Current Clinical Microbiology Reports (2018) 5:181–189
https://doi.org/10.1007/s40588-018-0098-6

MYCOLOGY (M NOVERR, SECTION EDITOR)

The Role of Neutrophils in Host Defense Against Invasive Fungal Infections

Jigar V. Desai [1] · Michail S. Lionakis [1]

Published online: 22 June 2018

Abstract

Purpose of Review Invasive fungal infections caused by the commensal yeast *Candida* and the ubiquitous, inhaled mold *Aspergillus* have emerged as major causes of morbidity and mortality in critically ill and immunosuppressed patient populations. Here, we review how neutrophils contribute to effective immunity against these infections.

Recent Findings Studies in mouse models of invasive candidiasis and aspergillosis and observations in hematological patients with chemotherapy-induced neutropenia and in patients with primary immunodeficiency disorders that manifest with these infections have highlighted the critical role of neutrophils and have identified key immune factors that promote neutrophil-mediated effective host defense against invasive fungal disease.

Summary Neutrophils are crucial in host protection against invasive candidiasis and aspergillosis. Recent advances in our understanding of the molecular cues that mediate protective neutrophil recruitment and effector function against these infections hold promise for developing immune-based strategies to improve the outcomes of affected patients.

Keywords Neutrophils · Recruitment · Effector function · Fungal killing · *Candida* · *Aspergillus*

Introduction

Neutrophils are the most abundant leukocytes in human blood with an estimated production in the bone marrow of approximately 10^{11} cells daily [1]. When acute infection develops, upon their recruitment from the blood into the infected tissue, neutrophils exert a variety of effector functions, which include binding, phagocytosis, and intracellular killing of microorganisms via oxidative and non-oxidative cytotoxic mechanisms, extracellular degranulation of antimicrobials that are prestored in specialized granules, formation of neutrophil extracellular traps (NETs), and generation of pro-inflammatory and anti-inflammatory cytokines, chemokines, and other mediators [2, 3].

Neutrophils represent the first line of innate immune defense against invasive infection caused by certain fungal pathogens such as *Candida* and *Aspergillus* species, among which *Candida albicans* and *Aspergillus fumigatus* are the most common species infecting humans and will be the focus on our review. Instead, other fungi such as *Cryptococcus neoformans*, *Pneumocystis jirovecii*, and the endemic dimorphic fungi *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis* do not rely on neutrophils but depend on an effective $CD4^+$ T cell-macrophage cross-talk for optimal host defense [4–9]. Indeed, patients with acquired and inherited quantitative and qualitative neutrophil defects are at heightened risk for developing invasive candidiasis and aspergillosis (but not cryptococcosis, pneumocystosis, or endemic dimorphic fungal disease) and experiencing worse outcomes from these infections [4, 5, 8].

In this review, we outline recent advances in immunological knowledge that pertains to the mechanisms by which neutrophils are mobilized and become activated in the fungal-infected tissues derived from mouse models of invasive candidiasis and aspergillosis and from patient cohorts at risk for developing these infections.

This article is part of the Topical Collection on *Mycology*

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

[1] Fungal Pathogenesis Section, Laboratory of Clinical Immunology and Microbiology (LCIM), National Institute of Allergy & Infectious Diseases (NIAID), National Institutes of Health (NIH), 9000 Rockville Pike, Bldg 10, Rm 11C102, Bethesda, MD 20892, USA

The Role of Neutrophils in Host Defense Against Candidemia and Invasive Candidiasis

Neutrophils are indispensable for effective host defense during invasive candidiasis in mice, and neutropenia is a well-known predisposing factor for development of candidemia and invasive candidiasis and for increased mortality after infection in humans [4, 10–13].

Protective Neutrophil Trafficking Into *C. albicans*-Infected Tissues

Mouse studies have shown that early neutrophil recruitment to the site of infection is of critical importance for *C. albicans* growth control [14, 15]. Of note, mouse tissues, such as the spleen and liver that promptly recruit large numbers of neutrophils within the first 24–48 h post-infection, are able to successfully control *C. albicans* proliferation [16]. In the infected kidneys, the glycoprotein ICAM-1 (intercellular adhesion molecule 1), which binds to integrins, is important for mediating neutrophil adhesion and diapedesis; in agreement, *Icam1*−/− mice are susceptible to systemic candidiasis and show decreased neutrophilic infiltrates in kidney histological sections [17, 18]. Additionally, a large number of CC- and CXC-families of chemokines, other chemoattractants, and pro-inflammatory mediators are highly and rapidly induced in the *C. albicans*-infected kidney; however, mobilization of neutrophils into the kidney is sluggish and this recruitment delay is associated with an ineffective immune response and inexorable fungal invasion within the renal parenchyma [16, 19, 20]. Thus far, the molecular cues that are responsible for early neutrophil trafficking into the *C. albicans*-infected kidney in vivo remain elusive.

Important insights into organ-specific neutrophil accumulation during invasive candidiasis have been recently derived from CARD9 (caspase recruitment domain-containing protein 9) deficiency, a rare autosomal recessive primary immunodeficiency disorder (PID) that manifests with fungal-specific infection susceptibility without predisposition to non-fungal infections, malignancy, atopy, or autoimmunity [21••, 22–24]. Strikingly, CARD9-deficient patients develop invasive candidiasis that has a unique tropism for involvement of the central nervous system (CNS) while typically sparing the kidney, liver, or spleen that are commonly affected in patients with iatrogenic immunosuppression who develop invasive candidiasis [13, 24].

CARD9 is an adaptor protein that relays signals downstream of several C-type lectin receptors (CLRs), such as dectin-1, dectin-2, dectin-3, and mincle that recognize carbohydrates on the fungal cell wall [22, 25, 26]. CARD9-deficient mice and humans exhibit a CNS-specific and fungal-specific inability to mobilize neutrophils during infection, whereas neutrophil recruitment into the fungal-infected kidney and bacterial-infected CNS is intact in CARD9 deficiency [21••]. The defect in neutrophil accumulation in the CARD9-deficient *C. albicans*-infected CNS is attributed to defects in the production of the CXC chemokines CXCL1, CXCL2, CXCL5, and CXCL8 (IL-8) in the *C. albicans*-infected CNS by resident glial cells and recruited myeloid phagocytes, while cell-intrinsic neutrophil chemotaxis and survival are intact [21••]. In addition to the significantly impaired trafficking to the infected CNS, the small numbers of neutrophils that are recruited into the tissue exhibit a defect in killing of unopsonized *C. albicans* yeast forms, which further contributes to infection susceptibility in these patients [21••, 27]. Recent clinical reports indicated that a small number of, but not all, CARD9-deficient patients benefited from adjunct immunotherapy with granulocyte-macrophage colony stimulating factor (GM-CSF) or granulocyte-colony stimulating factor (G-CSF) [28–31]; because these colony stimulating factors are known to exert pleiotropic effects on recruitment and/or effector function of neutrophils and other myeloid phagocytes including microglia, future work will be needed to examine whether the benefit seen in these patients relates to overcoming the aforementioned neutrophil recruitment and/or function defects.

