://doi.org/10.1093/cid/cix687.

63. Ghez D, Calleja A, Protin C, Baron M, Ledoux MP, Damaj G, et al. Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. Blood. 2018;131(17):1955–9. https://doi.org/10.1182/blood-2017-11-818286.

64. Varughese T, Taur Y, Cohen N, Palomba ML, Seo SK, Hohl TM, et al. Serious infections in patients receiving ibrutinib for treatment of lymphoid cancer. Clin Infect Dis. 2018;67(5):687–92. https://doi.org/10.1093/cid/ciy175.

65.• Bercusson A, Colley T, Shah A, Warris A, Armstrong-James D. Ibrutinib blocks Btk-dependent NF-kB and NFAT responses in human macrophages during Aspergillus fumigatus phagocytosis. Blood. 2018;132(18):1985–8. https://doi.org/10.1182/blood-2017-12-823393 **This work defined defects in innate signaling of human macrophages upon ibrutinib exposure that affects uptake of *Aspergillus*.**

66. Glotz D, Russ G, Rostaing L, Legendre C, Tufveson G, Chadban S, et al. Safety and efficacy of eculizumab for the prevention of antibody-mediated rejection after deceased-donor kidney transplantation in patients with preformed donor-specific antibodies. Am J Transplant. 2019. https://doi.org/10.1111/ajt.15397.

67. Socie G, Caby-Tosi MP, Marantz JL, Cole A, Bedrosian CL, Gasteyger C, et al. Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10-year pharmacovigilance analysis. Br J Haematol. 2019;185(2):297–310. https://doi.org/10.1111/bjh.15790.

68.• Merkhofer RM, Jr., O'Neill MB, Xiong D, Hernandez-Santos N, Dobson H, Fites JS et al. Investigation of genetic susceptibility to blastomycosis reveals interleukin-6 as a potential susceptibility locus. MBio. 2019;10(3). doi:https://doi.org/10.1128/mBio.01224-19. **This paper employed whole genome sequencing and showed that susceptibility to blastomycosis in individuals of Hmong ancestry in Wisconsin is associated with genetic variants surrounding the *IL6* locus**.

69. Browne SK, Burbelo PD, Chetchotisakd P, Suputtamongkol Y, Kiertiburanakul S, Shaw PA, et al. Adult-onset immunodeficiency in Thailand and Taiwan. N Engl J Med. 2012;367(8):725–34. https://doi.org/10.1056/NEJMoa1111160.

70. Saijo T, Chen J, Chen SC, Rosen LB, Yi J, Sorrell TC, et al. Anti-granulocyte-macrophage colony-stimulating factor autoantibodies are a risk factor for central nervous system infection by Cryptococcus gattii in otherwise immunocompetent patients. MBio. 2014;5(2):e00912–4. https://doi.org/10.1128/mBio.00912-14.

71. Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nat Rev Dis Primers. 2018;4:18026. https://doi.org/10.1038/nrdp.2018.26.

72. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet. 2003;362(9398):1828–38. https://doi.org/10.1016/S0140-6736(03)14904-5.

73. Segal BH. Aspergillosis. N Engl J Med. 2009;360(18):1870–84. https://doi.org/10.1056/NEJMra0808853.

74. Cunha C, Carvalho A. Genetic defects in fungal recognition and susceptibility to invasive pulmonary aspergillosis. Med Mycol. 2019;57(Supplement_2):S211–S8. https://doi.org/10.1093/mmy/myy057.

75. Khanna N, Stuehler C, Lunemann A, Wojtowicz A, Bochud PY, Leibundgut-Landmann S. Host response to fungal infections - how immunology and host genetics could help to identify and treat patients at risk. Swiss Med Wkly. 2016;146:w14350. https://doi.org/10.4414/smw.2016.14350.

76. Wojtowicz A, Bochud PY. Host genetics of invasive Aspergillus and Candida infections. Semin Immunopathol. 2015;37(2):173–86. https://doi.org/10.1007/s00281-014-0468-y.

77. Johnson MD, Plantinga TS, van de Vosse E, Velez Edwards DR, Smith PB, Alexander BD, et al. Cytokine gene polymorphisms and the outcome of invasive candidiasis: a prospective cohort study. Clin Infect Dis. 2012;54(4):502–10. https://doi.org/10.1093/cid/cir827.

78. Kumar V, Cheng SC, Johnson MD, Smeekens SP, Wojtowicz A, Giamarellos-Bourboulis E, et al. Immunochip SNP array identifies novel genetic variants conferring susceptibility to candidaemia. Nat Commun. 2014;5:4675. https://doi.org/10.1038/ncomms5675.

79. Lionakis MS, Swamydas M, Fischer BG, Plantinga TS, Johnson MD, Jaeger M, et al. CX3CR1-dependent renal macrophage survival promotes Candida control and host survival. J Clin Invest. 2013;123(12):5035–51. https://doi.org/10.1172/JCI71307.

80. Plantinga TS, Johnson MD, Scott WK, van de Vosse E, Velez Edwards DR, Smith PB, et al. Toll-like receptor 1 polymorphisms increase susceptibility to candidemia. J Infect Dis. 2012;205(6):934–43. https://doi.org/10.1093/infdis/jir867.

81. Roth S, Bergmann H, Jaeger M, Yeroslaviz A, Neumann K, Koenig PA, et al. Vav proteins are key regulators of Card9 signaling for innate antifungal immunity. Cell Rep. 2016;17(10):2572–83. https://doi.org/10.1016/j.celrep.2016.11.018.

82. Smeekens SP, Ng A, Kumar V, Johnson MD, Plantinga TS, van Diemen C, et al. Functional genomics identifies type I interferon pathway as central for host defense against Candida albicans. Nat Commun. 2013;4:1342. https://doi.org/10.1038/ncomms2343.

83.• Swamydas M, Gao JL, Break TJ, Johnson MD, Jaeger M, Rodriguez CA, et al. CXCR1-mediated neutrophil degranulation and fungal killing promote Candida clearance and host survival. Sci Transl Med. 2016;8(322):322ra10. https://doi.org/10.1126/scitranslmed.aac7718 **This paper revealed the first function of Cxcr1 in mice and identified this chemokine receptor as a critical mediator of neutrophil function against *Candida* in both mice and humans**.

84. Wojtowicz A, Tissot F, Lamoth F, Orasch C, Eggimann P, Siegemund M, et al. Polymorphisms in tumor necrosis factor-alpha increase susceptibility to intra-abdominal Candida infection in high-risk surgical ICU patients*. Crit Care Med. 2014;42(4):e304–8. https://doi.org/10.1097/CCM.0000000000000208.

85. Collar AL, Swamydas M, O'Hayre M, Sajib MS, Hoffman KW, Singh SP, et al. The homozygous CX3CR1-M280 mutation impairs human monocyte survival. JCI Insight. 2018;3(3). https://doi.org/10.1172/jci.insight.95417.

86. Break TJ, Jaeger M, Solis NV, Filler SG, Rodriguez CA, Lim JK, et al. CX3CR1 is dispensable for control of mucosal Candida albicans infections in mice and humans. Infect Immun. 2015;83(3):958–65. https://doi.org/10.1128/IAI.02604-14.

87. Cunha C, Aversa F, Lacerda JF, Busca A, Kurzai O, Grube M, et al. Genetic PTX3 deficiency and aspergillosis in stem-cell transplantation. N Engl J Med. 2014;370(5):421–32. https://doi.org/10.1056/NEJMoa1211161.

88.•• Fisher CE, Hohl TM, Fan W, Storer BE, Levine DM, Zhao LP, et al. Validation of single nucleotide polymorphisms in invasive aspergillosis following hematopoietic cell transplantation. Blood. 2017;129(19):2693–701. https://doi.org/10.1182/blood-2016-10-743294 **This paper evaluated a large number of transplant recipients with or without aspergillosis and validated several single nucleotide polymorphisms as modulators of aspergillosis risk in these patients.**

89. Gresnigt MS, Cunha C, Jaeger M, Goncalves SM, Malireddi RKS, Ammerdorffer A, et al. Genetic deficiency of NOD2 confers resistance to invasive aspergillosis. Nat Commun. 2018;9(1):2636. https://doi.org/10.1038/s41467-018-04912-3.