Anti-*C. albicans* Neutrophil Effector Functions

Assembly of the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase complex at the neutrophil phagosomal membrane and activation of myeloperoxidase (MPO) result in generation of reactive oxygen species (ROS), which along with the NADPH oxidase-induced K^+-flux-mediated activation of neutrophil proteases within the phagosome are thought to be responsible for pathogen (including *C. albicans*) killing [32, 33]. Moreover, calcineurin-mediated, NFAT (nuclear factor of activated T cells)-independent signaling, and Mac-1/Vav/PKCδ (protein kinase delta) activation, both dependent on the CLR dectin-1, contribute to ROS formation in mouse neutrophils [34–37]. In addition to the dectin-1 dependent activation, Mac-1 (also known as integrin $\alpha_M\beta_2$ or CR3) can also directly bind to *C. albicans* and regulates phagocytosis and intracellular *Candida* killing [38, 39]. Consonant with the important roles of oxidative killing mechanisms, NADPH oxidase- and MPO-deficient mouse and human neutrophils exhibit impaired *C. albicans* killing capacity and patients with chronic granulomatous disease (CGD) caused by mutations in any of the five subunits of the NADPH oxidase complex and those with complete MPO deficiency occasionally develop spontaneous invasive candidiasis [33, 40, 41, 42]. In addition to ROS, reactive nitrogen species (RNS, such as peroxynitrite $ONOO^-$) are also candidacidal as has been shown for macrophages in response to opsonized and nonopsonized *C. albicans* [43]. Neutrophils also produce peroxynitrite in response to bacterial components and

cytokines [44, 45]. However, whether *C. albicans* induces peroxynitrite production by neutrophils requires further investigation. However, the vast majority of CGD- and MPO-deficient patients who lack ROS production by neutrophils never develop the infection despite lifelong ubiquitous exposure to *C. albicans* commensal organisms, implying that lack of phagocyte ROS production in humans can be largely compensated in vivo by non-oxidative killing mechanisms of *C. albicans*. Recent studies have uncovered two important molecular signals involved in non-oxidative *C. albicans* killing. The endoplasmic reticulum transmembrane protein Jagunal homolog 1 (JAGN1) that modulates neutrophil *N*-glycosylation and the chemokine receptor CXCR1 were both shown to mediate cell-intrinsic neutrophil granulogenesis, degranulation, and non-oxidative *C. albicans* killing without affecting neutrophil recruitment from the blood into *C. albicans*-infected organs [46••, 47]. Of importance, similar to Cxcr1-deficient neutrophils, the dysfunctional *CXCR1-T276* allele was found to mediate degranulation and non-oxidative *C. albicans* killing in human neutrophils and was an independent risk factor for development of disseminated candidiasis in intensive care unit patients who suffered from candidemia [46••].

Two independent phagolysosomal mechanisms for *C. albicans* killing were recently characterized in human neutrophils as a function of *C. albicans* opsonization by evaluating patients with various PIDs [48••, 49]. On one hand, killing of opsonized *C. albicans* is dependent on the NADPH oxidase system as well as Fcγ receptors and protein kinase C (PKC). On the other hand, killing of unopsonized *C. albicans* occurs independently of the NADPH oxidase system and relies on complement receptor 3 (CR3), CARD9, and phosphoinositide-3-kinase (PI3K). While both killing mechanisms in human neutrophils depend on functional Syk activity, the CLR dectin-1 is dispensable. This observation is in keeping with the absence of invasive candidiasis in patients with *CLEC7A* mutations that result in functional dectin-1 deficiency and underscores the differences in molecular factors involved in fungal recognition and killing between mouse and human neutrophils [50]. Of interest, autophagy appears largely dispensable for *C. albicans* killing [51], while the precise role of NETs in regulating the balance between anti-*C. albicans* resistance and immunopathology in vivo requires further investigation [52, 53].

Elegant recent studies have uncovered an intricate cross-talk between tissue-resident and recruited mononuclear phagocytes and NK cells that boosts neutrophil fungicidal activity in *C. albicans*-infected tissues via the production of GM-CSF by NK cells. On one hand is IL-23p19 produced by resident dendritic cells via activation of Syk [54, 55] and on the other hand is IL-15 produced by recruited inflammatory Ly6C^{hi} monocytes via type I interferon activation [56••, 57], which both promote the production of GM-CSF by NK cells that leads to enhanced neutrophil candidacidal activity. In fact, a recent randomized clinical trial indicated that administration of GM-CSF in recipients of allogeneic hematopoietic stem cell transplantation (HSCT) may protect from invasive fungal infection (primarily invasive candidiasis)-related mortality [58].

Neutrophil-Mediated Immunopathology During Invasive Candidiasis

Although neutrophils are crucial for host defense during candidemia and invasive candidiasis, neutrophil-mediated control of *C. albicans* may come at the cost of immunopathology and tissue injury. In agreement with that, excessive neutrophil accumulation in mouse renal tissue is detrimental in the late phases of the infection [14], and leukotriene B_4-driven intravascular neutrophil clustering and occlusion in mouse lung tissue result in neutrophil-mediated capillaritis, pulmonary hemorrhage, and hypoxia [59•]. Pathogenic neutrophil effects may be seen in patients with renal candidiasis and in a subset of neutropenic patients with hepatosplenic candidiasis during neutrophil recovery; strikingly, these patients occasionally require administration of corticosteroid therapy given the worsening of their clinical status [60, 61]. The chemokine receptor CCR1, the TEC tyrosine kinase, the endoribonuclease MCPIP1, the interleukin IL-17C, and the suppressor of TCR signaling (STS) phosphatases are implicated in neutrophil-mediated immunopathology in infected tissue [19, 62, 63–67], while galectin-3 signaling is deleterious via cell-intrinsic impairment in neutrophil ROS formation [68]. These data indicate that pharmacological inhibition of these pathways may represent targeted therapeutic strategies in selected patients with invasive candidiasis.

The Role of Neutrophils in Host Defense against Aspergillosis and Other Invasive Mold Infections

Neutrophil depletion in mice renders them highly susceptible to invasive pulmonary aspergillosis [4, 7]. In keeping with these experimental observations, neutropenia is a well-established risk factor for development of invasive aspergillosis and suffering a worse outcome after infection in hematological malignancy patients and HSCT recipients [69]. In fact, patients with prolonged neutropenia and treatment-refractory invasive fungal infections (including aspergillosis) are occasionally treated with granulocyte transfusions, which when given in high doses may protect from infection-related mortality [70]. In addition, G-CSF and GM-CSF have been used extensively in neutropenic hematology patients to decrease the duration of neutropenia and ameliorate its impact on infection (including fungal) susceptibility, although convincing data on the impact of this intervention in improving patient

survival are lacking [71]. Recent evidence in mice indicates that macrophage colony-stimulating factor (M-CSF), but not G-CSF, instructs myeloid commitment in hematopoietic stem cells via direct activation of the myeloid transcription factor PU.1, and results in earlier enhanced production of mature myeloid donor cells post-transplantation and improved survival of transplanted mice when infected with *A. fumigatus* [72•]. These preclinical findings show promise for the potential use of M-CSF to decrease the duration of neutropenia and the incidence of invasive aspergillosis (and other infections) in HSCT recipients, and clinical studies are warranted to examine the efficacy of this intervention in patients.

Protective Neutrophil Trafficking Into *A. fumigatus*-Infected Tissues

Mouse studies have defined the molecular factors that mediate protective neutrophil recruitment in the *A. fumigatus*-infected lungs. Elegant studies from the Hohl and Obar labs have defined two distinct waves of signaling events that drive trafficking of neutrophils into the lungs [73•, 74•]. Early on, the first wave involves MyD88 expression on lung epithelial cells, which promotes the production of the CXC chemokines CXCL1 and CXCL5. Operating upstream of MyD88 signaling to recruit neutrophils is the IL-1α-IL-1β/IL-1R axis, not Toll-like receptors [73•, 74•, 75]. The second wave involves CARD9 expression on hematopoietic cells in the lung, which drives the production of the CXC chemokines CXCL1 and CXCL2. Both neutrophils and CCR2-expressing monocytes contribute to CXC chemokine production during lung infection. In line with the critical role of the production of CXC chemokines in promoting protective neutrophil recruitment are the findings by Mehrad and colleagues, which showed that neutralization of these CXC chemokines impairs neutrophil trafficking and *A. fumigatus* growth control in the lung, and that over-expression of CXCL1 in mice protects against invasive pulmonary aspergillosis [76]. Consonant to these findings in the lung, CXCL1 was also shown to be critical for protective neutrophil recruitment in the *A. fumigatus*-infected cornea [77]. Another chemoattractant signal that was recently shown to mediate protective neutrophil trafficking into the *A. fumigatus*-infected lung is eicosanoid leukotriene B_4 (LTB_4) via binding to its receptor LTB_4R1 [78]. Specifically, LTB_4 is produced early on during *A. fumigatus* infection by radiosensitive hematopoietic cells in the lung via a pathway that is, at least in part, dependent on hypoxia inducible factor 1α (HIF-1α).

The reliance on both IL-1R/MyD88 and CARD9 signaling for neutrophil recruitment into the *A. fumigatus*-infected lung may account for the clinical observation that invasive pulmonary aspergillosis is not seen in patients with inherited MYD88 or CARD9 deficiency, as each of these pathways may be able to compensate for the lack of the other in humans [23, 79, 80]. Of note, CARD9-deficient patients have been reported to develop extrapulmonary aspergillosis involving the CNS and intra-abdominal tissues while sparing the lungs [81•]. This observation identifies CARD9 deficiency as the first known inherited or iatrogenic condition that predisposes to strictly extrapulmonary aspergillosis. Interestingly, CARD9-deficient neutrophils do not exhibit impaired anti-*A. fumigatus* effector function. Instead, impaired accumulation of neutrophils in the extrapulmonary infected tissue was evident in affected patients, indicative of a neutrophil mobilization defect. Because CARD9-deficient patients with extrapulmonary aspergillosis do not have peripheral neutropenia nor do their neutrophils have cell-intrinsic chemotaxis defects [81•], the aforementioned observations suggest that impaired production of neutrophil-targeted chemoattractant molecules (CXC chemokines and/or other) in extrapulmonary tissue may drive susceptibility to aspergillosis in CARD9 deficiency.

Anti-*A. fumigatus* Neutrophil Effector Functions

Following their recruitment into the *A. fumigatus*-infected infected tissue, neutrophils uptake fungal conidia for intracellular destruction and inhibit the extracellular growth of larger fungal hyphal elements that cannot be internalized. Pentraxin-3 (PTX3) is a soluble collectin that covers the surface of *A. fumigatus* conidia in the alveolar spaces and promotes their uptake by mouse neutrophils and control of aspergillosis in mice [82]. Mechanisms include (a) deposition of complement and phagocytosis via CR3 and Fcγ receptor 2A (CD32) and (b) activation of myeloid differentiation protein 2 (MD-2) and TIR-domain-containing adapter-inducing interferon-β signaling (TRIF) [83, 84]. In keeping with the mouse findings, dysfunctional *PTX3* polymorphisms in humans are associated with impaired neutrophil uptake of *A. fumigatus* conidia and increased risk for development of invasive aspergillosis in HSCT and solid organ transplant recipients [85–87].

Neutrophils employ distinct mechanisms for *A. fumigatus* conidial and hyphal killing. For instance, in the mouse lung where rapid neutrophil deployment prevents conidial germination to hyphal elements, conidial killing does not depend on the neutrophil granule protein calprotectin (S100A8/A9), which acts to sequester zinc and manganese from *A. fumigatus* cells. Instead, in the mouse eye, germination of conidia to hyphae occurs, at least in part due to the sluggish mobilization of neutrophils to the infected tissue, and neutrophil-mediated inhibition of *A. fumigatus* hyphal growth requires calprotectin [88].