90. Bochud PY, Chien JW, Marr KA, Leisenring WM, Upton A, Janer M, et al. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. N Engl J Med. 2008;359(17):1766–77. https://doi.org/10.1056/NEJMoa0802629.

91. Mezger M, Steffens M, Beyer M, Manger C, Eberle J, Toliat MR, et al. Polymorphisms in the chemokine (C-X-C motif) ligand 10 are associated with invasive aspergillosis after allogeneic stem-cell transplantation and influence CXCL10 expression in monocyte-derived dendritic cells. Blood. 2008;111(2):534–6. https://doi.org/10.1182/blood-2007-05-090928.

92.•• Stappers MHT, Clark AE, Aimanianda V, Bidula S, Reid DM, Asamaphan P, et al. Recognition of DHN-melanin by a C-type lectin receptor is required for immunity to Aspergillus. Nature. 2018;555(7696):382–6. https://doi.org/10.1038/nature25974 **This paper discovered CLEC1A as a C-type lectin receptor important for the recognition of fungal melanin and revealed that genetic variation at this locus may influence the risk of human aspergillosis.**

93. Zaas AK, Liao G, Chien JW, Weinberg C, Shore D, Giles SS, et al. Plasminogen alleles influence susceptibility to invasive aspergillosis. PLoS Genet. 2008;4(6):e1000101. https://doi.org/10.1371/journal.pgen.1000101.

94. Kesh S, Mensah NY, Peterlongo P, Jaffe D, Hsu K, Van Den Brink M, et al. TLR1 and TLR6 polymorphisms are associated with susceptibility to invasive aspergillosis after allogeneic stem cell transplantation. Ann N Y Acad Sci. 2005;1062:95–103. https://doi.org/10.1196/annals.1358.012.

95. Sainz J, Salas-Alvarado I, Lopez-Fernandez E, Olmedo C, Comino A, Garcia F, et al. TNFR1 mRNA expression level and TNFR1 gene polymorphisms are predictive markers for susceptibility to develop invasive pulmonary aspergillosis. Int J Immunopathol Pharmacol. 2010;23(2):423–36. https://doi.org/10.1177/039463201002300205.

96. Cunha C, Di Ianni M, Bozza S, Giovannini G, Zagarella S, Zelante T, et al. Dectin-1 Y238X polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. Blood. 2010;116(24):5394–402. https://doi.org/10.1182/blood-2010-04-279307.

97. Garlanda C, Hirsch E, Bozza S, Salustri A, De Acetis M, Nota R, et al. Non-redundant role of the long pentraxin PTX3 in anti-fungal innate immune response. Nature. 2002;420(6912):182–6. https://doi.org/10.1038/nature01195.

98. Cunha C, Monteiro AA, Oliveira-Coelho A, Kuhne J, Rodrigues F, Sasaki SD, et al. PTX3-based genetic testing for risk of aspergillosis after lung transplant. Clin Infect Dis. 2015;61(12):1893–4. https://doi.org/10.1093/cid/civ679.

99. He Q, Li H, Rui Y, Liu L, He B, Shi Y, et al. Pentraxin 3 gene polymorphisms and pulmonary aspergillosis in chronic obstructive pulmonary disease patients. Clin Infect Dis. 2018;66(2):261–7. https://doi.org/10.1093/cid/cix749.

100. Goncalves SM, Lagrou K, Rodrigues CS, Campos CF, Bernal-Martinez L, Rodrigues F, et al. Evaluation of bronchoalveolar lavage fluid cytokines as biomarkers for invasive pulmonary aspergillosis in at-risk patients. Front Microbiol. 2017;8:2362. https://doi.org/10.3389/fmicb.2017.02362.

101. Marra E, Sousa VL, Gaziano R, Pacello ML, Arseni B, Aurisicchio L, et al. Efficacy of PTX3 and posaconazole combination in a rat model of invasive pulmonary aspergillosis. Antimicrob Agents Chemother. 2014;58(10):6284–6. https://doi.org/10.1128/AAC.03038-14.