In mouse lung neutrophils, *A. fumigatus* conidial killing depends at large on neutrophil-intrinsic NADPH oxidase activity that results in induction of fungal apoptosis-like programmed cell death via modulation of the *A. fumigatus* anti-apoptotic protein, AfBIR1, a homolog of human *SURVIVIN*

[89••]. In humans, CGD is the "signature" PID that underlies *A. fumigatus* infection susceptibility as these patients have a ~ 40% lifetime risk for developing the infection; a unique predisposition has been observed for infection with *Aspergillus nidulans*, a species of *Aspergillus* that is not seen in patients with iatrogenic immunosuppression, for reasons that remain largely unknown [79]. In contrast to NADPH oxidase-dependent ROS production, neutrophil MPO or serine protease activation does not appear essential for anti-*A. fumigatus* neutrophil killing in mice and, in agreement with that, MPO-deficient patients and patients with Papillon-Lefèvre syndrome who are deficient in cathepsin C do not develop invasive aspergillosis [4, 79, 90, 40].

Importantly, compensatory killing mechanisms do exist in phagocytes in the absence of NAPDH oxidase, which is reflected in the clinical observation that ~ 60% of CGD patients never develop invasive aspergillosis despite ubiquitous daily exposure to airborne *Aspergillus* conidia. One of these non-oxidative burst-dependent pathways involves iron sequestration by lactoferrin, which is present within neutrophil secondary granules [91]. Of note, the pattern of mold infection susceptibility in CGD patients has also unveiled the mold-specific dependence on neutrophil oxidative versus non-oxidative cytotoxicity for effective host defense; indeed, while CGD patients are at high risk for aspergillosis, they rarely develop infection by the ubiquitous molds *Rhizopus* or *Fusarium* species, indicating that these fungi can be effectively controlled by neutrophil non-oxidative cytotoxic mechanisms in the absence of oxidative burst [79]. In *Rhizopus* species and other *Mucorales* fungi, which not only cause infections in patients with neutropenia but also characteristically infect patients with diabetic ketoacidosis (DKA), it was recently shown that ketone bodies impair the anti-*Rhizopus* killing capacity of neutrophils; this neutrophil function defect along with the ketone body-, hyperglycemia-, and acidosis-induced up-regulation of fungal CotH and endothelial cell GRP78 that collectively promote *Rhizopus* angioinvasion shed light to the unique propensity of patients with DKA to develop mucormycosis, while they are not susceptible to other mold infections [92–94].

Mouse neutrophils express RORγt upon *A. fumigatus* exposure, which requires IL-6 and IL-23 signaling and is critical for expression of IL-17A, dectin-2, and IL-17RC by neutrophils. IL-17A/IL-17RC acts in an autocrine manner to promote neutrophil oxidative cytotoxicity and to protect against *A. fumigatus* keratitis in mice [95]. In humans, inherited deficiency in IL-17-dependent immunity, such as that seen with mutations in *IL17F*, *IL17RA*, *IL17RC*, or *ACT1*, is dispensable for anti-*Aspergillus* host defense. Instead, human IL-17 deficiency impairs immunity at the mucocutaneous barrier and predisposes to chronic mucocutaneous candidiasis, cutaneous staphylococcal disease, and pulmonary bacterial infections [96, 97].

Recent elegant studies in the Rivera lab uncovered a critical role for CCR2-expressing monocyte and neutrophil cross-talk in the *A. fumigatus*-infected mouse lung for priming of ROS production and fungicidal activity by neutrophils [98••, 99]. Specifically, the type III interferons IFN-λs are produced in vivo by recruited inflammatory $Ly6C^{hi}$ monocytes via the generation of type I interferon and act on neutrophils to promote their antifungal effector functions in the infected lung. In agreement, mice with neutrophil-specific deletion of IFNLR1 are highly susceptible to invasive aspergillosis and adoptive transfer of $CCR2^{+}$ monocytes or exogenous administration of recombinant IFN-α and IFN-λ rescues the impaired neutrophil effector function seen in CCR2-depleted mice, which lack monocyte influx in the infected lung [98, 99]. Therefore, type I/III interferons orchestrate monocyte-neutrophil crosstalk to prime neutrophil fungicidal activity during pulmonary aspergillosis [98••, 99], reminiscent of the cross-talk between NK cells and neutrophils that is orchestrated by IL-15/IL-23/GM-CSF for priming neutrophil fungicidal activity during renal candidiasis [56••, 55, 54].

Independent mechanisms for killing of *A. fumigatus* conidia versus hyphae were recently characterized in human neutrophils by evaluating patients with various PIDs [49, 100••]. Sensing of *A. fumigatus* conidia involves CR3 but not dectin-1, which drives PI3K-dependent non-oxidative intracellular conidial killing. When conidia escape from killing and germinate into hyphae, their extracellular destruction requires antibody-mediated opsonization, sensing via Fcγ receptors, and signaling via Syk, PI3K, and PKC to drive NADPH oxidase-mediated ROS production. Of interest, although *A. fumigatus* hyphae induce NET formation in human neutrophils, which depends on intact NADPH oxidase, NETs do not contribute to *A. fumigatus* killing, in agreement with the dispensable role of NETs in host defense in a mouse model of ocular aspergillosis [101].

Conclusions

Invasive infections by *Candida* and *Aspergillus* species have emerged as significant causes of infection-related mortality in vulnerable patients with acute illness and iatrogenic immunosuppression [7, 69, 102]. The high fatality rates of these infections despite administration of antifungal therapy and the continuously expanding patient populations at risk for such infections highlight the unmet medical need for development of better diagnostic and therapeutic interventions in order to improve the prognosis of these infections [12, 69, 103, 104]. Neutrophils play a critical role in host defense against invasive candidiasis and aspergillosis via their rapid deployment to the site of fungal invasion and by mediating fungal destruction using a panoply of effector mechanisms. Better understanding of the molecular cues that instruct recruitment and effector

function of neutrophils to the fungal-infected tissues should help devise immune-based strategies with a goal to complement conventional antifungal therapy and improve the outcome of infected patients.

Funding Information This work was supported by the Division of Intramural Research, NIAID, NIH.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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. Dancey JT, Deubelbeiss KA, Harker LA, Finch CA. Neutrophil kinetics in man. J Clin Invest. 1976;58(3):705–15. https://doi.org/10.1172/JCI108517.
2. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol. 2013;13(3):159–75. https://doi.org/10.1038/nri3399.
3. Amulic B, Cazalet C, Hayes GL, Metzler KD, Zychlinsky A. Neutrophil function: from mechanisms to disease. Annu Rev Immunol. 2012;30:459–89. https://doi.org/10.1146/annurev-immunol-020711-074942.
4. Lionakis MS, Levitz SM. Host control of fungal infections: lessons from basic studies and human cohorts. Annu Rev Immunol. 2017; https://doi.org/10.1146/annurev-immunol-042617-053318.
5. Swamydas M, Break TJ, Lionakis MS. Mononuclear phagocyte-mediated antifungal immunity: the role of chemotactic receptors and ligands. Cell Mol Life Sci. 2015;72(11):2157–75. https://doi.org/10.1007/s00018-015-1858-6.
6. Lionakis MS, Iliev ID, Hohl TM. Immunity against fungi. JCI Insight 2017;2(11):e93156. https://doi.org/10.1172/jci.insight.93156.
7. Hohl TM. Immune responses to invasive aspergillosis: new understanding and therapeutic opportunities. Curr Opin Infect Dis. 2017;30(4):364–71. https://doi.org/10.1097/QCO.0000000000000381.
8. LeibundGut-Landmann S, Wuthrich M, Hohl TM. Immunity to fungi. Curr Opin Immunol. 2012;24(4):449–58. https://doi.org/10.1016/j.coi.2012.04.007.
9. Hernandez-Santos N, Wiesner DL, Fites JS, McDermott AJ, Warner T, Wuthrich M, et al. Lung epithelial cells coordinate innate lymphocytes and immunity against pulmonary fungal infection. Cell Host Microbe. 2018;23:511–522.e5. https://doi.org/10.1016/j.chom.2018.02.011.
10. 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.
11. Lionakis MS, Netea MG. *Candida* and host determinants of susceptibility to invasive candidiasis. PLoS Pathog. 2013;9(1):e1003079. https://doi.org/10.1371/journal.ppat.1003079.
12. Desai JV, van de Veerdonk FL, Lionakis MS. Understanding the role of host immune responses in invasive candidiasis. Intensive Care Med. 2017; https://doi.org/10.1007/s00134-017-4988-5.
13. McCarty TP, Pappas PG. Invasive candidiasis. Infect Dis Clin N Am. 2016;30(1):103–24. https://doi.org/10.1016/j.idc.2015.10.013.
14. Romani L, Mencacci A, Cenci E, Del Sero G, Bistoni F, Puccetti P. An immunoregulatory role for neutrophils in $CD4^+$ T helper subset selection in mice with candidiasis. J Immunol. 1997;158(5):2356–62.
15. Dejima T, Shibata K, Yamada H, Hara H, Iwakura Y, Naito S, et al. Protective role of naturally occurring interleukin-17A-producing gammadelta T cells in the lung at the early stage of systemic candidiasis in mice. Infect Immun. 2011;79(11):4503–10. https://doi.org/10.1128/IAI.05799-11.
16. Lionakis MS, Lim JK, Lee CC, Murphy PM. Organ-specific innate immune responses in a mouse model of invasive candidiasis. J Innate Immun. 2011;3(2):180–99. https://doi.org/10.1159/000321157.
17. Davis SL, Hawkins EP, Mason EO Jr, Smith CW, Kaplan SL. Host defenses against disseminated candidiasis are impaired in intercellular adhesion molecule 1-deficient mice. J Infect Dis. 1996;174(2):435–9.
18. Cannom RR, French SW, Johnston D, Edwards JE Jr, Filler SG. *Candida albicans* stimulates local expression of leukocyte adhesion molecules and cytokines in vivo. J Infect Dis. 2002;186(3):389–96. https://doi.org/10.1086/341660.
19. Lionakis MS, Fischer BG, Lim JK, Swamydas M, Wan W, Richard Lee CC, et al. Chemokine receptor Ccr1 drives neutrophil-mediated kidney immunopathology and mortality in invasive candidiasis. PLoS Pathog. 2012;8(8):e1002865. https://doi.org/10.1371/journal.ppat.1002865.
20. MacCallum DM, Castillo L, Brown AJ, Gow NA, Odds FC. Early-expressed chemokines predict kidney immunopathology in experimental disseminated *Candida albicans* infections. PLoS One. 2009;4(7):e6420. https://doi.org/10.1371/journal.pone.0006420.
21. •• 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. **This study used mouse and human systems to demonstrate that CARD9 is critical for fungal- and brain-specific recruitment of neutrophils, via promoting the production of CXC chemokines by resident glial cells and recruited phagocytic cells.**
22. 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.
23. 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.
24. 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. 2015;135(6):1558–68.e2. https://doi.org/10.1016/j.jaci.2014.12.1930.
25. Drummond RA, Saijo S, Iwakura Y, Brown GD. The role of Syk/CARD9 coupled C-type lectins in antifungal immunity. Eur J Immunol. 2011;41(2):276–81. https://doi.org/10.1002/eji.201041252.

26. Drummond RA, Lionakis MS. Organ-specific mechanisms linking innate and adaptive antifungal immunity. Semin Cell Dev Biol. 2018; https://doi.org/10.1016/j.semcdb.2018.01.008.
27. 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.
28. Drummond RA, Zahra FT, Natarajan M, Swamydas M, Hsu AP, Wheat LJ, Gavino C, Vinh DC, Holland SH, Mikelis CM, Lionakis MS. GM-CSF Therapy in Human CARD9 Deficiency. J Allergy Clin Immunol. 2018 Jun 8. pii: S0091-6749(18)30846–7. https://doi.org/10.1016/j.jaci.2018.05.025.
29. 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.e7. https://doi.org/10.1016/j.jaci.2015.09.016.
30. Celmeli F, Oztoprak N, Turkkahraman D, Seyman D, Mutlu E, Frede N, et al. Successful granulocyte colony-stimulating factor treatment of relapsing *Candida albicans* meningoencephalitis caused by CARD9 deficiency. Pediatr Infect Dis J. 2016;35(4):428–31. https://doi.org/10.1097/INF.0000000000001028.
31. 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.
32. Reeves EP, Lu H, Jacobs HL, Messina CG, Bolsover S, Gabella G, et al. Killing activity of neutrophils is mediated through activation of proteases by K^+ flux. Nature. 2002;416(6878):291–7. https://doi.org/10.1038/416291a.
33. 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.
34. Greenblatt MB, Aliprantis A, Hu B, Glimcher LH. Calcineurin regulates innate antifungal immunity in neutrophils. J Exp Med. 2010;207(5):923–31. https://doi.org/10.1084/jem.20092531.
35. Li X, Utomo A, Cullere X, Choi MM, Milner DA Jr, Venkatesh D, et al. The beta-glucan receptor dectin-1 activates the integrin Mac-1 in neutrophils via Vav protein signaling to promote *Candida albicans* clearance. Cell Host Microbe. 2011;10(6):603–15. https://doi.org/10.1016/j.chom.2011.10.009.
36. Li X, Cullere X, Nishi H, Saggu G, Durand E, Mansour MK, et al. PKC-delta activation in neutrophils promotes fungal clearance. J Leukoc Biol. 2016;100(3):581–8. https://doi.org/10.1189/jlb.4A0915-405R.
37. 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.
38. Jawhara S, Pluskota E, Cao W, Plow EF, Soloviev DA. Distinct effects of Integrins alphaXbeta2 and alphaMbeta2 on leukocyte subpopulations during inflammation and antimicrobial responses. Infect Immun. 2017;85(1):e00644–16. https://doi.org/10.1128/IAI.00644-16.
39. Soloviev DA, Jawhara S, Fonzi WA. Regulation of innate immune response to *Candida albicans* infections by alphaMbeta2-Pra1p interaction. Infect Immun. 2011;79(4):1546–58. https://doi.org/10.1128/IAI.00650-10.
40. 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.
41. Lehrer RI. Measurement of candidacidal activity of specific leukocyte types in mixed cell populations I. Normal, myeloperoxidase-deficient, and chronic granulomatous disease neutrophils. Infect Immun. 1970;2(1):42–7.
42. 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.
43. Vazquez-Torres A, Jones-Carson J, Balish E. Peroxynitrite contributes to the candidacidal activity of nitric oxide-producing macrophages. Infect Immun. 1996;64(8):3127–33.
44. Gagnon C, Leblond FA, Filep JG. Peroxynitrite production by human neutrophils, monocytes and lymphocytes challenged with lipopolysaccharide. FEBS Lett. 1998;431(1):107–10.
45. Evans TJ, Buttery LD, Carpenter A, Springall DR, Polak JM, Cohen J. Cytokine-treated human neutrophils contain inducible nitric oxide synthase that produces nitration of ingested bacteria. Proc Natl Acad Sci U S A. 1996;93(18):9553–8.
46.•• 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 study described the first biological function of CXCR1 in mice by showing that the chemokine receptor mediates granulogenesis, degranulation and non-oxidative *Candida* killing of neutrophils. It also showed that the dysfunctional *CXCR1-T276* allele in humans results in impaired neutrophil degranulation and *Candida* killing and is associated with development of disseminated candidiasis in patients with candidemia.**
47. Wirnsberger G, Zwolanek F, Stadlmann J, Tortola L, Liu SW, Perlot T, et al. Jagunal homolog 1 is a critical regulator of neutrophil function in fungal host defense. Nat Genet. 2014;46(9):1028–33. https://doi.org/10.1038/ng.3070.
48.•• Gazendam RP, van Hamme JL, Tool AT, van Houdt M, Verkuijlen PJ, Herbst M, et al. Two independent killing mechanisms of *Candida albicans* by human neutrophils: evidence from innate immunity defects. Blood. 2014;124(4):590–7. https://doi.org/10.1182/blood-2014-01-551473. **This study examined neutrophil anti-*Candida* killing mechanisms using cells from patients with primary immunodeficiency disorders and defined the signaling pathways that are important for control of opsonized versus unopsonized yeast cells.**
49. Gazendam RP, van de Geer A, Roos D, van den Berg TK, Kuijpers TW. How neutrophils kill fungi. Immunol Rev. 2016;273(1):299–311. https://doi.org/10.1111/imr.12454.
50. Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spriel AB, Venselaar H, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med. 2009;361(18):1760–7. https://doi.org/10.1056/NEJMoa0901053.
51. Smeekens SP, Malireddi RK, Plantinga TS, Buffen K, Oosting M, Joosten LA, et al. Autophagy is redundant for the host defense against systemic *Candida albicans* infections. Eur J Clin Microbiol Infect Dis. 2014;33(5):711–22. https://doi.org/10.1007/s10096-013-2002-x.
52. Urban CF, Reichard U, Brinkmann V, Zychlinsky A. Neutrophil extracellular traps capture and kill *Candida albicans* yeast and hyphal forms. Cell Microbiol. 2006;8(4):668–76. https://doi.org/10.1111/j.1462-5822.2005.00659.x.
53. Branzk N, Lubojemska A, Hardison SE, Wang Q, Gutierrez MG, Brown GD, et al. Neutrophils sense microbe size and selectively release neutrophil extracellular traps in response to large pathogens. Nat Immunol. 2014;15(11):1017–25. https://doi.org/10.1038/ni.2987.
54. Whitney PG, Bar E, Osorio F, Rogers NC, Schraml BU, Deddouche S, et al. Syk signaling in dendritic cells orchestrates innate resistance to systemic fungal infection. PLoS Pathog.

2014;10(7):e1004276. https://doi.org/10.1371/journal.ppat.1004276.

55. Bar E, Whitney PG, Moor K, Reis e Sousa C, LeibundGut-Landmann S. IL-17 regulates systemic fungal immunity by controlling the functional competence of NK cells. Immunity. 2014;40(1):117–27. https://doi.org/10.1016/j.immuni.2013.12.002.

56.•• Dominguez-Andres J, Feo-Lucas L, Minguito de la Escalera M, Gonzalez L, Lopez-Bravo M, Ardavin C. Inflammatory Ly6C(high) monocytes protect against candidiasis through IL-15-driven NK cell/neutrophil activation. Immunity. 2017;46(6):1059–72.e4. https://doi.org/10.1016/j.immuni.2017.05.009. **This study elegantly outlined a IL-15 and type I interferon circuit of inflammatory monocyte-NK cell cross-talk that results in GM-CSF production for priming of candidacidal activity in the *Candida*-infected kidney.**

57. del Fresno C, Soulat D, Roth S, Blazek K, Udalova I, Sancho D, et al. Interferon-beta production via dectin-1-Syk-IRF5 signaling in dendritic cells is crucial for immunity to *C. albicans*. Immunity. 2013;38(6):1176–86. https://doi.org/10.1016/j.immuni.2013.05.010.

58. Wan L, Zhang Y, Lai Y, Jiang M, Song Y, Zhou J, et al. Effect of granulocyte-macrophage colony-stimulating factor on prevention and treatment of invasive fungal disease in recipients of allogeneic stem-cell transplantation: a prospective multicenter randomized phase IV trial. J Clin Oncol. 2015;33(34):3999–4006. https://doi.org/10.1200/JCO.2014.60.5121.

59.• Lee EKS, Gillrie MR, Li L, Arnason JW, Kim JH, Babes L, et al. Leukotriene B4-mediated neutrophil recruitment causes pulmonary capillaritis during lethal fungal sepsis. Cell Host Microbe. 2018;23(1):121–33.e4. https://doi.org/10.1016/j.chom.2017.11.009. **This study identified leukotriene B4-dependent accumulation of neutrophils in the *Candida*-infected lung vasculature as a key mediator of capillaritis, pulmonary hemorrhage and hypoxia.**

60. Legrand F, Lecuit M, Dupont B, Bellaton E, Huerre M, Rohrlich PS, et al. Adjuvant corticosteroid therapy for chronic disseminated candidiasis. Clin Infect Dis. 2008;46(5):696–702. https://doi.org/10.1086/527390.

61. Tomashefski JF Jr, Abramowsky CR. Candida-associated renal papillary necrosis. Am J Clin Pathol. 1981;75(2):190–4.

62. Lionakis MS, Albert ND, Swamydas M, Lee CR, Loetscher P, Kontoyiannis DP. Pharmacological blockade of the chemokine receptor CCR1 protects mice from systemic candidiasis of hematogenous origin. Antimicrob Agents Chemother. 2017;61(3):e02365–16. https://doi.org/10.1128/AAC.02365-16.

63. Garg AV, Amatya N, Chen K, Cruz JA, Grover P, Whibley N, et al. MCPIP1 endoribonuclease activity negatively regulates Interleukin-17-mediated signaling and inflammation. Immunity. 2015;43(3):475–87. https://doi.org/10.1016/j.immuni.2015.07.021.

64. Zwolanek F, Riedelberger M, Stolz V, Jenull S, Istel F, Koprulu AD, et al. The non-receptor tyrosine kinase Tec controls assembly and activity of the noncanonical caspase-8 inflammasome. PLoS Pathog. 2014;10(12):e1004525. https://doi.org/10.1371/journal.ppat.1004525.

65. Naseem S, Frank D, Konopka JB, Carpino N. Protection from systemic *Candida albicans* infection by inactivation of the Sts phosphatases. Infect Immun. 2015;83(2):637–45. https://doi.org/10.1128/IAI.02789-14.

66. Huang J, Meng S, Hong S, Lin X, Jin W, Dong C. IL-17C is required for lethal inflammation during systemic fungal infection. Cell Mol Immunol. 2016;13(4):474–83. https://doi.org/10.1038/cmi.2015.56.

67. Carpino N, Naseem S, Frank DM, Konopka JB. Modulating host signaling pathways to promote resistance to infection by *Candida albicans*. Front Cell Infect Microbiol. 2017;7:481. https://doi.org/10.3389/fcimb.2017.00481.

68. Wu SY, Huang JH, Chen WY, Chan YC, Lin CH, Chen YC, et al. Cell intrinsic galectin-3 attenuates neutrophil ROS-dependent killing of *Candida* by modulating CR3 downstream Syk activation. Front Immunol. 2017;8:48. https://doi.org/10.3389/fimmu.2017.00048.

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

70. Price TH, Boeckh M, Harrison RW, McCullough J, Ness PM, Strauss RG, et al. Efficacy of transfusion with granulocytes from G-CSF/dexamethasone-treated donors in neutropenic patients with infection. Blood. 2015;126(18):2153–61. https://doi.org/10.1182/blood-2015-05-645986.

71. Mhaskar R, Clark OA, Lyman G, Engel Ayer Botrel T, Morganti Paladini L, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. Cochrane Database Syst Rev. 2014;10:CD003039. https://doi.org/10.1002/14651858.CD003039.pub2.

72.• Kandalla PK, Sarrazin S, Molawi K, Berruyer C, Redelberger D, Favel A, et al. M-CSF improves protection against bacterial and fungal infections after hematopoietic stem/progenitor cell transplantation. J Exp Med. 2016;213(11):2269–79. https://doi.org/10.1084/jem.20151975. **This study showed that M-CSF administration in transplanted mice drives hematopoietic stem cell commitment and early myeloid donor engraftment, which results in improved outcome of aspergillosis.**

73.• Caffrey AK, Lehmann MM, Zickovich JM, Espinosa V, Shepardson KM, Watschke CP, et al. IL-1alpha signaling is critical for leukocyte recruitment after pulmonary *Aspergillus fumigatus* challenge. PLoS Pathog. 2015;11(1):e1004625. https://doi.org/10.1371/journal.ppat.1004625. **This study showed that IL-1alpha is a critical early mediator of neutrophil recruitment in the *Aspergillus*-infected lung.**

74.• Jhingran A, Kasahara S, Shepardson KM, Junecko BA, Heung LJ, Kumasaka DK, et al. Compartment-specific and sequential role of MyD88 and CARD9 in chemokine induction and innate defense during respiratory fungal infection. PLoS Pathog. 2015;11(1):e1004589. https://doi.org/10.1371/journal.ppat.1004589. **This study defined the sequential role of IL-1R/MyD88 and CARD9 expression in lung epithelial and hematopoietic cells, respectively, for driving protective neutrophil recruitment in the *Aspergillus*-infected lung.**

75. Karki R, Man SM, Malireddi RK, Gurung P, Vogel P, Lamkanfi M, et al. Concerted activation of the AIM2 and NLRP3 inflammasomes orchestrates host protection against *Aspergillus* infection. Cell Host Microbe. 2015;17(3):357–68. https://doi.org/10.1016/j.chom.2015.01.006.

76. Mehrad B, Strieter RM, Moore TA, Tsai WC, Lira SA, Standiford TJ. CXC chemokine receptor-2 ligands are necessary components of neutrophil-mediated host defense in invasive pulmonary aspergillosis. J Immunol. 1999;163(11):6086–94.

77. Leal SM Jr, Cowden S, Hsia YC, Ghannoum MA, Momany M, Pearlman E. Distinct roles for dectin-1 and TLR4 in the pathogenesis of *Aspergillus fumigatus* keratitis. PLoS Pathog. 2010;6:e1000976. https://doi.org/10.1371/journal.ppat.1000976.

78. Caffrey-Carr AK, Hilmer KM, Kowalski CH, Shepardson KM, Temple RM, Cramer RA, et al. Host-derived leukotriene B4 is critical for resistance against invasive pulmonary aspergillosis. Front Immunol. 2017;8:1984. https://doi.org/10.3389/fimmu.2017.01984.

79. Lionakis MS, Netea MG, Holland SM. Mendelian genetics of human susceptibility to fungal infection. Cold Spring Harb Perspect Med 2014;4(6):pii:a019638. https://doi.org/10.1101/cshperspect.a019638.

80. Picard C, Casanova JL, Puel A. Infectious diseases in patients with IRAK-4, MyD88, NEMO or IkappaBalpha deficiency. Clin Microbiol Rev. 2011;24(3):490–7. https://doi.org/10.1128/CMR.00001-11.
81.• 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. https://doi.org/10.1172/jci.insight.89890. **This study uncovered the critical contribution of CARD9 in promoting protection against extrapulmonary aspergillosis in humans while sparing the lungs.**
82. 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.
83. Moalli F, Doni A, Deban L, Zelante T, Zagarella S, Bottazzi B, et al. Role of complement and Fc{gamma} receptors in the protective activity of the long pentraxin PTX3 against *Aspergillus fumigatus*. Blood. 2010;116(24):5170–80. https://doi.org/10.1182/blood-2009-12-258376.
84. Bozza S, Campo S, Arseni B, Inforzato A, Ragnar L, Bottazzi B, et al. PTX3 binds MD-2 and promotes TRIF-dependent immune protection in aspergillosis. J Immunol. 2014;193(5):2340–8. https://doi.org/10.4049/jimmunol.1400814.
85. 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.
86. Wojtowicz A, Lecompte TD, Bibert S, Manuel O, Rueger S, Berger C, et al. PTX3 polymorphisms and invasive mold infections after solid organ transplant. Clin Infect Dis. 2015;61(4):619–22. https://doi.org/10.1093/cid/civ386.
87. 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.
88. Clark HL, Jhingran A, Sun Y, Vareechon C, de Jesus Carrion S, Skaar EP, et al. Zinc and manganese chelation by neutrophil S100A8/A9 (calprotectin) limits extracellular *Aspergillus fumigatus* hyphal growth and corneal infection. J Immunol. 2016;196(1):336–44. https://doi.org/10.4049/jimmunol.1502037.
89.•• Shlezinger N, Irmer H, Dhingra S, Beattie SR, Cramer RA, Braus GH, et al. Sterilizing immunity in the lung relies on targeting fungal apoptosis-like programmed cell death. Science. 2017;357(6355):1037–41. https://doi.org/10.1126/science.aan0365. **This study reveals a fungal apoptosis-like programmed cell death pathway as the target of neutrophil NADPH oxidase activity in the *Aspergillus*-infected lung.**
90. Vethanayagam RR, Almyroudis NG, Grimm MJ, Lewandowski DC, Pham CT, Blackwell TS, et al. Role of NADPH oxidase versus neutrophil proteases in antimicrobial host defense. PLoS One. 2011;6(12):e28149. https://doi.org/10.1371/journal.pone.0028149.
91. Zarember KA, Sugui JA, Chang YC, Kwon-Chung KJ, Gallin JI. Human polymorphonuclear leukocytes inhibit *Aspergillus fumigatus* conidial growth by lactoferrin-mediated iron depletion. J Immunol. 2007;178(10):6367–73.
92. Gebremariam T, Lin L, Liu M, Kontoyiannis DP, French S, Edwards JE Jr, et al. Bicarbonate correction of ketoacidosis alters host-pathogen interactions and alleviates mucormycosis. J Clin Invest. 2016;126(6):2280–94. https://doi.org/10.1172/JCI82744.
93. Gebremariam T, Liu M, Luo G, Bruno V, Phan QT, Waring AJ, et al. CotH3 mediates fungal invasion of host cells during mucormycosis. J Clin Invest. 2014;124(1):237–50. https://doi.org/10.1172/JCI71349.
94. Liu M, Spellberg B, Phan QT, Fu Y, Fu Y, Lee AS, et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. J Clin Invest. 2010;120(6):1914–24. https://doi.org/10.1172/JCI42164.
95. Taylor PR, Roy S, Leal SM Jr, Sun Y, Howell SJ, Cobb BA, et al. Activation of neutrophils by autocrine IL-17A-IL-17RC interactions during fungal infection is regulated by IL-6, IL-23, RORgammat and dectin-2. Nat Immunol. 2014;15(2):143–51. https://doi.org/10.1038/ni.2797.
96. 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.
97. 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.
98.•• Espinosa V, Dutta O, McElrath C, Du P, Chang YJ, Cicciarelli B et al. Type III interferon is a critical regulator of innate antifungal immunity. Sci Immunol. 2017;2(16):pii:eaan5357. https://doi.org/10.1126/sciimmunol.aan5357. **This study elegantly outlined type I and III** interferon**-dependent cross-talk between inflammatory monocytes and neutrophils in the *Aspergillus*-infected lung that results in enhanced neutrophil effector function.**
99. Espinosa V, Jhingran A, Dutta O, Kasahara S, Donnelly R, Du P, et al. Inflammatory monocytes orchestrate innate antifungal immunity in the lung. PLoS Pathog. 2014;10(2):e1003940. https://doi.org/10.1371/journal.ppat.1003940.
100.•• Gazendam RP, van Hamme JL, Tool AT, Hoogenboezem M, van den Berg JM, Prins JM, et al. Human neutrophils use different mechanisms to kill *Aspergillus fumigatus* conidia and hyphae: evidence from phagocyte defects. J Immunol. 2016;196(3):1272–83. https://doi.org/10.4049/jimmunol.1501811. **This study examined neutrophil anti-*Aspergillus* killing mechanisms using cells from patients with primary immunodeficiency disorders and defined the signaling pathways that are important for control of conidia versus hyphae.**
101. Clark HL, Abbondante S, Minns MS, Greenberg EN, Sun Y, Pearlman E. Protein Deiminase 4 and CR3 Regulate Aspergillus fumigatus and β-Glucan-Induced Neutrophil Extracellular Trap Formation, but Hyphal Killing Is Dependent Only on CR3. Front Immunol. 2018 May 29;9:1182. https://doi.org/10.3389/fimmu.2018.01182.
102. 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.
103. 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.
104. 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;31(6):833–43.e5. https://doi.org/10.1016/j.ccell.2017.04.012.